swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Sunlenca

International non-proprietary name: lenacapavir
Pharmaceutical form: solution for injection
Dosage strength(s): 463.5 mg/1.5 mL
Route(s) of administration: subcutaneous use
Marketing authorisation holder: Gilead Sciences Switzerland Sàrl
Marketing authorisation no.: 68385
Decision and decision date: approved on 7 July 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinity
AUC_{last}	Area under the concentration versus time curve from time zero to the last quantifiable
AUC_{tau}	Area under the concentration versus time curve over the dosing interval
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BIC	Bictegravir
BID	Twice daily
BSEP	Bile salt export pump
BVY	Bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CA	Capsid
CC_{50}	Cytotoxicity concentration
CD4	Cluster of differentiation 4
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed plasma/serum concentration of drug
COBI	Cobicistat
CrCl	Creatinine clearance
CSR	Clinical study report
C_{trough}	Concentration at the end of the dosing interval
CYP	Cytochrome P450
DART	Development and reproductive toxicology
DDI	Drug-drug interaction
DTG	Dolutegravir
DVY	Emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
EC_{50}	Half maximal effective concentration
EFD	Embryofoetal development
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ERA	Environmental risk assessment
EFV	Efavirenz
EVG	Elvitegravir
Fa	Fraction absorbed
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
FTC	Emtricitabine
FTR	Fostemsavir
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
hERG	Human ether-a-go-go related gene

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HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HPLC	High-performance liquid chromatography
HTE	Heavily treatment-experienced
IC_{50}	Half-maximal inhibitory concentration
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IMAB	Ibalizumab
INN	International non-proprietary name
INSTI	Integrase strand-transfer inhibitors
IQ	Inhibitory quotient
ISR	injection site reaction
ITT	Intention-to-treat
IV	Intravenous
Ka	First-order absorption rate
K_D	Dissociation constant
LEN	Lenacapavir
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MDR	Multidrug resistance
Min	Minimum
MIs	Maturation inhibitors
MRHD	Maximum recommended human dose
N/A	Not applicable
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NO(A)EL	No observed (adverse) effect level
NRTI	Nucleoside reverse transcriptase inhibitor
OATP	Organic anion transporting polypeptide
OBR	Optimised background regimen
OSS	Overall susceptibility score
PBMCs	Peripheral blood mononuclear cells
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
P-gp	P-glycoprotein
PI	Protease inhibitor
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PO	peroral
PopPK	Population pharmacokinetics
PPND	Pre- and postnatal development
PSP	Pediatric study plan (US FDA)
PWH	People with HIV
RAP	Resistance analysis population
RH	Relative humidity
RMP	Risk management plan
RNA	Ribonucleic acid
RPV	Rilpivirine
RTV	Ritonavir
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SwissPAR	Swiss Public Assessment Report

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$T_{1/2}$	Half-life
TAF	Tenofovir alafenamide
TEAE	Treatment-emergent adverse event
TFV	Tenofovir
Tmax	Time to reach Cmax
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
tQT	Thorough QT
UGT1A1	Uridine 5'-diphospho-glucuronosyltransferase 1A1
Vp	Peripheral volume of distribution
WT	Wild-type

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for lenacapavir as lenacapavir sodium in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Sunlenca, in combination with other antiretrovirals, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations (see section "Properties/Effects").

2.2.2 Approved indication

Sunlenca, in combination with optimised background antiretroviral therapy, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations (see section "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:
Initiation of treatment with lenacapavir requires lenacapavir injection to be given with lenacapavir film-coated tablets.

Adults
The recommended lenacapavir treatment regimen in adults consists of a 2-day initiation dosing period (oral tablets and subcutaneous injections) followed by maintenance dosing once every 6 months (subcutaneous injections).
Initiation
On treatment Day 1, the recommended dose of lenacapavir is 927 mg administered by subcutaneous injection and 600 mg taken as oral tablets. On treatment Day 2, the recommended dose is 600 mg taken as oral tablets.

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).

Table 1: Recommended treatment regimen for lenacapavir: initiation and maintenance dosing schedule

Treatment time	
	Dosage of Sunlenca: Initiation
Day 1	927 mg subcutaneous injection (2 x 1.5 mL vials[a]) 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg oral (2 x 300 mg tablets)
	Dosage of Sunlenca: Maintenance
Every 6 months (26 weeks)[b] +/- 2 weeks	927 mg subcutaneous injection (2 x 1.5 mL vials[a])

a 2 injections, each at separate site.
b From the date of last injection

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Special Dosage Recommendations
Elderly
No dose adjustment of lenacapavir is required in elderly patients (see section “Pharmacokinetics”).

Renal impairment
No dose adjustment of lenacapavir is required in patients with mild, moderate, or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Lenacapavir has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) (see section “Pharmacokinetics”).

Hepatic impairment
No dose adjustment of lenacapavir is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Lenacapavir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section “Pharmacokinetics”).

Paediatric population
The safety and efficacy of lenacapavir in children under the age of 18 years old has not been established. No data are available.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 April 2022
Formal control completed	21 April 2022
List of Questions (LoQ)	9 September 2022
Response to LoQ	25 November 2022
Preliminary decision	16 February 2023
Response to preliminary decision	11 April 2023
Final decision	7 July 2023
Decision	approval

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3 Medical context

HIV infection is of major public health significance and, if left untreated, a life-threatening disease. Approximately 38 million people are infected worldwide with approximately 26 million on antiretroviral treatment.

Advances in combination antiretroviral (ARV) therapy (ART) for HIV 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.

However, a subset of people with HIV (PWH) experiences virologic and immunologic failure over the long term. These can be due to factors such as lack of adherence to treatment, interruption in access to treatment, drug or food interactions, toxicities, inappropriate ARV combinations, or pre-existing resistance mutations. Moreover, heavily treatment-experienced (HTE) PWH with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable viral suppression because they might not have a single fully active ARV agent available, and are even less likely to have 2 or 3 active agents.

Suboptimal therapy will not allow for maintenance of virologic suppression, leading to ongoing viraemia and decreasing CD4 cell count, putting patients at risk of AIDS-defining opportunistic infections, other comorbidities (AIDS and non-AIDS related), and ultimately death. The goal of treatment for ART−experienced PWH with multidrug resistance (MDR) who are experiencing virologic failure is, of course, to establish virologic suppression, but if maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimise the development of further resistance that may compromise future regimens. Therefore, newer treatment options that are not impacted by resistance to existing ARV classes are needed. For patients infected with MDR HIV-1, fostemsavir, a drug that functions as a gp120 attachment inhibitor, is available.

Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function for the treatment of HIV-1 infection. Lenacapavir inhibits HIV-1 at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production and proper capsid core formation. Viruses produced in the presence of lenacapavir display aberrantly 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. Lenacapavir is anticipated to be active against HIV-1 viruses that have developed resistance to existing classes of ARVs (e.g. nucleoside/nucleotide reverse transcriptase inhibitors, protease inhibitors, integrase strand-transfer inhibitors). Lenacapavir exists in 2 dosage forms, an oral film-coated tablet for initial loading and a long-acting solution for subcutaneous injection since it has low human clearance.

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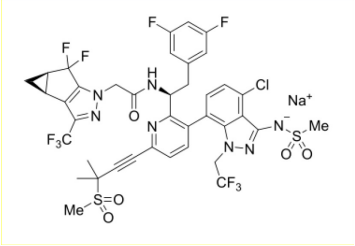
4 Quality aspects

4.1 Drug substance

INN:	-
USAN:	Lenacapavir sodium
Chemical name:	Sodium (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridine-3-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)(methylsulfonyl)amide
Molecular formula:	$C_{39}H_{31}ClF_{10}N_7NaO_5S_2$
Molecular mass:	990.3
Molecular structure:	



Physico-chemical properties:
Lenacapavir sodium is a light yellow to yellow solid. It contains 3 chirality centres and 1 axis of chirality. The compound is practically insoluble at lower pH values and slightly soluble at higher pH values. Lenacapavir exhibits polymorphism.

Synthesis:
The synthesis of lenacapavir sodium consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps, and intermediates.

Specification:
The drug substance specification includes tests for appearance, identification, clarity of solution, water content, sodium content, assay, impurity content, residual solvents, organic volatile impurities, bacterial endotoxins, and microbiological examination. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
The stability of the drug substance was investigated with commercial scale batches which were manufactured by the proposed commercial manufacturing site. The stability samples were stored under long term conditions (30°C/75% RH) and accelerated conditions (40°C/75% RH) as defined in the corresponding ICH Guideline on stability studies. Based on these studies, an adequate retest period was defined.

4.2 Drug product

Description and composition:
Lenacapavir injection, 309 mg/mL, is a sterile, preservative-free, clear, yellow to brown solution for subcutaneous administration.

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Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including principles of quality by design as described in ICH Guidelines Q8 to Q10.

Manufacture:
Lenacapavir injection, 309 mg/mL, is manufactured as a sterile, preservative-free, clear, yellow to brown solution. Control of the manufacturing process is ensured through defined operating parameters based on results of the development studies. In addition, in-process controls with adequate acceptance criteria are established.

Specification:
The drug product specifications include tests for appearance, identification, assay, degradation product content, viscosity, particulate matter, sterility, bacterial endotoxins, and container closure integrity. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug product.

Container Closure System:
The container closure system for lenacapavir injection is a glass vial with a rubber stopper. It is sealed with an aluminium seal.

Stability:
Appropriate stability data from commercial scale batches of Sunlenca are provided. The stability study was carried out according to ICH stability guidelines. Based on the results of this study, an adequate shelf life was established. Degradation impurities are formed after exposure to light, the drug product should be kept protected from light in the outer carton.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

5.1 Pharmacology

Lenacapavir bound with high affinity (K_D = 1.4 nM) at the intermolecular interface between two adjacent capsid monomers within the same capsid hexamer.
Various *in vitro* experiments demonstrated that lenacapavir exerts antiviral activity and inhibits HIV replication at multiple stages at clinically relevant concentrations. The data showed antiviral activity (EC_{50} = 0.025 nM) in wild-type HIV-1 infected MT-2 cells (T-lymphoblastoid cell line), but a lack of activity against an HIV-1 variant carrying the M66I mutation in the capsid. This is in line with the 100-fold reduced binding affinity to HIV strains carrying this mutation.
Lenacapavir showed high antiviral activity in the early phase of target cell infection (EC_{50} = 0.023 nM) and an 18-fold reduced activity in the late stage (i.e. assembly and capsid core formation). This indicates that it also targets some capsid-mediated processes essential for the late stages of HIV replication. In contrast, lenacapavir had no effect on the HIV-1 entry into peripheral blood mononuclear cells (PBMCs). Furthermore, the compound was ineffective regarding the accumulation of reverse transcription products, but reduced the accumulation of integration products and abortive 2-long terminal repeat circles formed in the nucleus. This indicates that lenacapavir inhibits an essential process in the HIV replication cycle that occurs after reverse transcription but before the integration of viral DNA. The produced viral particles showed irregular morphology and were non-infectious. A dose-dependent reduction of mature HIV-1 released into the cell culture supernatant in the presence of lenacapavir (EC_{50} = 0.305 nM) was demonstrated in virus-producing cells.
Taken together, the data demonstrate that lenacapavir is a selective inhibitor of HIV-1 capsid function. It inhibits HIV replication at multiple stages important for the viral lifecycle, including capsid-mediated nuclear uptake, virus assembly and release, and capsid core formation.

Lenacapavir was not cytotoxic in various human cell lines non-permissive to HIV-1 infection, in primary human hepatocytes or in normal resting and activated human PBMCs (CC_{50} > 44 µM). In cellular infection assays, lenacapavir exerted potent antiviral activity in HIV-1 infected MT-4 cells, $CD4^+$ T-lymphocytes, and in monocyte-derived macrophages (EC_{50} = 0.03-0.19 nM).
The antiviral activity of lenacapavir was dependent on multiplicity of infection, with EC_{50} values ranging from 0.028 nM to 0.455 nM, which are in the clinically relevant range. The investigators did not observe any indication of mitochondrial toxicity. The compound showed *in vitro* synergistic activity in combination with other HIV drugs. Antagonistic antiviral interaction did not occur.

Lenacapavir did not exert *in vitro* antiviral activity against hepatitis C virus or human rhinovirus at clinically relevant levels. A Lead Profiling Safety Screen with 87 targets did not identify any clinically relevant off-target activity at 10 µM. The lack of an hERG study is acceptable due to the solubility limitations and the availability of *in vivo* data. Lenacapavir did not cause any cardiovascular changes in the repeated-dose toxicity study in dogs up to 100 mg/kg/dose, corresponding to a safety margin of 20-fold based on free C_{max}. The compound demonstrated a non-significant but persistent increase in tidal volume (9%) and a dose-dependent decrease in respiration rate (up to 13% at 100 mg/kg) in a stand-alone plethysmography study in rats. In a 4-dose (twice monthly) toxicity study in rats with doses up to 100 mg/kg, the treatment with lenacapavir did not impact the central nervous system or locomotor activities (safety margin: 1.4).

5.2 Pharmacokinetics

The pharmacokinetic profile of lenacapavir in rats and dogs was characterised by slow absorption due to the low cell permeability, sustained release after subcutaneous (SC) injection, large tissue distribution, and slow elimination. Bioavailability after subcutaneous injection was relatively high (60%), while it was low (2-22%) after oral administration, similar to that in humans (6%).

In rats and dogs, SC administration of lenacapavir induced slow adsorption and sustained drug release at all administered doses. In comparison to humans, T_{max} is achieved faster. Mean bioavailability is around 60% and $t_{1/2}$ up to 21 days, which is lower than in humans (8-12 weeks). Total lenacapavir plasma exposure (AUC_{inf}) increased with dose, but the increase was less than dose proportional in rats at higher doses.
After single oral administration, slow absorption, with average T_{max} ranging from 8.7 to 18.7 h (slower compared to humans: 4 h), was observed in the tested nonclinical species. The mean volume of distribution (2.22 L/kg) was larger than the total body water volume, and the mean absolute oral bioavailability was low (2.2-22%) and comparable to that in humans.
In the repeated-dose toxicity studies in rats and dogs, lenacapavir plasma exposure (C_{max} and AUC) increased approximately dose-proportionally at lower doses and less than dose-proportionally at higher doses.
Slight accumulation of lenacapavir was observed after multiple monthly subcutaneous doses in dogs, and after daily oral doses in rats and dogs. There were no sex-related differences in PK parameters.
High plasma protein binding was observed in all tested species, mostly to albumin and, to a lesser extent, to α1-acid glycoprotein. Binding to human hepatic microsomes was also high, with a mean fraction bound of 89.2%. Lenacapavir blood-to-plasma ratio was similar across species including humans, with mean values ranging from 0.59 to 0.67, indicating minimal binding to blood cells.
In rats (Wistar Han and Long-Evans) administered 3 mg/kg of [^{14}C]lenacapavir via the intravenous route, radioactivity was widely distributed to most tissues, with a peak concentration at 0.5 h, and detectable up to 14 days. In the liver, radioactivity persisted up to 42 days. No significant melanin binding was observed.
Lenacapavir was detected in rat pups, suggesting milk or placental transfer, as no specific studies of placental transfer or excretion into milk were conducted. The potential for lenacapavir to pass the placenta or to be excreted into milk is not known. This is reflected in the information for the healthcare professionals.
Metabolic conversion of lenacapavir *in vitro* and *in vivo* was low. There are no major human metabolites.
Faecal and biliary elimination were the main excretion routes in rats, dogs and humans.

5.3 Toxicology

The toxicology programme was conducted in rats and dogs with study durations up to 39 weeks for the subcutaneous route and one month for the oral route of administration, adequate to support long-term treatment. Both species were considered relevant based on their pharmacokinetic profiles. Intravenous, subcutaneous, and oral administration routes were tested to support selected pharmaceutical formulations intended for the marketing authorisation. Rabbits were used as a second species in embryofoetal development (EFD) studies. In pivotal studies, rats were dosed SC every 3 months (up to 100 mg/kg) and dogs were dosed monthly (up to 411 mg/kg) to achieve adequate exposure multiples to assess systemic toxicity. In repeated dose toxicity studies via the oral route, animals were dosed daily (up to 30 mg/kg). Skin (injection sites) and liver are considered as target organs of toxicity in both species.
Dose-dependent dermal observations occurred 24 h post dose and persisted throughout the observation period. Dermal findings included oedema (very slight to severe) and erythema, which correlated with the macroscopic observation of subcutaneous injection site thickening and the microscopic observations of granulomatous inflammation with macrophage infiltration. Oedema and erythema were not considered adverse as they were localised to the region of the injection site and formed due to the depot formation, nor did they affect the integrity of the overlaying skin or the health and wellbeing of the animal. Similar dermal observations were observed in a local tolerance study in rabbits after single SC administration. Injection site reactions were seen in the clinical trials as mentioned in the information for the healthcare professionals.
Effects on liver after oral administration of lenacapavir were mild in rats and characterised by slight increases in liver enzymes (in female rats at ≥10 mg/kg/day) and liver weight (at 30 mg/kg/day), without any microscopic correlates. In dogs, a dose of 411 mg/kg (SC) resulted in hepatobiliary

degeneration associated with adverse clinical observations that necessitated cessation of dosing and early termination. A dose-dependent increase in liver parameters occurred in animals administered ≥10 mg/kg (oral), which correlated with microscopic findings (hepatocyte degeneration, individual hepatocyte necrosis, and mixed cell infiltrate) and reduced production of coagulation factors and fibrinogen. The findings were partially reversible. There were no adverse liver findings in dogs after subcutaneous dosing up to 40 mg/kg.
The applicant provided sufficient evidence to link the adverse liver findings in dogs with the inhibition of the Bile Salt Export Pump (BSEP) transporter causing the intracellular concentrations of bile acids to rise above a toxic threshold. It was also shown that lenacapavir is a much more potent inhibitor of the dog (IC_{50} = 0.124 µM) than the human BSEP transporter (IC_{50} =1.15 µM), and the relevant concentration of lenacapavir needed for the inhibition of BSEP is not achieved in humans, but in dogs Therefore, the liver findings in dogs are not considered relevant to humans.
Lenacapavir was not genotoxic *in vitro* or *in vivo* under the tested conditions. In a carcinogenicity study in RasH2 mice with lenacapavir, doses up to 300 mg/kg once every 3 months by subcutaneous injection did not identify any relevant concerns. A two-year study in rats is ongoing.
In a fertility and early embryonic development study in rats (SC up to 100 mg/kg), there were no lenacapavir-related effects on male reproductive performance, sperm parameters, or female reproductive performance. However, it should be noted that exposure at the highest doses was below clinically relevant levels, i.e. there is no safety margin.
The EFD studies in pregnant rats (oral; up to 30 mg/kg/day) and rabbits (IV; once a day; up to 20 mg/kg/day) did not identify any concern for reproductive toxicity. There were no effects on the number of corpora lutea, intrauterine growth, mean litter proportions of post-implantation loss, mean number and percentage of viable foetuses, mean foetal body weights, or foetal sex ratios. There were no foetal external or visceral malformations or variations in rats and rabbits at exposures (AUC) approximately 16 and 108 times the exposure in humans at the recommended human dose of lenacapavir. However, it is of note that the appropriate exposure for the DART study was achieved only in rabbits. In the PPND study, lenacapavir treatment up to 300 mg/kg (SC) did not cause any adverse events in the dams, F1 or F2 generation (safety margin 4). The calculation of safety margins based on the total exposure is considered adequate considering the comparable high plasma protein binding of lenacapavir in human and nonclinical species at clinically relevant concentrations of lenacapavir. Lenacapavir did not demonstrate phototoxic potential. There are no concerns with regard to impurities and excipients. The description of the safety findings from the nonclinical studies and their evaluation in the RMP is accepted. The applicant was requested to provide pending ERA studies as a post-approval requirement.

5.4 Nonclinical conclusions

Overall, the pharmacology and toxicological profile of lenacapavir were adequately characterised in the nonclinical studies. No safety issues for clinical use were identified. From a nonclinical point of view, the application is approvable.

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6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption and Biopharmaceutical Development

Lenacapavir was classified as a BCS IV compound (low solubility, low permeability).

The commercial formulations are 300 mg tablets containing lenacapavir sodium and a 309 mg/mL solution for subcutaneous injection, also containing lenacapavir sodium. Both formulations were administered in the pivotal Phase 2/3 study GS-US-200-4625.

Administration of the 300 mg tablet with a high-fat, high-calorie meal or a light meal caused a delay of the median tmax from 4 h after fasted administration to 5 or 6 h, respectively. Lenacapavir Cmax and AUC were barely affected by fed administration. The largest change of exposures was a 1.45-fold increase of Cmax after administration with a high-fat, high-calorie meal. These data support the administration of lenacapavir independently of meals.

The selection of the final s.c. formulation was based on the time of lenacapavir plasma concentrations being above the target concentration for efficacy: The lower bound of the 90% confidence interval (90% CI) of lenacapavir Ctrough concentrations should be at least 4-fold greater than the in vitro protein-adjusted EC95 (3.87 ng/mL; MT-4 cells), corresponding to IQ4 (15.5 ng/mL).

The median lenacapavir tmax after a single 927 mg s.c. administration of the commercial formulation without oral loading was 77 to 84 days.

The selection of the commercial oral and s.c. formulation was comprehensible from a pharmacokinetic point of view.

The estimated absolute bioavailability of lenacapavir after oral administration was 6.24%. After s.c. administration, it was 103 %.

Dose Proportionality

After administration of single subcutaneous doses in the range of 30 mg to 900 mg, lenacapavir exposures increased proportionally to the administered doses.

After administration of single oral doses of the tablet in the range of 50 mg to 1800 mg, there was a less than dose proportional increase of lenacapavir exposures. The deviation from dose proportionality increased with increasing doses as expected for a BCS IV compound.

Pharmacokinetics after multiple Dosing

Based on simulations, a 1.17-fold accumulation of AUCtau Day 1 to Week 26 was estimated for 2 subcutaneous administrations on Day 1 and at Week 26.

A comparison of the lead-in dosing administered in the Phase 2/3 study GS-US-200-4625 (600 mg lenacapavir p.o. on Days 1 and 2, 300 mg p.o. on Day 3, 927 mg lenacapavir s.c. on Day 15), and the simplified lead-in (927 mg lenacapavir s.c. plus 600 mg lenacapavir p.o. on Day 1, 600 mg lenacapavir p.o. on Day 2) indicated that the simplified lead-in was similar or even slightly better than the Phase 2/3 lead-in regarding the maintenance of lenacapavir plasma concentrations > IQ4.

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This was confirmed by simulations with the final pop PK model. Comparing simulated data of both regimens, the simplified dosing regimen was superior regarding the percentage of subjects with lenacapavir Ctrough > IQ4 across all weight quartiles on Day 15 and comparable/identical to the Phase2/3 regimen in Week 26 and at steady state. However, there are no clinical data available to support the simplified lead-in treatment.

Distribution

The lenacapavir *in vitro* fraction unbound at a lenacapavir concentration of 2 µM was 1.46%.

Lenacapavir appeared to bind mainly to serum albumin *in vitro*. The *ex vivo* fraction unbound was 0.21% and was not significantly affected by severe renal impairment or moderate hepatic impairment. At lenacapavir concentrations of 100 ng/mL and 500 ng/mL, no concentration-dependent protein binding was observed.

The *in vitro* blood/plasma ratio was 0.64. The *in vitro* data were in good agreement with the *ex vivo* measurements after administration of ^{14}C-labelled lenacapavir.

The lenacapavir volume of distribution after intravenous administration ranged from 1793 to 1986 L.

Metabolism - In vitro Data

Lenacapavir was very stable in both hepatic microsomes and in cryopreserved hepatocytes. CYP3A5 and UGT1A1 appeared to be the only enzyme involved in its metabolism.

Metabolism & Elimination - Clinical Data

After intravenous administration of a ^{14}C-labelled dose, unchanged lenacapavir was the predominant species in plasma, accounting for 68.8% of the total radioactivity in plasma. No single metabolite contributed > 10% of total radioactivity exposure through 1176 hours (49 days) post-dose. The total radioactivity exposure from the sum of all identified components in the plasma was approximately 88%.

Faeces samples for metabolite profiling were collected up to 56 days post-dose. In these samples, the majority of the radioactivity was associated with unchanged lenacapavir and accounted for approximately 5% of the dose (43.4% of the AUC0-t calculated from the radioactivity versus time profiles in faeces). All the metabolites in faeces were detected at trace levels (in each case <1% of the dose or < 10% of the AUC.

The excretion of radioactivity in urine was too low to allow the identification of metabolites.

Lenacapavir was metabolised via oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation.

After intravenous administration of a ^{14}C-labelled dose, 0.237% and 76.1% of the administered radioactive dose were excreted in urine and faeces, respectively. The excretion of radioactivity was very slow. Approximately 75% of the radioactive dose was recovered in faeces within 67 days post-dose. Considering the challenges in conducting a mass balance study for a compound like lenacapavir with a long elimination half-life, the total recovery of 76% is acceptable.

After single-dose oral administration, the lenacapavir half-life was about 12 days, independently of the administered dose. After single subcutaneous administration of the commercial formulation, it was about 80 days.

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Special Populations/Intrinsic Factors

The lenacapavir Cmax and AUCinf were 2.6- fold and 1.8-fold higher in subjects with severe renal impairment compared to healthy controls. Lenacapavir exposures were up to 1.41-fold and up to 2.1-fold higher in subjects with mild or moderate renal impairment.

The lenacapavir total Cmax and AUCinf were 2.6- fold and 1.5-fold higher in subjects with moderate hepatic impairment compared to healthy controls.
The unbound lenacapavir Cmax and AUCinf were 5.1- fold and 2.8-fold higher in subjects with moderate hepatic impairment compared to healthy controls.

The impact of additional demographic and other factors on lenacapavir PK were investigated in a pop PK analysis including 5 Phase 1 studies, the Phase 2 study GS-US-200-4334, and the Phase 2/3 study GS-US-200-4625.

The dataset included 384 subjects aged 18 to 78 years with a body weight range between 41.4 and 164 kg. Only 5 (2.4%) subjects (HIV patients) were ≥ 65 years old.

The majority of the subjects (86.7%) had normal renal function. The dataset included 45 (11.7%) subjects with mild renal impairment, 6 (1.6%) subjects with moderate renal impairment and no subjects with severe renal impairment.

The majority of the subjects were male (77.6%). Of the subjects in the dataset, 45.1% were healthy and 54.9% were HIV-positive.

The final lenacapavir pop PK model was a 2-compartment model with first-order absorption after oral administration, parallel direct (first-order) and transit compartment absorption after subcutaneous (SC) administration, and first-order elimination from the central compartment. The model included the following covariate relationships:

- Dose on oral bioavailability (decrease with increasing dose) and CL (increase with increasing dose)
- Co-administration of boosters (COBI/RTV) on oral bioavailability.
- Allometric scaling of volume and clearance terms for body weight with fixed factors
- Age and gender on CL
- Healthy subject status on CL and Vp

The final model described the data sufficiently well to be suitable for simulations.

Using the “typical subject” (70 kg, 34 years, male, unboosted HIV patient) as a reference, the co-administration of boosters had the largest impact on lenacapavir exposures (approximately 59 % ↑), followed by body weight and subject status after oral administration. The effects of age and gender were negligible. The estimated “worst-case scenarios” were a 62.9% decrease and a 2.29-fold increase of AUCtau, a 52.9% decrease and 2.27-fold increase of Cmax, and a 61.6% decrease and a 2.59-fold increase of Day 15 Ctrough.

After s.c. administration, body weight, age and subject status had a comparable impact on lenacapavir exposures. The largest estimated change was a 50.2 % decrease of lenacapavir Cmax in healthy subjects. The estimated “worst-case scenarios” were a 60.1% decrease and a 1.75-fold increase of AUCtau, a 68.1% decrease and 1.68-fold increase of Cmax, and a 55.4% decrease and a 1.88-fold increase of Week 26 Ctrough.

Using a healthy subject (70 kg, 34 years, male, unboosted) as a reference, the lenacapavir AUCtau after oral administration (Day 1 -15 in Study GS-US-200-4625) was 84.1% and 71.1% higher in

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treatment-experienced and treatment-naïve HIV patients, respectively. The lenacapavir Ctrough on Day 15 was 81.5 % and 58.6% higher. The increase of Cmax in treatment-experienced and treatment-naïve HIV patients was less. The estimated “worst-case scenarios” were a 34.6% decrease and a 3.96-fold increase of AUCtau, a 30.9% decrease and 3.29-fold increase of Cmax, and a 35.6% decrease and a 4.28-fold increase of Day 15 Ctrough.

After s.c. administration, the lenacapavir AUCtau (Day 15 to Week 26) was 47.4% and 26.8% higher in treatment-experienced and treatment-naïve HIV patients. The largest estimated change of lenacapavir exposures was a 51.1% of lenacapavir Cmax in treatment-experienced HIV patients. The estimated “worst-case scenarios” were a 33.9% decrease and a 2.46-fold increase of AUCtau, a 33.9% decrease and 2.42-fold increase of Cmax, and a 32.8% decrease and a 2.23-fold increase of Week 26 Ctrough.

The estimated lenacapavir exposures were up to 2.1-fold higher in female HIV patients compared to males. This comparison did not account for differences in body weight between genders.

The effect of age on lenacapavir exposures was negligible in HIV patients. However, only 5 patients ≥ 65 years were available for the comparison.

The effect of ethnicity on lenacapavir exposures was negligible in HIV patients. Differences in lenacapavir exposures between Black and White HIV patients were negligible, while the lenacapavir exposures were about 2-fold higher in Asian HIV patients compared to Black HIV patients in a comparison not accounting for differences in body weight.

The maximum difference in lenacapavir exposures across the weight quartiles in HIV patients was 129.4 % for Cmax between Day 15 and Week 26. The difference for Ctrough on Day 15 and Week 26 was 48.3% and 43.7%, respectively.

The maximum differences in lenacapavir exposures across eGFR quartiles in HIV patients was 45.7% for Cmax between Days 1 and 15.

Compared to healthy subjects, the lenacapavir exposures in heavily treatment-experienced HIV patients was up to 3.26-fold higher after oral administration and up to 1.99-fold higher after s.c. administration.

The lenacapavir exposures in boosted HIV patients compared to HIV patients without boosters were up to 1.52-fold higher after oral lenacapavir administration. After s.c. doses, lenacapavir exposures were up to 1.4-fold higher in boosted patients compared to non-boosted patients.

The data support the dosing recommendations described in the information for health care professionals.

Interactions

EFFECT OF OTHER DRUGS ON LENACAPAVIR

In vitro Data

CYP3A5 and UGT1A1 appeared to be the only enzymes involved in lenacapavir metabolism. Furthermore, lenacapavir was a substrate of P-gp, but not of BCRP, OATP1B1, or OATP1B3.

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Clinical Data

Perpetrator	Geometric mean ratio (GMR) (90% CI)
Cobicistat (COBI, strong CYP and P-gp inhibitor)	lenacapavir Cmax: 209.74 (161.98, 271.60) lenacapavir AUClast: 171.07 (132.27, 221.25) lenacapavir AUCinf: 227.62 (174.98, 296.09)
Darunavir/cobicistat (DRV/COBI, strong CYP3A inhibitor, and an inhibitor and inducer of P-gp)	lenacapavir Cmax: 229.65 (178.75, 295.05) lenacapavir AUClast: 153.88 (118.45, 199.92) lenacapavir AUCinf: 194.16 (149.59, 252.01)
Voriconazole (VORI, strong CYP3A inhibitor)	lenacapavir Cmax; 109.49 (81.30, 147.45) lenacapavir AUClast: 147.51 (108.81, 199.98) lenacapavir AUCinf: 141.19 (109.89, 181.40)
Atazanavir/cobicistat (ATV/COBI, strong CYP3A, P-gp, and UGT1A1 inhibitor)	lenacapavir Cmax; 659.99 (498.87, 873.14) lenacapavir AUClast: 398.59 (294.69, 539.12) lenacapavir AUCinf: 421.44 (319.01, 556.75)
Rifampicin (RIF, strong CYP3A, P-gp, and UGT1A1 inducer)	lenacapavir Cmax; 44.72 (33.56, 59.58) lenacapavir AUClast: 21.43 (15.84, 28.97) lenacapavir AUCinf: 15.50 (12.16, 19.75)
Efavirenz (EFV, moderate CYP3A and P-gp inducer)	lenacapavir Cmax; 64.14 (44.52, 92.41) lenacapavir AUClast: 46.61 (32.68, 66.49) lenacapavir AUCinf: 43.63 (32.12, 59.27)
Famotidine (FAM, H2RA, acid-reducing agent)	lenacapavir Cmax; 100.57 (75.22, 134.45) lenacapavir AUClast: 137.39 (102.53, 184.09) lenacapavir AUCinf: 127.74 (100.17, 162.89)

The clinical interaction data were in agreement with the *in vitro* data. The inhibition of CYP3A4 alone had a small effect on lenacapavir exposures, but the inhibition of multiple pathways involved in the disposition or elimination of lenacapavir resulted in substantial increases of its exposures. As expected, the simultaneous inhibition or induction of P-gp, UGT1A1, and CYP3A4 constituted the “worst-case scenario”.

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EFFECT OF LENACAPAVIR ON OTHER DRUGS

In vitro Data

Due to the limited solubility of lenacapavir, the outcome of the *in vivo* DDI risk assessment based on the *in vitro* data strongly depended on the values of ka and Fa used in the respective calculations.

For the most conservative scenario (ka= 0.1/min and Fa= 1.0), the following DDI risks were identified:

- Direct inhibition of intestinal CYP3A4
- Direct inhibition of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and UGT1A1
- Time-dependent inhibition of CYP3A4
- Induction of CYP3A4
- Inhibition of P-gp and BCRP
- Inhibition of OATP1B1 and OATP1B3

For the "realistic" scenario" (estimated values for ka = 0.0287/min and Fa= 0.0624), the following DDI risks were identified:

- Direct inhibition of CYP3A4
- Time-dependent inhibition of CYP3A4
- Inhibition of OATP1B1 and OATP1B3

No DDI risk was identified regarding the inhibition of OAT1, OAT3, OCT2, MATE1, or MATE2-K.

Clinical Data

Victim	**GMR (90% CI)**
Pitavastatin (OATP substrate)	Simultaneous Administration with LEN: PIT Cmax: 99.88 (83.57, 119.38) PIT AUClast: 114.05 (101.05, 128.72) PIT AUCinf: 111.44 (99.63, 124.65) Staggered Administration (3 days after the last dose of LEN): PIT Cmax : 85.13 (68.72, 105.47) PIT AUClast : 89.64 (76.95, 104.43) PIT AUCinf : 96.40 (87.06, 106.74)
Rosuvastatin (BCRP substrate)	ROS Cmax: 157.48 (138.08, 179.62) ROS AUClast: 126.06 (112.50, 141.25) ROS AUCinf: 130.72 (119.20, 143.35)
Tenofovir alafenamide TAF (P-gp substrate)	TAF Cmax: 124.46 (98.34, 157.53) TAF AUClast: 131.83 (109.22, 159.13)
Tenofovir TFV (P-gp substrate)	TFV Cmax: 123.08 (105.25, 143.93) TFV AUClast: 138.58 (115.14, 166.78) TFV AUCinf: 147.39 (126.95, 171.11)
Midazolam (CYP3A4 substrate)	Simultaneous Administration with LEN: MDZ Cmax: 193.64 (180.63, 207.59) MDZ AUClast: 311.00 (287.17, 336.81) MDZ AUCinf: 358.99 (329.52, 391.10) 1-OH-MDZ Cmax: 54.07 (49.67, 58.86) 1-OH-MDZ AUClast: 68.49 (64.47, 72.75)

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	1-OH-MDZ AUCinf: 75.71 (71.63, 80.02) Staggered (1 day) Administration with LEN: MDZ Cmax: 215.69 (201.84, 230.49) MDZ AUClast: 354.56 (331.85, 378.81) MDZ AUCinf: 407.58 (377.09, 440.54) 1-OH-MDZ Cmax: 52.01 (47.59, 56.83) 1-OH-MDZ AUClast: 75.52 (71.70, 79.54) 1-OH-MDZ AUCinf: 83.65 (79.78, 87.71)

The clinical interaction data covered the *in vitro* signals from the “realistic scenario” plus BCRP. Apart from the inhibition of CYP3A4, the interaction potential of lenacapavir as a perpetrator appeared to be low.

The data support the dosing recommendations described in the information for health care professionals.

Pharmacodynamics

Secondary Pharmacology (Safety)

The potential effect of lenacapavir on QTcF was investigated in a dedicated tQT study after oral administration of 600 mg lenacapavir twice daily (BID) for 8 days. Supratherapeutic lenacapavir exposures were achieved. Compared to the first dose (Day 6 in the tables), the lenacapavir exposures after 7 days of BID dosing (Day 12 in the tables) were about 4-fold higher. Compared to the lenacapavir exposures after therapeutic dosing, the Cmax achieved in the tQT study was up to 8.8-fold higher.

Moxifloxacin showed the expected effect, i.e. the demonstration of assay sensitivity was successful.

On both Day 6 and 12, the upper limit of the 90% CI never exceeded 10 ms after administration of lenacapavir.

The result of the by-time-point analysis was supported by exposure-response analyses. There was no apparent relationship between lenacapavir plasma concentrations and QTcF. The estimated slope in the model with time-matched QTcF baseline values was not statistically significant. The predicted upper limit of the 90% CI did not exceed 10 ms at therapeutic and supratherapeutic lenacapavir exposures.

No QTcF values > 450 ms were observed in the tQT study. After lenacapavir treatment, 1 subject had a QTcF prolongation > 30 ms. No QTcF prolongations > 60 ms were observed after lenacapavir treatment.

In summary, the potential of lenacapavir to cause QT prolongations seems low.

Lenacapavir had no appreciable effect on PRS, QRS, or heart rate.

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6.2 Dose finding and dose recommendation

The lenacapavir dosing regimen applied in the pivotal Phase 2/3 study GS-US-200-4625 and the proposed commercial dosing regimen are different:

- Study GS-US-200-4625: oral lenacapavir 600 mg on days 1 and 2, oral lenacapavir 300 mg on day 8, then sc lenacapavir injection 927 mg on day 15 and every 6 months thereafter

- Proposed “simplified” commercial dosing regimen: oral lenacapavir 600 mg and SC lenacapavir injection 927 mg on Day 1, oral lenacapavir 600 mg on Day 2 followed by SC lenacapavir injection 927 mg every 6 months (26 weeks) thereafter.

The GS-US-200-4625 dosing regimen was based on modelling and simulations targeting an exposure whereby the lower bound of the 90% CI of the Ctrough was at least 4-fold higher than the *in vitro* paEC95 (3.87 ng/mL = IQ1; MT-4 cells), corresponding to an IQ4 (15.5 ng/mL) within a few days of dosing initiation, and through the end of the dosing interval (every 26 weeks).

The selected target concentration (IQ4) was supported with/by results of the dose ranging proof-of-concept study GS-US-200-4072, where a near maximal (94%) antiviral activity (decline in HIV-1 RNA) was observed at lenacapavir concentrations ≥ 15.5 ng/mL, indicating that substantial increases in antiviral activity at higher lenacapavir concentrations are unlikely. Likewise, dosing in a manner that maintains lenacapavir concentrations at or above IQ4 (15.5 ng/mL) in the majority of participants for the duration of treatment should ensure maintenance of maximum virologic effect (Study GS-US-200-4072).

The 14-day oral lead-in period in Study GS-US-200-4625 served to achieve the target concentration rapidly and to obtain tolerability data prior to the administration of the long-acting s.c. formulation.

The proposed “simplified” commercial dosing regimen is expected to produce similar lenacapavir mean concentrations well above IQ4. It was supported by simulations (Pop PK Analysis) and by the observed data in healthy subjects in Study GS-US-200-5709. However, a comparison of the percentage of patients not achieving the target concentration on Day 15 and at Week 26 of both dosing regimen by weight quartiles and for the minimum and maximum weight of the subjects included in the pop PK dataset (41.4 to 164 kg) should be provided. As mentioned above, there was no exposure-response relation for the primary efficacy endpoint, but the response rate of the secondary efficacy endpoint was lower in the lowest lenacapavir exposure quartile compared to the higher quartiles.

The proposed ± 2 weeks dosing window for the administration of the s.c. treatment every 26 weeks was also supported by simulations (Pop PK Analysis).

6.3 Efficacy

Pivotal studies

Efficacy of lenacapavir is supported by a single Phase 2/3 study in HTE PWH (**Study GS-US-200-4625**). Additional data comes from a Phase 2 study of lenacapavir in treatment-naïve PWH (**Study GS-US-200-4334**).

Study **GS-US-200-4625** was a Phase 2/3 study to evaluate the safety and efficacy of lenacapavir in combination with an optimised background regimen (OBR) in heavily treatment-experienced HIV-1 infected non-pregnant adults or adolescents aged ≥ 12 years and weighing ≥ 35 kg, harbouring

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multidrug resistance, who were failing their current regimen (defined as plasma HIV-1 RNA ≥ 400 copies/mL). MDR was defined as a resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes (except for the M184V/I resistance to emtricitabine or lamivudine) and participants had ≤ 2 fully active ARV medications remaining from the 4 main classes that can be effectively combined to form a viable regimen.

The study was performed from November 2019 to September 2021 in 31 study centres (including 19 in the USA and 4 in the EU).

The study design was in line with the FDA recommendations.

Eligible participants were included in **Cohort 1** or **Cohort 2** depending on HIV-1 RNA results at the beginning of the study.

Eligible participants with a < 0.5 $\log_{10}$ HIV-1 RNA decline compared with the screening visit and HIV-1 RNA ≥ 400 copies/mL at the cohort-selection visit were randomised, in a blinded fashion, in a 2:1 ratio to receive either oral lenacapavir or placebo for 14 days (Cohort 1). Participants received lenacapavir (**Cohort 1A**) or placebo (**Cohort 1B**) on Day 1 (2x300 mg), Day 2 (2x300 mg), and Day 8 (1x300 mg) while they continued their failing regimen. This was the Functional Monotherapy Period.

After each participant completed the Functional Monotherapy Period, the participant's treatment assignment was unblinded. Participants who had been randomised to receive **oral** lenacapavir during the Functional Monotherapy Period received **SC** lenacapavir injection (927 mg) and initiated their OBR on Day 1 SC (i.e. 14 days after the first dose of oral LEN) (**Cohort 1A**). Participants who had been randomised to receive placebo during the Functional Monotherapy Period received oral lenacapavir on Days 15, 16, and 22, and initiated their OBR on Day 15, at the end of the Functional Monotherapy Period (**Cohort 1B**). They also received SC lenacapavir injection (927 mg) at Day 1 SC (i.e. 14 days after the first dose of oral LEN) while continuing their OBR. After the Day 1 SC visit, all Cohort 1 participants continued with study visits at Weeks 4, 10, 16, 22, 26, 36, and 52. Participants received their subsequent SC lenacapavir injection at the Week 26 visit. This was the Maintenance Period for Cohort 1.

Participants were enrolled into **Cohort 2** if Cohort 1 was fully enrolled or if they did not meet the criteria for randomisation in Cohort 1 (i.e. they had ≥ 0.5 $\log_{10}$ copies/mL HIV-1 RNA decline compared with the screening visit or HIV-1 RNA < 400 copies/mL at the cohort-selection visit). All Cohort 2 participants received oral lenacapavir at Days 1, 2, and 8. Participants initiated an OBR on Day 1. This was the Oral Lead-in Period. At Day 1 SC (i.e. 14 days after the first dose of oral LEN) participants received SC lenacapavir and continued their OBR. After the Day 1 SC visit, participants continued with study visits at Weeks 4, 10, 16, 22, 26, 36, and 52 (study visits week identified by the number of weeks that had elapsed since the Day 1 SC visit when lenacapavir was first administered by injection). Participants received their subsequent SC lenacapavir injection at the Week 26 visit. This was the Maintenance Period for Cohort 2.

The primary efficacy endpoint 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 Functional Monotherapy Period. The **main secondary endpoint** was the proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment. The endpoints are adequate and in line with FDA guidelines for HIV drug evaluation.

The **Full Analysis Set** (FAS) was the primary analysis set for efficacy analyses. 2 FASs were defined for this study: **(i)** FAS for the Functional Monotherapy Period analysis that included all participants who were randomised in the Functional Monotherapy Period and received at least 1 dose of blinded study drug. This was the primary analysis set for the primary efficacy endpoint; **(ii)** FAS for the All Lenacapavir Analysis that included all participants who were enrolled in the study and received at

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least 1 dose of SC LEN. This was the primary analysis set for the secondary efficacy endpoint and other efficacy endpoints. A secondary analysis of the primary efficacy endpoint based on the Per-Protocol Analysis Set for the Functional Monotherapy Period analysis was also performed to evaluate the robustness of the primary endpoint based on the FAS. Other efficacy endpoints were summarised by visit using descriptive statistics.

In this part of the evaluation report, results from the 52-week clinical study report (CSR) from both study GS-US-200-4025 and study GS-US-200-4334 are described.

Overall, **72 participants were enrolled** in the study, 36 in Cohort 1 (with 24 assigned to receive lenacapavir and 12 assigned to receive placebo during the Functional Monotherapy Period) and 36 in Cohort 2. All 72 participants completed the Functional Monotherapy or Oral Lead-in Period, and all received Day 1 SC LEN. Overall, the number of evaluable participants was low. Although HIV-1 treatment failure and multiresistance is uncommon nowadays, similar recent studies with other first-in-class molecules treating multiresistant HIV-1 enrolled a substantially higher number of patients.

At Week 52, 23/24 subjects in Cohort 1A were evaluable (1 lost to follow-up at Day 292), 12/12 in Cohort 1B and 34/36 in Cohort 2 (1 death at Day 90 which was unrelated to study drug, metastatic cancer) and 1 at the investigator's discretion (Day 110, COVID-19).

In Cohort 1, demographic and baseline characteristics were generally similar between the lenacapavir and placebo groups. The majority of participants were male (72.2%) and the median age was 54 years (range 24 to 71 years). In Cohort 2, the majority of participants were male (77.8%) and the median age was 49 years (range 23 to 78 years).

There was an imbalance in patient characteristics within Cohort 1, with subjects in the placebo group presenting more advanced disease characteristics than subjects in the lenacapavir group. Patients in the placebo group had a higher viral load, 4.93 $\log_{10}$ vs 4.19 $\log_{10}$ in the lenacapavir group, with a difference of 0.74 $\log_{10}$. Furthermore, 50% (6/12) of the placebo patients had a viral load of >100,000 copies/mL, compared to just 4.2% (1/24) in the lenacapavir group. Patients in the placebo group also presented a lower CD4 count of 85 cells/mL, compared to 172 cells/mL in the lenacapavir group. Therefore, a post hoc analysis of the primary efficacy endpoint with adjustment for baseline HIV-1 RNA using rank analysis of covariance was provided with the primary efficacy endpoint results (see below).

Participants enrolled in this study had mostly HIV-1 subtype B (77.8%), followed by HIV-1 subtypes AE (15.3%), AG and C (2.8%), and BF (1.4%). This is consistent with the epidemiology in Western/Central Europe and North America, where the most ubiquitous HIV-1 subtype is B (approx. 85%). At baseline, HIV-1 resistance mutations to the nucleoside reverse transcriptase inhibitor (NRTI) class were found in 98.6% of participants, to the nonnucleoside reverse transcriptase inhibitor (NNRTI) class in 94.4%, to the protease inhibitor (PI) class in 83.1%, and to the integrase strand-transfer inhibitor (INSTI) class in 66.7%. The median number of ARV agents with resistance approached the total number of ARV agents per class (median of 4 out of a total of 4, median of 5 out of a total of 6, median of 5 out of a total of 7, and median of 7 out of a total of 9, for INSTIs, NNRTIs, NRTIs, and PIs, respectively). Almost half (45.8%) of the participants had HIV-1 with 4-class resistance. Phenotypic resistance to the entry inhibitor maraviroc was found in 67.2% of participants. All participants were phenotypically sensitive to lenacapavir at baseline.

The median number of ARVs in the failing regimen for Cohort 1 was 3 (range: 1 to 7) and for Cohort 2 was 4 (range: 2 to 7). The median number of ARVs in the OBR for Cohort 1 and Cohort 2 was 4 (range: 2 to 7). This supports the fact that these patients had few remaining treatment options. Considering overall susceptibility scores (OSSs) in the Cohort 1 lenacapavir, there was a gain of 1 active ARV between failing regimen and OBR compared to gains of 0.8 in the Cohort 1 placebo group

and 0.5 in the Cohort 2. This indicates that the OBR regimen could be slightly better improved in the Cohort 1 lenacapavir group in comparison to the other cohorts.

Results for the **Primary Efficacy endpoint at Day 15** in the Cohort 1 indicate that a significantly greater percentage of participants receiving lenacapavir had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period than those receiving placebo (21/24, 87.5% versus 2/12, 16.7%; P < 0.0001). To address the imbalance in baseline HIV-1 RNA levels and CD4 counts between the lenacapavir and placebo groups in Cohort 1, a post-hoc analysis of the primary efficacy endpoint with adjustment for baseline HIV-1 RNA using rank analysis of covariance was provided and confirmed that the difference between the groups remained statistically significant: 87.5% versus 16.7%; P = 0.0003. This was also the case when post-hoc analyses of the primary efficacy endpoint were conducted in participants with comparable or clinically relevant CD4 cell counts. These showed that the difference between groups remained significant between participants in the lenacapavir group with a low baseline CD4 cell count (median: 98.5 cells/µL; n = 12) and participants in the placebo group (median: 84.5 cells/µL; n = 12) (P = 0.0008). These post-hoc analyses are acceptable from a statistical point of view. Scatterplots of change from baseline in HIV-1 RNA for individual participants in relation to baseline HIV-1 RNA levels and baseline CD4 cell counts were provided by the applicant with the answer to the LoQ. These indicated that there was no difference in LEN treatment efficacy depending on HIV or CD4 baseline levels.

In absolute numbers, the mean change from baseline in HIV-1 RNA for the Functional Monotherapy Period was of -1.93 $\log_{10}$ copies/mL for participants who received lenacapavir and of -0.29 for participants who received placebo.

Results of the **Secondary Efficacy End Point at Week 52** indicate that percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively. The percentages of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 52 were updated with the answer to the LoQ and were 72.2% (26 of 36 participants) and 77.8% (28 of 36 participants), respectively.

Overall, the virological response remained stable between Weeks 26 and 52.

Within **subgroups** (analyses updated with response to the LoQ but limited by the small sample size) there was a trend at Week 52 towards a lower efficacy of lenacapavir in terms of viral load reduction in participants with <200 CD4 cells/µL in comparison to those with >200 CD4 cells/µL (71.7% vs 88.5%) or those with > 100,000 copies/mL vs <=100,000 copies/mL (64.3% vs 81.0%). Low CD4 cell counts and high HIV-1 RNA levels are factors known to limit virologic response, even in treatment-naïve patients.

Regarding CD4 counts, the mean baseline CD4 cell count of participants in Cohorts 1 and 2 was 212 cells/µL. Overall for both cohorts, the mean (SD) changes from baseline were 89 (106.7) cells/µL, 97 (116.7) cells/µL, and 109 (131.7) cells/µL at Weeks 26, 52, and 62, respectively.

Considering categorical distributions of CD4 cell counts, at baseline 63.9% of participants (n=46) were importantly immunocompromised (< 200 cells/µL) and 23.6% (n=17) severely immunocompromised (< 50 cells/µL). At Week 26, 38.8% (n=26) had < 200 cells/µL and no participant had a CD4 count < 50 cells/µL. At Week 52, 34.1% (n=14) had < 200 cells/µL and 2.4% (n=1) of participants had < 50 cells/µL. This shows that the number of significantly immunocompromised patients decreased over time with lenacapavir treatment.

Importantly, analyses by various subgroups of OBR (including presence of INSTI, number of changes induced by the OBR) indicate that lenacapavir efficacy was not significantly influenced by the changes in ART between the failing regimen and the OBR. At both Week 26 and Week 52, a direct correlation between the OSS for the OBR and treatment response was not observed, as the mean OSSs for the

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OBR for participants with treatment success and treatment failure were very similar, and a wide range of OSSs were observed for both participants with treatment success and participants with treatment failure. This supports the intrinsic lenacapavir efficacy independently from the rest of the antiretroviral regimen.

In study GS-US-200-4625, significantly more participants in Cohort 1 lenacapavir (37.5%, 9/24) were on a failing regimen that contained either fostemsavir (FTR) and/or ibalizumab (IMAB) in comparison to placebo (16.7%, 2/12). To assess a potential confounding effect of FTR or IMAB treatment on lenacapavir efficacy, the applicant was requested in the LoQ to provide information on the starting date of FTR and/or IMAB treatment and to compare viral load evolution up to Day 15. Most participants receiving FTR and/or IMAB as part of their failing regimen had started them > 1 year before enrolling in the study. A comparison of the virologic response in participants receiving lenacapavir with FTR and/or IMAB with that in participants receiving lenacapavir without FTR or IMAB indicated that the decline in HIV-1 load was driven by lenacapavir without a confounding effect of FTR and/or IMAB.

Emergence of capsid genotypic and phenotypic resistance to lenacapavir was evaluated at Week 26 and Week 52. Out of the 72 participants enrolled in the study, 42 had data through Week 26. 14 met the criteria for virologic failure. 6 participants (8.3%) in the resistance analysis population (RAP) did not have emergence of lenacapavir-associated capsid (CA) resistance mutations. 8 (11.1%) of 14 (19.4%) participants in the final RAP had emerging lenacapavir-associated mutations in CA. The M66I CA mutation was observed in 6 participants (8.3%) and exhibited a median fold change in lenacapavir susceptibility of 234-fold above wild-type (WT). 1 participant had the emergence of a K70H CA mutation associated with a 265-fold decrease in lenacapavir susceptibility compared to WT. 1 participant had a Q67H + K70R CA resistance pattern that was associated with a 14.8-fold decrease in lenacapavir susceptibility.

The virologic profiles for these 8 participants with emergent CA resistance suggest that lenacapavir may have been the sole ARV in these participants at the time of virologic failure. Indeed, 3 participants were receiving a regimen with no fully active ARVs based on the baseline OSS in addition to lenacapavir. Furthermore, 3 participants had a rebound back to baseline level after development of lenacapavir resistance although they were receiving active drugs in their regimen (OSS = 1 to 3) and 2 participants had HIV-1 RNA resuppression after they experienced a viral load rebound at the time of lenacapavir resistance emergence, suggestive of potential treatment adherence issues at the time of rebound.

Out of 72 participants enrolled in the study, 43 had data through Week 52. 13 met the criteria for virologic failure. Of the 12 participants with available data in the final RAP, 4 participants in the RAP did not have emergence of lenacapavir-associated CA resistance mutations. Eight patients had developed lenacapavir-associated resistance mutations in CA. These were the same as those described at Week 26 (see above). It must be noted that 1 of the 2 patients that had resuppression after experiencing a viral load rebound experienced a new viral rebound at Week 52 with 2 additional lenacapavir-associated resistance mutations (N74D and A105T) in addition to M66I.

Overall, lenacapavir resistance emergence results are relatively reassuring, but the barrier to resistance of lenacapavir is lower than for some other ARVs, in particular INSTIs. This highlights the risk that patients with treatment adhesion problems could end up on a lenacapavir monotherapy (because of its long half-life after subcutaneous administration) and thus develop resistance. A statement to explicitly mention this issue has been inserted in the information for healthcare professionals.

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Key supportive studies

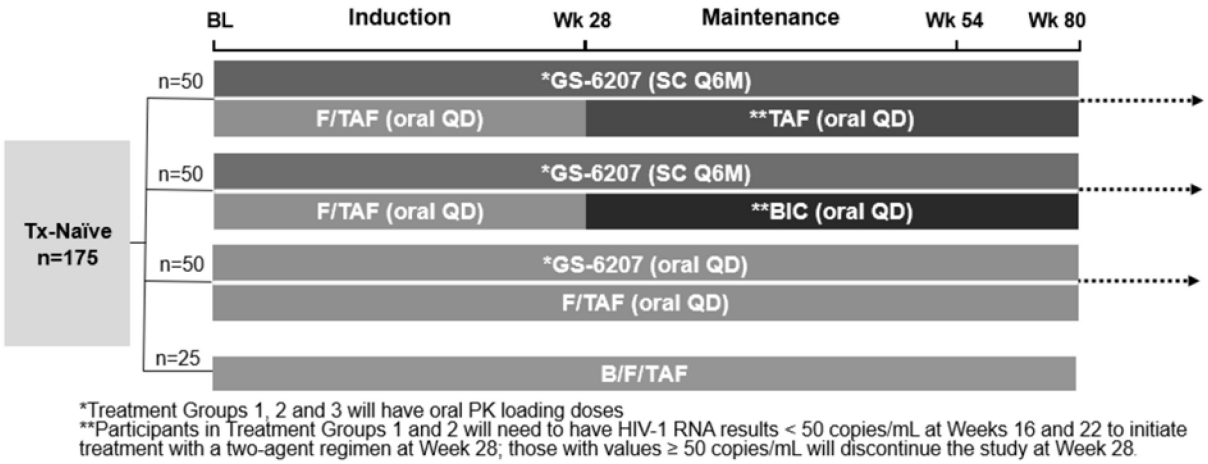
Additional data come from a Phase 2 study of lenacapavir. Study **GS-US-200-4334** was a Phase 2 randomised, open-label, active-controlled, multicentre non-inferiority study to evaluate the safety and efficacy of lenacapavir in combination with other antiretroviral agents in non-pregnant adult PWH aged ≥ 18 years that were treatment-naïve. Of note, the inclusion criteria required patients to present CD4 cell counts ≥ 200 cells/μL at screening.

This study was conducted in the USA (40 sites) and the Dominican Republic (1 site).

The **primary endpoint** of the study was the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54. The **main secondary endpoints** were the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 and the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell count at Weeks 28, 38, 54, and 80.

Treatment-naïve PWH were randomised in a 2:2:2:1 ratio to 1 of the 4 treatment groups. Randomisation was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening (Figure 1).

Figure 1: GS-US-200-4334 Study Schema



*Treatment Groups 1, 2 and 3 will have oral PK loading doses
**Participants in Treatment Groups 1 and 2 will need to have HIV-1 RNA results < 50 copies/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28; those with values ≥ 50 copies/mL will discontinue the study at Week 28.

BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®, BVY); BL = baseline; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®, DVY); GS-6207 = lenacapavir, LEN; PK = pharmacokinetic(s); QD = once daily; Q6M = every 6 months; SC = subcutaneous; TAF = tenofovir alafenamide; Tx-naïve = treatment naive; Wk = week

The dosing of lenacapavir was similar to that for the pivotal study for 2 arms (i.e. oral loading dose followed by subcutaneous administration every 6 months). One arm was oral lenacapavir throughout the study duration.

Lenacapavir was co-administered, depending on the treatment groups and time on the study, with either emtricitabine + tenofovir alafenamide, tenofovir alafenamide alone, or bictegravir alone. The control arm was bictegravir + emtricitabine + tenofovir alafenamide.

A compilation of the results from the interim CSR and the Week 54 CSR is presented here.

Of 249 participants screened, 183 were randomised, and 182 received at least 1 dose of study drug. Of these 182 participants, 22 participants (12.1%) prematurely discontinued the study drug during the Main Phase (i.e. data collected on or before Week 80): 17 of 105 participants (16.2%) in the

subcutaneous lenacapavir total group, 4 of 52 participants (7.7%) in the oral lenacapavir group, and 1 of 25 participants (4.0%) in the bictegravir + emtricitabine + tenofovir alafenamide (Biktarvy) group. The review of the reasons for study drug discontinuation in the lenacapavir groups does not raise specific concerns (the reason in most cases was subject decision or lost to follow-up).

Baseline and disease characteristics were similar across the treatment groups. Most participants were male (93.4%) and the median age was 29 years (range: 19 to 72 years). Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.37 (3.86, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) baseline CD4 cell count was 437 (332, 599) cells/µL. Among the 182 participants, most had HIV-1 RNA ≤ 100,000 copies/mL (85.2%, 155 participants) and a CD4 cell count range of ≥ 350 to < 500 cells/µL (31.9%, 58 participants) or ≥ 500 cells/µL (37.4%, 68 participants). The genotype distribution of HIV-1 was comparable between treatment groups, with subtype B predominant in all groups (92.9% overall), which is reflective of the treatment-naïve population based primarily in the United States.

In the FAS at Week 54, 100% (105/105) of the patients in the lenacapavir groups and 96.2% (25/26) in the Biktarvy group were evaluable. **Results for the primary efficacy endpoint**, i.e. the proportion of participants in the FAS with HIV-1 RNA <50 copies/mL, were as follows in the different groups:

SC lenacapavir + (DVY → TAF):	90.4% (47 of 52 participants)
SC lenacapavir + (DVY → BIC):	84.9% (45 of 53 participants)
Oral lenacapavir + DVY:	84.6% (44 of 52 participants)
lenacapavir total:	86.6% (136 of 157 participants)
BVY:	92.0% (23 of 25 participants)

Overall, the percentages of participants in the FAS with HIV-1 RNA < 50 copies/mL at Week 54 were similar in each treatment group, but there was a non-significant numerically lower response in the lenacapavir-containing groups in comparison to the Biktarvy group.

For the main secondary efficacy endpoints, the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28 and 38 were also similar in each treatment group, with no significant difference between each of the lenacapavir-containing groups and the Biktarvy group (but a non-significant numerically lower response in the lenacapavir-containing groups). 5 participants who had the virologic outcome of HIV-1 RNA <50 copies/mL at Week 28 had that of HIV-1 RNA ≥ 50 copies/mL at Week 54. Data at Week 80 are not yet available.

The changes from baseline in HIV-1 RNA at Weeks 28, 38, and 54 were similar across the treatment groups, at approx. - 3 $\log_{10}$ copies/mL. This diminution was essentially attained at Week 4 and was stable thereafter.

The mean (SD) changes from baseline in CD4 cell counts at Week 28 were similar across treatment groups with no significant differences between each of the LEN-containing groups and the BVY group:

SC lenacapavir + (DVY → TAF):	172 (178.2) cells/µL
SC lenacapavir + (DVY → BIC):	158 (164.1) cells/µL
Oral lenacapavir + DVY:	206 (154.6) cells/µL
BVY:	163 (157.7) cells/µL

These changes were maintained at Weeks 38 and 54. Increases in CD4 absolute numbers were more important in the GS-/US-200-4334 study than in the GS-US-200-4625 pivotal study, which is expected as patients were treated earlier in their disease course and were not profoundly immunocompromised.

All sensitivity analyses using imputation methods (Missing = Failure and Missing = Excluded) showed similar results.

Within subgroups, the efficacy of lenacapavir (pooled groups) to reduce HIV-1 viral load < 50 copies/mL at Week 54 was lower than for Biktarvy in patients with an initial viral load > 100,000 copies/mL (16/23, 69.6% vs 4/4, 100%) but the small size of the groups precludes any further analysis.

Regarding lenacapavir resistance in study GS-US-200-4334, all participants were sensitive to lenacapavir based on genotypic and phenotypic assessments.

Out of a total of 157 participants receiving lenacapavir, through Week 28 1 participant in the SC lenacapavir + (DVY → BIC) treatment group (1 of 53, 1.9%) developed resistance. He developed genotypic and phenotypic resistance to both lenacapavir (Q67H + K70R) and emtricitabine (FTC) (M184M/I). Through Week 54, 2 participants developed resistance: one participant in the SC lenacapavir + (DVY → BIC) who was already described at Week 28 and 1 new participant in the oral lenacapavir + DVY group who developed genotypic and phenotypic resistance to lenacapavir (Q67H).

Hence, the emergence of resistance mutations in treatment-naïve participants through Week 54 in Study GS-US-200-4334 occurred in 2 of 157 (1.3%) participants who received oral or SC lenacapavir. As previously mentioned, the barrier to resistance of lenacapavir seems to be lower than for INSTIs.

Nonclinical virology reports

Lenacapavir displayed similar antiviral activity against various HIV-1 subtypes, i.e. Group M (subtypes A, A1, B, BF, C, D, E, F, G, H), Group N, Group O, CRF01_AE, and CRF02_AG. The median EC_{50} value was 0.04 nM, ranging between 0.02 and 0.16 nM. It must be noted that values can vary depending on the assay used. Lenacapavir also showed antiviral activity against 2 HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1 (mean EC_{50} value of 0.80 nM).

Capsid sequence conservation studies indicated that there was a high degree of sequence conservation within the lenacapavir binding site in the HIV-1 capsid, especially at amino acid positions associated with lenacapavir resistance *in vitro*. Resistance mutations were observed in approx. 1% of the CRF01_AE subtype (Q67H variant that confers ~ 6-fold resistance) in a database of approx. 10,000 sequences and in 1 out of 104 treatment-naïve patients for whom deep sequencing was performed (T107N substitution conferring 4-fold resistance).

Antiviral activity of lenacapavir against a panel of HIV-1 patient isolates showed that lenacapavir displayed WT-like activity regardless of the level of patient exposure to antiretroviral therapy (that is, in treatment-naïve or treatment-experienced patients). The antiviral activity of lenacapavir was not affected by the presence of naturally occurring gag polymorphisms, unlike maturation inhibitors or PIs. This was also the case for the antiviral activity of lenacapavir against a panel of site-directed mutant viruses harbouring HIV Gag Cleavage site mutations.

The antiviral potency of lenacapavir was not affected by resistance to the 4 main ARV classes (NRTIs, NNRTIs, INSTIs, PIs) in a panel of patient HIV-1 isolates (n=40), indicating a lack of cross-resistance.

Dose escalation resistance selections indicate that the *in vitro* rates of viral resistance emergence to lenacapavir was essentially similar (albeit slower) than for efavirenz (EFV) and elvitegravir (EVG). At low lenacapavir concentrations, it selected for virus encoding the capsid N74D variant, whereas at higher drug concentrations it selected for the capsid Q67H+N74D double mutant.

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Resistance experiments performed at clinically relevant fixed drug concentrations in various cell-based assays showed that, within its projected human plasma exposure range (i.e. IQ = 4 to 8), lenacapavir breakthrough viruses encoded the capsid mutants N74D, L56I, or Q67H ± a secondary capsid mutation (N74S or T107N). Lenacapavir breakthrough frequency was superior to dolutegravir (DTG) and emtricitabine (FTC) and comparable to rilpivirine (RPV). There was no emergence of virus at higher drug concentrations (IQs of 8, 16, 24, 40). Hence, the clinical target plasma exposure for lenacapavir (C_{min} corresponding to an IQ of 5 or higher) is likely to provide a barrier to drug resistance emergence similar to that of some frequently used antiretrovirals. However, some antiretrovirals (such as the INSTI dolutegravir in the experiment presented) clearly have a higher resistance barrier.

In vitro antiviral susceptibility assays with site-directed HIV-1 capsid mutants showed that some mutations (T107N and Q67H) conferred low level resistance (approx. 5-fold), while K70N, N74D, the double mutant Q67H+N74S, A105E, and Q67Y conferred moderate GS-6207 resistance (approx. 30-fold), L56I and M66I, as well as 4 additional double mutant viruses (M66I+Q67H, Q67H+N74D, Q67H+T107N, N74D+T107N), all conferred high level GS-6207 resistance (62- to >3,226-fold). Interestingly, except for Q67H, other capsid mutants tested displayed severely diminished replication capacity.

The susceptibility of lenacapavir was also determined (using different assays) in site-directed mutants harbouring lenacapavir *in vitro*-selected resistance mutations, and relative susceptibility to lenacapavir ranged from approx. a 3.8- (for T107N) to >2757-fold (for Q76H+N74D) change in comparison to the wild-type virus. In general, reduced susceptibility was higher in double mutants than in single mutants. Interestingly, the majority of lenacapavir resistance associated mutations markedly compromised viral fitness *in vitro*. No cross-resistance with PIs or maturation inhibitors (MIs) was noted in these lenacapavir-resistant mutants.

Lenacapavir activity tested on a panel of 36 individual site-directed HIV-1 capsid mutants showed that two capsid polymorphic variants, Q50E and N57H, conferred low-level (3-fold) and high-level (>5,000-fold) resistance, respectively, relative to WT. These variants have been detected in HIV-1 at a low (1%) prevalence exclusively in either subtype C (Q50E) or subtype D (N57H) isolates.

6.4 Safety

Overall safety database

The primary study supporting the safety and efficacy of lenacapavir is the Phase 2/3 study in HTE PWH (Study GS-US-200-4625), which is further supported by a Phase 2 study of lenacapavir in treatment-naïve PWH (Study GS-US-200-4334). The duration of follow-up in these studies was essentially 1 year. Supportive safety data are also provided from 2 Phase 1 studies in healthy participants (Studies GS-US-200-4538 and GS-US-200-5709).

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

In the response to the LoQ, the applicant acknowledged that the small clinical safety database limits the ability to detect less common safety signals and increases reliance on post-marketing pharmacovigilance. The applicant will also gather additional safety information from studies with larger populations. These should include at least 464 participants who will receive oral lenacapavir as part of a coformulated bictegravir/lenacapavir tablet (ongoing Phase 2/3 Study GS-US-621-6289), and at least 125 participants who will receive subcutaneous lenacapavir in combination with broadly neutralising antibodies (Phase 2 Study GS-US-536-5939). It is additionally

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planned that more than 5,000 participants will receive subcutaneous lenacapavir as pre-exposure prophylaxis (Phase 2 Study GS-US-528-6020 and ongoing Phase 3 Studies GS-US-412-5624 and GS-US-528-9023). These data will be provided by the applicant to Swissmedic as soon as they are available (clinical charge).

Adverse events

In study GS-US-200-4625, the percentages of participants who experienced AEs during the Functional Monotherapy Period for Cohort 1 were 37.5% (9/24 participants) in the lenacapavir group and 25.0% (3/12 participants) in the placebo group. Of these, AEs related to study drug were 16.7% (4/24) and 8.3% (1/12) in the lenacapavir and placebo groups, respectively, and none were Grade 3 or higher. There were no SAEs, deaths, or AEs leading to discontinuation of study drug. Nausea was the only AE reported in more than 1 participant (lenacapavir 12.5%, 3/24 participants vs placebo 8.3% 1/12).

At Week 52, the percentage of participants who received lenacapavir in Cohorts 1 and 2 and experienced an AE was 93.1% (67/72). AEs related to study drug occurred in 66.7% of participants (48/72). The most commonly reported AEs were all related to the subcutaneous administration route, with injection site pain (37.5%, 27/72), injection site swelling (33.3%, 24/72 participants), injection site erythema (27.8%, 20/72), injection site nodule (25.0%, 18/72), injection site induration (15.3%, 11/72). The median (Q1, Q3) total duration of any study drug-related injection site reactions was 8 (3, 67) days, but for some the duration was much longer: injection site nodule 180 (111, 330) days, injection site induration 118 (15, 182) days. Of note, the duration of injection site reactions was even longer following the Day 1 injection (e.g. injection site nodule 235 (72, 422) days, injection site induration 99 (22, 224) days) than after the second injection. Hence, the duration of some injection site reactions can be particularly long, and this has been explicitly described in the updated information for healthcare professionals since it might lead to potential compliance issues. The next AEs in order of frequency were diarrhoea (12.5%, 9/72) and nausea (12.5%, 9/72). 22.2% of AEs (16/72) were Grade 3 or higher, of which 5.6% (4/72) were deemed to be related to the study drug. These were essentially injection site reactions and cases of rash, abdominal abscess, and immune reconstitution inflammatory syndrome. 8 participants (11.1%) experienced SAEs, none related to the study drug (including COVID-19, septic shock, renal impairment, shock, pneumonia, anal squamous cell carcinoma, impaired healing, anal cancer, and angina pectoris). There were 2 cases of premature study discontinuation (including 1 death) and 1 case of study drug discontinuation due to grade 1 AE of injection site nodule during the Extension Phase (i.e. after receiving the Week 52 injection). One participant in Cohort 2 died on Study Day 90 from a metastatic lymphoma that was unrelated to the study drug.

Regarding hypersensitivity reactions, 4 patients (5.6%) presented rashes considered to be related to study drug, including one of Grade 3 that was probably related to the change in the OBR rather than the lenacapavir. None of the reported rashes led to discontinuation of study drug or the study.

Laboratory abnormalities were identified in the majority of participants during both the Functional Monotherapy Period and the Maintenance Period of study GS-US-200-4625. These were essentially of Grade 1 or 2. During the Functional Monotherapy Period 3 participants (12.5%) in the verum group (none in the placebo) presented Grade 3 laboratory abnormalities (increased creatinine, non-fasting hyperglycaemia, and increased lipase) that were considered to be not clinically relevant. During the Maintenance Period the majority of the participants had at least 1 graded laboratory abnormality, the majority of which were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 16/72 participants (22.2%), and Grade 4 laboratory abnormalities were reported for 5 participants (6.9%): 2 high AST levels, 3 high creatinine or low eGFR levels. Most laboratory abnormalities were described as either transient or improved or returned to normal. A detailed summary of creatinine values and eGFR results up to Week 52 (study GS-US-200-4625) and Week 54 (study GS-US-200-4334) was

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provided by the applicant with the response to LoQ, showing that lenacapavir did not have a negative influence on renal function.

In study GS-US-200-4334, at Week 54 similar percentages of participants in the lenacapavir total (87.9%, 138/157 participants) and Biktarvy (84.0%, 21/25 participants) groups had an AE. The majority of the AEs reported were Grade 1 or 2 in severity. The percentages of participants with Grade 3 or higher AEs were also similar between the lenacapavir total (8.3%, 13 participants) and Biktarvy groups (8.0%, 2 participants). Adverse events related to the study drug occurred at a higher frequency in the subcutaneous lenacapavir group (58.1%, 61/105) than in the oral lenacapavir + DVY (15.4%, 8/52) or Biktarvy (16.0%, 4/25) groups, mainly because of injection site reactions.1 participant (1.0%, 1 of 105) in the subcutaneous lenacapavir total group presented a Grade 3 injection site nodule. No other AEs related to study drug were Grade 3 or higher. Serious AEs were reported for 6.4% (10 of 157 participants) in the lenacapavir total group and none of the participants in the BVY group. None were considered to be related to the study drugs.

The most commonly reported AEs for the lenacapavir total (157 participants), excluding injection site reactions (ISRs), were headache and nausea (each 13.4%, 21 participants). For the subcutaneous lenacapavir total (105 participants), the injection site reactions were: injection site erythema (31.4%, 33 participants), injection site swelling (27.6%, 29 participants), and injection site pain (23.8%, 25 participants). Overall, 57 of 103 participants (55.3%) who received a subcutaneous injection had a study drug-related ISR; all were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule. As for study GS-US-200-4625, the duration of injection site reactions could be very long. Adverse events that led to a premature discontinuation of the study drug occurred in 3 participants (2.9%) in the subcutaneous lenacapavir group and no participants in the other treatment groups. These were all related to Grade 1 injection site reactions (injection site induration, injection site erythema, injection site swelling). In the Oral LEN + DVY group (52 participants), the most commonly reported AEs were headache (13.5%, 7/52), nausea, and lymphadenopathy (each 11.5%, 6 participants).

The majority of the participants had at least 1 graded laboratory abnormality that was Grade 1 or Grade 2. Grade 3 laboratory abnormalities were reported for 16.6% of participants (26 of 157) in the lenacapavir total group and 24.0% of participants (6 of 25) in the BVY group. Grade 4 laboratory abnormalities were reported for 8.3% of participants (13 of 157) in the LEN total group only. These were 4 cases of ALT or AST elevations, 2 cases of hyperbilirubinaemia, 6 cases of elevated CK, 2 cases of high creatinine or low eGFR, 1 case of elevated triglycerides, 1 case of elevated lipase, 1 case of non-fasting hyperglycaemia. Overall, these were transient, and participants presented various causes leading to these abnormalities independently of lenacapavir exposure.

Of 4 events of hypersensitivity reactions, none were related to the study drug. No deaths were reported by Week 54.

6.5 Final clinical benefit risk assessment

A subset of people with HIV experience virologic and immunologic failure over the long term because of significant drug resistance, leading to ongoing viraemia, decreasing CD4 cell counts and therefore a risk of AIDS-defining opportunistic infections, comorbidities (AIDS and non-AIDS related), and death. These patients might have limited or no treatment options to achieve durable HIV viral suppression. Lenacapavir is a novel first-in-class molecule that inhibits HIV-1 at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production and proper capsid core formation.

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Beneficial effects and associated uncertainties

Clinical Pharmacology
The simplified lenacapavir dosing regimen of 927 mg s.c. plus 600 mg p.o. on Day 1, 600 mg p.o. on Day 2 followed by 927 mg s.c. every 6 months is expected to achieve the target concentrations rapidly and to maintain them over the entire 6-month dosing interval. Updated simulations indicated superiority over the now adopted Phase 2/3 lead-in treatment over the first 15 treatment days from a pharmacokinetic point of view (percentage of subjects with lenacapavir Ctrough > IQ4). However, no clinical efficacy and safety data are available to support the simplified lead-in treatment.

The lenacapavir tablets can be administered independently of meals. The absolute bioavailability of lenacapavir after s.c. administration is high.

From a pharmacokinetic point of view, no dose adjustments are required for patients with mild or moderate hepatic impairment, or mild, moderate, or severe renal impairment. No data are available on subjects with severe hepatic impairment or end-stage renal disease (ESRD). Nor are dose adjustments required for other demographic factors like age, gender, etc. However, the total number of subjects ≥ 65 years in the pop PK dataset was small (n=5).

The interaction potential of lenacapavir as a perpetrator is limited. The respective dosing recommendations proposed by the Applicant are reasonable from a pharmacokinetic point of view. The potential for QTcF prolongations at supratherapeutic exposures was low for lenacapavir.

Clinical
Efficacy of lenacapavir is primarily supported by a single phase 2/3 study in HTE PWH (Study GS-US-200-4625), which showed that, during the Functional Monotherapy Period (i.e. Days 1, 2, and 8 of the oral lead-in treatment), a significantly greater percentage of participants receiving lenacapavir had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline than those receiving placebo (21/24, 87.5% vs. 2/12, 16.7%). The mean changes from baseline HIV-1 viral load were of -1.93 $\log_{10}$ copies/mL for participants who received lenacapavir and of -0.29 $\log_{10}$ copies/mL for participants who received placebo. At Week 52, during the maintenance period in which lenacapavir was administered subcutaneously in addition to an OBR, the percentage of participants with HIV-1 RNA < 50 copies/mL was 83.3% in Cohort 1 (30 of 36 participants) and 72.2% in Cohort 2 (26 of 36 participants). The mean baseline CD4 cell count in participants in Cohorts 1 and 2 was 212 cells/µL. Overall for both cohorts, the mean (SD) changes from baseline CD4 count were 89 (106.7) cells/µL, 97 (116.7) cells/µL, 109 (131.7) cells/µL at Weeks 26, 52, and 62, respectively.

As for all similar studies, in study GS-US-200-4625 the exact contribution of the newly investigated drug cannot be fully separated from the effect of the optimisation of the background antiretroviral regimen, which could be significantly improved in some cases. Furthermore, there were imbalances in baseline characteristics between the lenacapavir and placebo arms of the Cohort 1 functional monotherapy period, with participants in the lenacapavir arm presenting a more favourable profile (i.e. lower viral load, higher CD4 counts, higher OSSs for the failing background regimen). However, subgroup and sensitivity analyses indicated that lenacapavir efficacy was not significantly influenced by the changes in ART between the failing regimen and the OBR, and at both Week 26 and Week 52, a direct correlation between the OSS for the OBR and treatment response was not observed. There was a trend towards a lower efficacy of lenacapavir in participants with <200 CD4 cells/µL in comparison to those with >200 CD4 cells/µL (71.7% vs 88.5%) or those with > 100,000 copies/mL vs <=100,000 copies/mL (64.3% vs 81.0%).

A Phase 2 study in treatment-naïve PWH (Study GS-US-200-4334) supports the results of the pivotal study. Lenacapavir (either oral or subcutaneous) was included in different ARV treatment schemes and compared to a regular triple therapy of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy). This indicated that the proportion of participants with HIV-1 RNA <50 copies/mL at Week 54 in the

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various lenacapavir groups was 86.6% (136/157), which is numerically lower than the 92% (23/25) in the Biktarvy group. Furthermore, data indicate that the efficacy of lenacapavir in patients with an initial viral load > 100,000 copies/mL is lower than for comparative well-established regimens. Change from baseline in HIV-1 viral load was similar across treatment groups, of approx. - 3 $\log_{10}$ copies/mL. In parallel with the control of viraemia, CD4 counts significantly increased from baseline (mean increase of approx. 160 cells/µL).

Unfavourable effects and associated uncertainties

Clinical Pharmacology
The interaction potential of lenacapavir as a victim requires dosing recommendations regarding the co-administration of CYP3A4, P-gp and UGT1A1 inhibitors and inducers, which were implemented by the Applicant and are reasonable from a pharmacokinetic point of view, apart from the co-administration of strong simultaneous inhibitors of CYP3A4, P-gp, and UGT1A1, which should be contraindicated due to the currently limited safety data.

The descriptive exposure-response analysis of the secondary efficacy endpoint (proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 (lenacapavir plus background therapy)) included in the primary submission indicated a lower response rate in the lower lenacapavir exposure quartile compared to the higher quartiles. As the simulated lenacapavir Ctrough at Week 26 was lower and its variability was higher for the proposed “simplified” regimen compared to the Phase 2/3 regimen, an effect on efficacy cannot be excluded, especially for patients with higher body weight.

The point regarding the lower and more variable Ctrough at Week 26 for the simplified regimen was clarified with the responses to the LoQ. However, a weight dependency of efficacy (percentage of patients with lenacapavir Ctrough > IQ4) was observed for both the Phase 2/3 and the simplified regimen. On Day 15, the simplified regimen was superior, whereas at later time points both regimens were comparable. At steady state, the percentage of subjects with lenacapavir troughs > IQ4 decreased from 81.7% in the first weight quartile to 65.1% in the fourth weight quartile.

Overall, lenacapavir was a well-tolerated treatment, even though the low number of participants exposed to the drug does not allow for the evaluation of infrequent adverse events. The subcutaneous administration route was associated with a significant number of injection site reactions which, in some instances, persisted for months and, in some cases, lead to study discontinuation. This might preclude patient adhesion to subcutaneous treatment.
Resistance mutations of HIV-1 to lenacapavir could be generated *in vitro* and were shown to be essentially absent at baseline in patients. In the pivotal study in HTE patients, a significant number of participants (11.1%, 8/72) developed resistance at Week 52. Resistance development in these patients was probably due to the fact that lenacapavir was, at certain times, the only active molecule against the HIV-1 infection (e.g. because of overall treatment adhesion issues). This highlights the fact that lenacapavir does not present a genetic resistance barrier as high as some other antiretrovirals. In consequence, patient adhesion to the overall ARV treatment is of paramount importance. In the supportive study, the emergence of resistance mutations occurred in 1.3% (2/157) of treatment-naïve participants through Week 54.

Benefit-Risk Assessment

Clinical Pharmacology
The characterisation of the lenacapavir clinical pharmacology profile was sufficient and revealed no major issues. The lenacapavir interaction potential was appropriately addressed in the information for healthcare professionals.

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Clinical
Efficacy data is based on a very limited dataset, and uncertainties remain concerning long-term outcomes, especially in the light of potential resistance development, for which the applicant has a comprehensive monitoring programme. Nevertheless, the submitted data indicate that lenacapavir efficiently lowers viral load in heavily treatment-experienced patients with multiresistant HIV-1 infection, for which treatment options might be extremely limited. In this population, the benefit/risk of lenacapavir is considered to be positive.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Sunlenca was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

SUNLENCA®

Composition

Active substances

Lenacapavir as lenacapavir sodium

Excipients

Solution for injection
Macrogol 300 (E1521), water for injection.

One 1.5 ml single-dose vial of Sunlenca contains 10.99 mg sodium.

Film-coated tablet
Tablet core: mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium, copovidone, magnesium stearate, poloxamer 407.
Film-coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172), iron oxide red (E172).

One film-coated tablet Sunlenca contains maximal 17.93 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection containing lenacapavir sodium equivalent to 463.5 mg of lenacapavir per 1.5 ml single-dose vial (309 mg/ml) for subcutaneous injection (s.c.).
Sterile, clear, yellow to brown solution with no visible particles.

Film-coated tablet containing lenacapavir sodium equivalent to 300 mg of lenacapavir.
Beige, capsule-shaped, film-coated tablets, of dimensions 10 mm x 21 mm, debossed with “GSI” on one side of the tablet and “62L” on the other side of the tablet.

Indications/Uses

Sunlenca, in combination with optimised background antiretroviral therapy, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations (see section “Properties/Effects”).

Dosage/Administration

Therapy should be initiated by a healthcare professional experienced in the management of HIV infection.
Prior to starting lenacapavir, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients 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 associated with missed doses. In addition, the healthcare professional should counsel patients about the importance of adherence to an optimised background regimen (OBR) to further reduce the risk of viral rebound and potential development of resistance.
Initiation of treatment with lenacapavir requires Sunlenca injection to be given with Sunlenca film-coated tablets.
Each injection should be administered by a healthcare professional.

Usual dosage

Initiation of treatment

On treatment Day 1 and Day 2, the recommended dose of Sunlenca 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 therapy

The recommended dose is 927 mg of Sunlenca administered by subcutaneous injection once every 6 months (26 weeks) from the date of the last injection (+/- 2 weeks).

Table 1: Recommended treatment regimen for Lenacapavir-Gilead: initiation and maintenance dosing schedule

Treatment time	
	Dosage of Sunlenca: Initiation
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablet)
Day 15	927 mg subcutaneous injection (2 x 1.5 mL vials[a])
	Dosage of Sunlenca: Maintenance
Every 6 Months	927 mg subcutaneous injection (2 x 1.5 mL vials[a])

(26 weeks)[b] +/- 2 weeks	

a Two injections, each at a separate site.
b From the date of the last injection.

Missed dose

Missed dose (of film-coated tablet during initiation of treatment)

If the Day 2 oral dose (600 mg) is missed by:

- less than 6 days, the patient should take the oral dose as soon as possible, and 300 mg on Day 8.
- 6 days or more, the patient should take the oral dose as soon as possible, and 300 mg on Day 15.

If the Day 8 oral dose (300 mg) is missed by:

- less than 6 days, the patient should take 300 mg as soon as possible.
- 6 days or more, the patient should take 300 mg on Day 15.

Regardless of when the Day 2 or Day 8 oral dose is being taken, subcutaneous injection should be administered on Day 15 as described in Table 1.

If the patient vomits within 3 hours of taking an oral dose of Sunlenca, another oral dose should be taken. If the patient vomits more than 3 hours after taking an oral dose of Sunlenca there is no need to take another oral dose of Sunlenca and the scheduled dosing regimen should continue.

Missed dose (of subcutaneous injection during mainteanance therapy)
During the maintainance period, if more than 28 weeks have elapsed since the last injection and if clinically appropriate to continue Sunlenca treatment, the initiation dosage regimen should be restarted from Day 1 (see table 1).

Special dosage instructions

Patients with hepatic disorders

No dose adjustment of Sunlenca is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Sunlenca has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section “Pharmacokinetics”).

Patients with renal disorders

No dose adjustment of Sunlenca is required in patients with mild, moderate, or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Sunlenca has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) (see section “Pharmacokinetics”).

Elderly patients

No dose adjustment of Sunlenca is required in elderly patients (see section “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Sunlenca in children under the age of 18 years old has not been demonstrated. No data are available.

Mode of administration

Solution for injection
For subcutaneous use.
Sunlenca injections should be administered into the abdomen (two injections, each at a separate site) by a healthcare professional. For instructions on preparation and administration, see ‘Instructions for Use’ in the package leaflet. ‘Instructions for Use’ are also available as a card in the injection kit.

Use aseptic technique. Visually inspect the solution in the vials for particulate matter and discoloration prior to administration. Sunlenca injection is a yellow to brown solution. Do not use Sunlenca injection if the solution contains particulate matter or discoloration. Once the solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible (see “Other information/Instruction for handling”).

The injection kit components are for single use only (see “Other information/Instruction for handling”). Use of vial access device is required. Two 1.5 mL injections are required for a complete dose.

Film-coated tablet
For oral use.
Sunlenca should be taken orally with or without food (see section “Pharmacokinetics”). The film-coated tablet should not be chewed, crushed, or split.

Contraindications

Co-administration with strong inducers of CYP3A, P-gp and UGT1A1, such as rifampicin, carbamazepine, phenytoin or St. John's wort is contraindicated (see section "Interactions").
Co-administration with strong inhibitors of CYP3A, P-gp and UGT1A1 together (i.e. substances that strongly inhibit all 3 pathways), such as atazanavir/cobicistat is contraindicated (see section "Interactions").

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Long-acting properties of a lenacapavir injection

Residual concentrations of lenacapavir injection may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer), therefore, the release characteristics of lenacapavir beyond the active dosing period has to be taken into consideration in the individual benefit/risk assessment and when the medicinal product is discontinued (see "Warnings and Precautions" (Use of other medicinal products after discontinuation of lenacapavir), "Pregnancy and Lactation", "Undesirable effects", "Pharmacokinetics" and "Overdosage").

Risk of resistance following treatment discontinuation

If Sunlenca is discontinued, to minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen where possible, no later than 28 weeks after the final injection of Sunlenca.
If virologic failure is suspected, an alternative regimen should be adopted where possible.

Use of other medicinal products after discontinuation of lenacapavir

If Sunlenca is discontinued, residual concentrations of lenacapavir may remain in the systemic circulation of patients for prolonged periods. These concentrations may affect the exposures of other medicinal products (i.e. sensitive CYP3A substrates) that are initiated within 9 months after the last subcutaneous dose of Sunlenca (see section "Interactions"). Based on the known metabolism/elimination mechanisms, these concentrations are not expected to affect the exposures of other antiretroviral agents that are initiated after discontinuation of Sunlenca. A possible increase in residual lenacapavir concentrations must be considered when concurrent strong inhibitors of CYP3A, P-gp and UGT1A1 together (i.e. substances that strongly inhibit all 3 pathways), such as atazanavir/cobicistat are used after lenacapavir interruption.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients should be advised that Sunlenca or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Co-administration of other medicinal products

Co-administration with medicinal products that are moderate inducers of CYP3A and P-gp (e.g. efavirenz, rifapentine, rifabutin) is not recommended (see "Interactions").

Excipients

Sunlenca contains less than 1 mmol sodium (23 mg) per injection or film-coated tablet, which means it is almost 'sodium-free'.

Interactions

Effect of other agents on the pharmacokinetics of lenacapavir

Lenacapavir is a substrate of CYP3A, P-gp and UGT1A1. Strong inducers of CYP3A, P-gp, and UGT1A1, such as rifampicin, may significantly decrease plasma concentrations of lenacapavir resulting in loss of therapeutic effect and development of resistance, therefore co-administration is contraindicated (see section "Contraindications"). Moderate inducers of CYP3A and P-gp, such as

efavirenz, may also significantly decrease plasma concentrations of lenacapavir, therefore co-administration is not recommended (see section “Warnings and precautions”).

Strong inhibitors of CYP3A, P-gp and UGT1A1 together (i.e., all 3 pathways), such as atazanavir/cobicistat, may significantly increase plasma concentrations of lenacapavir. Co-administration is therefore contraindicated (see section “Contraindications”).

Strong CY3A4 inhibitors alone (e.g. voriconazole) or strong inhibitors of CYP3A and P-gp together (e.g. cobicistat) do not result in a clinically meaningful increase in lenacapavir exposures.

Effect of lenacapavir on the pharmacokinetics of other agents

Lenacapavir is a moderate inhibitor of CYP3A. Caution is advised if Sunlenca is co-administered with a sensitive CYP3A substrate with a narrow therapeutic index. Lenacapavir is not a clinically meaningful inhibitor of P-gp and BCRP and does not inhibit OATP.

Interactions between lenacapavir and potential co- administered medicinal products are listed in Table 2 (where 90% confidence interval [CI] of the geometric least-squares mean [GLSM] ratio were within “↔”, extended above “↑”, or extended below “↓” the predetermined equivalence boundaries; a value of 1.00 corresponds to no change of the pharmacokinetic parameters and where once daily is indicated as “q.d.” and twice daily is indicated as “b.i.d.”).

TABLE 2: Interactions between Sunlenca and other medicinal products[1]

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
ANTIMYCOBACTERIALS		
Rifampicin[a,b, c] (600 mg q.d.)	Lenacapavir: ↓ AUC: 0.16 (0.12, 0.20) ↓C_{max}: 0.45 (0.34, 0.60)	Co-administration is contraindicated (see section “Contraindications”).
Rifabutin Rifapentine[r]	Interaction not studied. Co-administration of rifabutine and rifapentine may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration is not recommended (see section “Warnings and Precautions”).
ANTICONVULSANTS		
Carbamazepine Phenytoin	Interaction not studied. Co-administration of carbamazepine or phenytoin with lenacapavir may decrease lenacapavir	Co-administration is contraindicated (see section “Contraindications”).

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
	plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
Oxcarbazepine Phenobarbital	Interaction not studied. Co-administration of oxcarbazepine or phenobarbital with lenacapavir may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration is not recommended (see section “Warnings and Precautions”). Alternative anticonvulsants should be considered.
HERBAL PRODUCTS		
St. John’s wort *(Hypericum perforatum)*	Interaction not studied. Co-administration of St. John’s wort may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration is contraindicated (see section “Contraindications”).

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
ANTIRETROVIRAL AGENTS		
Atazanavir/cobicistat[b,d,e] (300 mg/150 mg q.d.)	Lenacapavir: ↑ AUC: 4.21 (3.19, 5.57) ↑ C_{max}: 6.60 (4.99, 8.73)	Co-administration is contraindicated (see section "Contraindications")..
Efavirenz[b,d,f] (600 mg q.d.)	Lenacapavir: ↓ AUC: 0.44 (0.32,0.59) ↓ C_{max}: 0.64 (0.45, 0.92)	Co-administration is not recommended (see section "Warnings and Precautions").
Etravirine Nevirapine Tipranavir/ritonavir	Interaction not studied. Co-administration of etravirine, nevirapine, or tipranavir/ritonavir may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
Cobicistat[b,d,g] (150 mg q.d.)	Lenacapavir: ↑ AUC: 2.28 (1.75, 2.96) ↑ C_{max}: 2.10 (1.62, 2.72)	No dose adjustment of lenacapavir is required.
Darunavir/cobicistat[b,d,h] (800 mg/150 mg q.d.)	Lenacapavir: ↑ AUC: 1.94 (1.50, 2.52) ↑ C_{max}: 2.30 (1.79, 2.95)	
Ritonavir	Interaction not studied. Co-administation of ritonavir may increase lenacapavir plasma concentrations.	
Tenofovir alafenamide[d,i,j] (25 mg)	Tenofovir alafenamide: ↑ AUC: 1.32 (1.09, 1.59) ↑ Cmax: 1.24 (0.98, 1.58) Tenofovir[k]: ↑ AUC: 1.47 (1.27, 1.71) ↑ Cmax: 1.23 (1.05, 1.44)	No dose adjustment of tenofovir alafenamide is required.
ERGOT DERIVATIVES		
Dihydroergotamine[r] Ergotamine[r] Methylergonovine[r]	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	Co-administration is not recommended.
PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied. Concentration of PDE-5 inhibitors may be increased when co-administered with lenacapavir.	Use of PDE-5 inhibitors for pulmonary arterial hypertension: Co-administration with tadalafil is not recommended. Use of PDE-5 inhibitors for erectile dysfunction:

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
		Sildenafil: A starting dose of 25 mg is recommended. Vardenafil: No more than 5 mg in a 24-hour period. Tadalafil: • For use as needed: no more than 10 mg every 72 hours • For once daily use: dose not to exceed 2.5 mg
CORTICOSTEROIDS (systemic)		
Dexamethasone Hydrocortisone/cortisone	Interaction not studied. Plasma concentrations of corticosteroids may be increased when co-administered with lenacapavir.	Co-administration of Sunlenca with corticosteroids whose exposures are significantly increased by CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Initiate with the lowest starting dose and titrate carefully while monitoring for safety.
HMG-CoA REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	Initiate lovastatin and simvastatin with the lowest starting dose and titrate carefully while monitoring for safety (e.g. myopathy).
Atorvastatin		No dose adjustment of atorvastatin is required.
Pitavastatin[d,i,l] (2 mg single dose; Simultaneous) Pitavastatin[d,i,l] (2 mg single dose; 3 days after lenacapavir)	Pitavastatin: ↔ AUC: 1.11 (1.00, 1.25) ↔ Cmax: 1.00 (0.84, 1.19) Pitavastatin: ↔ AUC: 0.96 (0.87, 1.07) ↔ Cmax: 0.85 (0.69, 1.05)	No dose adjustment of pitavastatin and rosuvastatin is required.
Rosuvastatin[d,i,m] (5 mg single dose)	Rosuvastatin: ↑ AUC: 1.31 (1.19, 1.43) ↑ C_{max}: 1.57 (1.38, 1.80)	

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
ANTIARRHYTHMICS		
Digoxin	Interaction not studied. Concentration of digoxin may be increased when co-administered with lenacapavir.	Caution is warranted and therapeutic concentration monitoring of digoxin is recommended.
SEDATIVES/HYPNOTICS		
Midazolam[d,l,n] (2.5 mg single dose; oral; simultaneous administration)	Midazolam: ↑ AUC: 3.59 (3.30, 3.91) ↑ C_{max}: 1.94 (1.81, 2.08) 1-hydroxymidazolam[o]: ↓ AUC: 0.76 (0.72, 0.80) ↓ C_{max}: 0.54 (0.50, 0.59)	Caution is warranted when midazolam or triazolam, is co-administered with Sunlenca.
Midazolam[d,l,n] (2.5 mg single dose; oral; 1 day after lenacapavir)	Midazolam: ↑ AUC: 4.08 (3.77, 4.41) ↑ C_{max}: 2.16 (2.02, 2.30) 1-hydroxymidazolam[o]: ↓ AUC: 0.84 (0.80, 0.88) ↓ C_{max}: 0.52 (0.48, 0.57)	
Triazolam	Interaction not studied. Concentration of triazolam may be increased when co-administered with lenacapavir.	
ANTICOAGULANTS		
Direct Oral Anticoagulants (DOACs) Rivaroxaban Betrixaban[r] Dabigatran Edoxaban	Interaction not studied. Concentration of DOAC may be increased when co-administered with lenacapavir.	Consult the Physician Information of the DOAC for further information on use in combination with combined moderate CYP3A and P-gp inhibitors.
ANTIFUNGALS		
Voriconazole[a,b,p,q] (400 mg b.i.d./200 mg b.i.d.)	Lenacapavir: ↑ AUC: 1.41 (1.10, 1.81) ↔ Cmax: 1.09 (0.81, 1.47)	No dose adjustment of lenacapavir is required.
Itraconazole Ketoconazole	Interaction not studied. Plasma concentration of lenacapavir may be increased when co-administered with itraconazole or ketoconazole.	

Medicinal product by therapeutic areas	Effects on concentrations. Mean ratio (90% confidence interval) for AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
H2-RECEPTOR ANTAGONISTS		
Famotidine[a,b] (40 mg q.d., 2 hours before lenacapavir)	Famotidine: ↑ AUC: 1.28 (1.00, 1.63) ↔ Cmax: 1.01 (0.75, 1.34)	No dose adjustment of famotidine is required.
ORAL CONTRACEPTIVES		
Ethinylestradiol Progestins	Interaction not studied. Plasma concentrations of ethinylestradiol and progestins may be increased when co-administered with lenacapavir.	Lenacapavir can be co-administered with oral contraceptives.
GENDER AFFIRMING HORMONES		
17β-estradiol Anti-androgens Progestogen Testosterone	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	No dose adjustment of these gender affirming hormones is required.

[1] This table is not all inclusive.

a Fasted
b This study was conducted using lenacapavir 300 mg single dose.
c Evaluated as a strong inducer of CYP3A, and an inducer of P-gp and UGT.
d Fed.
e Evaluated as a strong inhibitor of CYP3A, and an inhibitor UGT1A1 and P-gp.
f Evaluated as a moderate inducer of CYP3A and an inducer of P-gp.
g Evaluated as a strong inhibitor of CYP3A and an inhibitor of P-gp.
h Evaluated as a strong inhibitor of CYP3A, and an inhibitor and inducer of P-gp.
i This study was conducted using lenacapavir 600 mg single dose following a loading regimen of 600 mg twice daily for 2 days, single 600 mg doses of lenacapavir were administered with each co-administered medicinal product.
j Evaluated as a P-gp substrate.
k Tenofovir alafenamide is converted to tenofovir in vivo.
l Evaluated as an OATP substrate.
m Evaluated as an BCRP substrate.
n Evaluated as a CYP3A substrate.
o Major active metabolite of midazolam.
p Evaluated as a strong inhibitor of CYP3A.
q This study was conducted using voriconazole 400 mg loading dose twice daily for a day, followed by 200 mg maintenance dose twice daily.
r Not approved in Switzerland

Pregnancy, lactation

Pregnancy

There are no or limited amount of data from the use of lenacapavir in pregnant women. The effects of lenacapavir on human pregnancy are not known.

Animal studies do not indicate direct or indirect effects in relation to reproductive toxicity (see section “Preclinical data”).

Sunlenca should be used during pregnancy or in women of child-bearing potential who plan to become pregnant or do not use a reliable contraceptive method only if the potential benefit justifies the potential risk to the foetus.

Residual concentrations of lenacapavir may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer) (see section “Warnings and Precautions”). The potential of subsequent fetal exposure should be considered.

Lactation

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants,

It is unknown whether lenacapavir is excreted in human milk. After administration to rats during pregnancy, lenacapavir was detected at low levels in the plasma of nursing rat pups, without effects on these nursing pups.

Fertility

There are no data on the effects of lenacapavir on human male or female fertility. Animal studies indicate no effects on lenacapavir on male or female fertility (see section “Preclinical data”).

Effects on ability to drive and use machines

Sunlenca is expected to have no influence on the ability to drive and use machines.

No corresponding studies have been performed

Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on data from heavily treatment experienced adult patients with HIV who received Sunlenca in a Phase 2/3 study (GS-US-200-4625; “CAPELLA”; n = 72) through Week 52 (median duration on study of 54 weeks), as well as supportive data in treatment-naïve adult patients with HIV who received Sunlenca in a Phase 2 study (GS-US-200-4334; “CALIBRATE”; n = 157) through Week 54 (median duration of exposure of 66 weeks).
The most common adverse reactions in heavily treatment experienced adult patients were injection site reactions (ISRs) (63%) and nausea (4%).

List of adverse reactions

A tabulated list of adverse reactions is presented in Table 3. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000).

TABLE 3: Tabulated list of adverse reactions

Frequency[a]	Adverse reaction
Gastrointestinal disorders	
Common	nausea
General disorders and administration site conditions	
Very common	injection site reactions (63%)[b]

a Frequency based on all patients (Cohorts 1 and 2) in CAPELLA (see section "Properties/Effect").
b Includes injection site swelling, pain, erythema, nodule, induration, pruritus, extravasation, discomfort, mass, haematoma, oedema and ulcer.

Description of specific adverse reactions and additional information

Local injection site reactions (ISR)

Most patients had ISRs that were mild (Grade 1, 42%) or moderate (Grade 2, 18%). Three percent of patients experienced a severe (Grade 3) ISR that resolved within 1 to 8 days. No patients experienced a Grade 4 ISR.

The ISRs reported in more than 1% of patients were swelling (31%), pain (31%), erythema (25%), nodule (24%), induration (15%), pruritus (4%) and extravasation (3%). ISRs reported in 1% of patients included discomfort, mass, haematoma, oedema and ulcer.

The median duration of all ISRs excluding nodules and indurations was 6 days. The median duration of nodules and indurations was 180 and 118 days, respectively.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is currently limited experience with overdose of lenacapavir.

Treatment

If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sunlenca consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. As lenacapavir is highly protein bound, it is unlikely to be significantly removed by dialysis.

Properties/Effects

ATC code

J05AX31

Mechanism of action

Lenacapavir is a multistage, selective inhibitor of 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 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).

Lenacapavir has activity that is specific to human immunodeficiency virus (HIV-1).

Pharmacodynamics

Antiviral activity and selectivity in vitro
The antiviral activity of lenacapavir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. The EC_{50} and selectivity (CC_{50}/EC_{50}) values ranged from 30 to 190 pM and 140,000 to >1,670,000, respectively, for wild-type (WT) HIV-1 virus. The protein-adjusted EC_{95} for lenacapavir was 4 nM (3.87 ng per mL) in the MT-4 T-cell line for wild-type HIV-1 virus.

In a study of lenacapavir in combination with representatives from the main classes of antiretroviral agents (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand-transfer inhibitors [INSTIs], and protease inhibitors [PIs]), synergistic antiviral effects were observed. No antagonism was observed for these combinations.

Lenacapavir displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, A1, AE, AG, B, BF, C, D, E, F, G, H.

Lenacapavir was 15- to 25-fold less active against HIV-2 isolates relative to HIV-1.

Resistance

In Cell Culture

HIV-1 variants with reduced susceptibility to lenacapavir have been selected in cell culture. In vitro resistance selections with lenacapavir identified 7 mutations in CA: L56I, M66I, Q67H, K70N, N74D/S, and T107N singly or in dual combination. Phenotypic susceptibility to lenacapavir was reduced 4- to >3,226-fold, relative to WT virus. HIV-1 variants with >10-fold reduction in susceptibility to lenacapavir compared to WT virus displayed diminished replication capacity in primary human CD4+ T lymphocytes and macrophages (0.03 – 28% and 1.9 – 72% of WT virus, respectively).

In Heavily Treatment Experienced Patients

In GS-US-200-4625 (‘CAPELLA’), 29% (21/72) of heavily treatment experienced-patients met the criteria for resistance analyses through Week 52 (HIV-1 RNA ≥50 copies/mL at confirmed virologic failure [suboptimal virologic response at Week 4, virologic rebound, or viremia at last visit]) and were analysed for lenacapavir-associated mutation emergence. Lenacapavir-associated capsid mutations were found in 11.1% (n = 8) of these patients. The M66I CA mutation was observed in 8.3% (n = 6) of patients, alone or in combination with other Sunlenca-associated capsid mutations including N74D, Q67Q/H/K/N, K70K/N/R/S, T107T/C, and T107A. One patient had a K70H CA mutation emerging along with T107T/N, and one patient had emergence of both Q67H and K70R in CA.

Phenotypic analyses indicated that the M66I and K70H mutations were associated with an average decrease in lenacapavir susceptibility of 234-fold and 265-fold, respectively, when compared to WT. The Q67H + K70R CA resistance pattern was associated with a 15-fold decrease in lenacapavir susceptibility.

Cross Resistance

The *in vitro* antiviral activity of lenacapavir was determined against a broad spectrum of HIV-1 site-directed mutants and patient-derived HIV-1 isolates with resistance to the 4 main classes of antiretroviral agents (NRTIs, NNRTIs, INSTIs and PIs; n = 58), as well as to viruses resistant to maturation inhibitors (n = 24), and to viruses resistant to the entry inhibitors (EI) class (fostemsavir, ibalizumab, maraviroc, and enfuvirtide; n = 42). These data indicated that lenacapavir remained fully active against all variants tested, thereby demonstrating a non-overlapping resistance profile. In addition, the antiviral activity of lenacapavir in patient isolates was unaffected by the presence of naturally occurring Gag polymorphisms.

Effects on electrocardiogram

In a parallel-design t/QT study, lenacapavir had no clinically relevant effect on the QTcF interval. At supratherapeutic exposures of lenacapavir (9-fold higher than the therapeutic exposures of Sunlenca), the predicted mean (upper 90% confidence interval) increase in QTcF interval was 2.6 (4.8) msec, and there was no association (p = 0.36) between observed lenacapavir plasma concentrations and change in QTcF interval.

Clinical efficacy

The efficacy and safety of Sunlenca in HIV-1 infected, heavily treatment experienced patients with multidrug resistance is based on 52-week data from a partially randomised, placebo-controlled, double-blind, multicentre study, GS-US-200-4625 ('CAPELLA').

CAPELLA was conducted in 72 heavily treatment-experienced patients with multiclass resistant HIV-1. Patients were required to have a viral load ≥ 400 copies/mL, documented resistance to at least two antiretroviral medications from each of at least 3 of the 4 classes of antiretroviral medications (NRTI, NNRTI, PI and INSTI), and ≤ 2 fully active antiretroviral medications from the 4 classes of antiretroviral medications remaining at baseline due to resistance, intolerability, drug access, contraindication, or other safety concerns.

The trial was composed of two cohorts. Patients were enrolled into the randomised cohort (Cohort 1) if they had a < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the screening visit. Patients were enrolled into the non-randomised cohort (Cohort 2) if they had a ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the screening visit or after Cohort 1 reached its planned sample size. Patients were administered 600 mg, 600 mg, and 300 mg lenacapavir orally on Days 1, 2, and 8, respectively, followed by 927 mg subcutaneously on Day 15 and 927 mg subcutaneously every 6 months thereafter (see section "Pharmacokinetics").

Cohort 1 (n = 36, randomised): In the 14-day functional monotherapy period, patients in cohort 1 were randomised in a 2:1 ratio in a blinded fashion, to receive either lenacapavir or placebo, while continuing their failing regimen. This period was to establish the virologic activity of Sunlenca. After the functional monotherapy period, patients who had received Sunlenca continued on Sunlenca along with an OBR; patients who had received placebo during this period initiated Sunlenca along with an OBR.

Patients in cohort 1 had a mean age of 52 years (range: 24 to 71), 72% were male, 46% were White, 46% were Black, and 9% were Asian. Twenty-nine percent of patients identified as Hispanic/Latino. The median baseline plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL (range: 2.3 to 5.4). Four percent of patients receiving lenacapavir and 50% of patients receiving placebo had baseline viral loads greater

than 100,000 copies/mL. The median baseline CD4+ cell count was 127 cells/mm^3 (range: 6 to 827). Seventy-five percent of patients had CD4+ cell counts below 200 cells/mm^3. The percentage of patients in the randomised cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 97%, 94%, 78% and 75%, respectively. In cohort 1, 53% of patients had no fully active agents, 31% had 1 fully active agent, and 17% had 2 or more fully active agents within their initial failing regimen.

Cohort 2 (n = 36, non-randomised): Patients in cohort 2 initiated Sunlenca and an OBR on Day 1.

Patients in cohort 2 had a mean age of 48 years (range: 23 to 78), 78% were male, 36% were White, 31% were Black, 33% were Asian, and 14% of patients identified as Hispanic/Latino. The median baseline plasma HIV-1 RNA was 4.5 log_{10} copies/mL (range: 1.3 to 5.7). Nineteen percent of patients had baseline viral loads greater than 100,000 copies/mL. The median baseline CD4+ cell count was 195 cells/mm^3 (range 3 to 1296). Fifty-three percent of patients had CD4+ cell counts below 200 cells/mm^3. The percentage of patients in the non-randomised cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 100%, 100%, 83% and 64%, respectively. In cohort 2, 31% of patients had no fully active agents, 42% had 1 fully active agent, and 28% had 2 or more fully active agents within their initial failing regimen.

The primary efficacy endpoint was the proportion of patients in cohort 1 achieving ≥ 0.5 log_{10} copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. The results of the primary endpoint analysis demonstrated the superiority of Sunlenca compared with placebo, as shown in Table 4.

TABLE 4: Proportion of Patients Achieving a ≥ 0.5 log_{10} Decrease in Viral Load (Cohort 1)

	Sunlenca (n = 24)	**Placebo (n = 12)**
Proportion of Patients Achieving a ≥ 0.5 log_{10} Decrease in Viral Load	87.5%	16.7%
Treatment Difference (95% CI); p-value	70.8% (34.9% to 90.0%); p < 0.0001	

The results at Weeks 26 and 52 are provided in Table 5 and Table 6.

TABLE 5: Virologic Outcomes (HIV-1 RNA < 50 copies/mL) at Weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	[Sunlenca] plus OBR (n= 36)	
	Week 26	**Week 52**
HIV-1 RNA < 50 copies/mL	81%	83%
HIV-1 RNA ≥ 50 copies/mL[c]	19%	14%
No virologic data in Week 26 or Week 52 Window	0	3%
Discontinued Study Drug Due to AE or Death[d]	0	0
Discontinued Study Drug Due to Other Reasons[e] and Last Available HIV-1 RNA < 50 copies/mL	0	3%
Missing Data During Window but on Study Drug	0	0

a Week 26 window was between Days 184 and 232 (inclusive).
b Week 52 window was between Days 324 and 414 (inclusive).
c Includes patients who had ≥ 50 copies/mL in the Week 26 or 52 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

TABLE 6: Virologic Outcomes (HIV-1 RNA < 50 copies/mL) by Baseline Covariates at Weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	[Sunlenca] plus OBR (n = 36)	
	Week 26	**Week 52**
Baseline plasma viral load (copies/mL)		
≤ 100,000	86% (25/29)	86% (25/29)
> 100,000	57% (4/7)	71% (5/7)
Baseline CD4+ (cells/mm^3)		
< 200	78% (21/27)	78% (21/27)
≥ 200	89% (8/9)	100% (9/9)
Baseline INSTI resistance profile		
With INSTI resistance	85% (23/27)	81% (22/27)
Without INSTI resistance	63% (5/8)	88% (7/8)
Number of fully active ARV agents in the OBR		
0	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)
≥ 2	81% (13/16)	94% (15/16)
Use of DTG and/or DRV in the OBR		
With DTG and DRV	83% (10/12)	83% (10/12)
With DTG, without DRV	83% (5/6)	83% (5/6)
Without DTG, with DRV	78% (7/9)	89% (8/9)
Without DTG or DRV	78% (7/9)	78% (7/9)

ARV = antiretroviral; DRV=darunavir; DTG=dolutegravir; INSTI = integrase strand-transfer inhibitor; OBR = optimised background regimen
a Week 26 window was between Days 184 and 232 (inclusive).
b Week 52 window was between Days 324 and 414 (inclusive).

In cohort 1, at Weeks 26 and 52, the median change from baseline in CD4+ cell count was 72 cells/mm^3 (range: -101 to 522) and 68 cells/mm^3 (range: -194 to 467), respectively.

In cohort 2, at Week 26, 81% (29/36) of patients achieved HIV-1 RNA < 50 copies/mL and the median change from baseline in CD4+ cell count was 88 cells/mm^3 (range: -103 to 459).

Pharmacokinetics

Absorption

Oral Administration

Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring 4 hours after administration of Sunlenca. Absolute bioavailability following oral administration of lenacapavir is low (approximately 6 to 10%). Lenacapavir is a substrate of Pgp.

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

Subcutaneous Administration

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

Pharmacokinetic Parameters

Simulated steady state exposures of lenacapavir following recommended dosing regimen in heavily treatment experienced patients with HIV are provided in Table 7.

TABLE 7: Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration

	[a] Day 1 and 2: 600 mg (oral), Day 8: 300 mg (oral), Day 15: 927 mg (SC)		
Parameter Mean (%CV)[a]	**Days 1 to Day 15**	**Day 15 to end of Month 6**	**Steady state**
C_{max} (ng/ mL)	69.6 (56)	87 (71.8)	97.2 (70.3)
AUC_{tau} (h•ng/mL)	15600 (52.9)	250000 (66.6)	300000 (68.5)
C_{trough} (ng/mL)	35.9 (56.8)	32.7 (88)	36.2 (90.6)

CV = Coefficient of Variation; SC = subcutaneous
a Simulated exposures utilizing population PK analysis.

Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 28.5% to 84.1% higher in HIV-1 infected, heavily treatment experienced patients as compared to participants without HIV-1 infection based on population PK analysis.

Distribution

The apparent volume of distribution was 19240 litres after oral administration and ranged from 9500 to 11700 litres after subcutaneous administration.
Lenacapavir is highly bound to plasma proteins (> 98.5%).

Metabolism

Following a single intravenous dose of radiolabelled lenacapavir to healthy subjects, the predominant part of the total radioactivity in plasma was unchanged lenacapavir (69%).
Metabolism played a lesser role in lenacapavir elimination. Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation; primarily via CYP3A and UGT1A1. No single circulating metabolite accounted for > 10% of plasma drug-related exposure.

Elimination

Following a single intravenous dose of radiolabelled-lenacapavir to healthy subjects, 76% of the total radioactivity was recovered from feces and < 1% from urine. Unchanged lenacapavir was the predominant moiety in feces (33%). The median half-life following oral and subcutaneous 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 subcutaneous administration.

Linearity/non-linearity

The single dose pharmacokinetics of lenacapavir after oral administration are non-linear and less than dose proportional over the dose range of 50 to 1800 mg.

The single dose pharmacokinetics of lenacapavir after subcutaneous injection (309 mg/mL) are dose proportional over the dose range of 309 to 927 mg.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of a single 300 mg oral dose of lenacapavir were evaluated in a dedicated study in subjects with moderate hepatic impairment (Child-Pugh Class B). Lenacapavir mean exposures were increased (1.47-fold and 2.61-fold for AUC_{inf} and C_{max}, respectively) in patients with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function; however, the increase was not considered clinically relevant. The pharmacokinetics of lenacapavir have not been studied in patients with severe hepatic impairment (Child-Pugh C) (see section “Posology/Administration”).

Renal impairment

The pharmacokinetics of a single 300 mg oral dose of lenacapavir were evaluated in a dedicated study in subjects with severe renal impairment (estimated creatinine clearance ≥ 15 and < 30 mL/minute). Lenacapavir exposures were increased (1.84-fold and 2.62-fold for AUC_{inf} and C_{max}, respectively) in subjects with severe renal impairment compared with subjects with normal renal function; however, the increase was not considered clinically relevant. The pharmacokinetics of lenacapavir have not been studied in patients with end-stage renal disease, including those on dialysis (see section “Posology/Administration”). As lenacapavir is greater than 98.5% protein bound, dialysis is not expected to alter exposures of lenacapavir.

Elderly patients

Population pharmacokinetics analysis showed that age (≥ 65 to 78 years) did not have a clinically meaningful influence on the systemic lenacapavir exposures.

Gender, and race

Population PK analyses using data from adult trials did not identify any clinically relevant differences in the exposure of lenacapavir due to gender, race/ethnicity or weight.

Preclinical data

Based on conventional nonclinical toxicology studies, the preclinical data on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity do not indicate any hazards to humans.

Genotoxicity

Lenacapavir was not mutagenic or clastogenic in conventional genotoxicity assays.

Carcinogenicity

Lenacapavir was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 300 mg/kg/dose once every 13 weeks, which resulted in exposures of approximately 37 times the exposure in humans at the recommended human dose.

Reproductive toxicity

In rats, male and female fertility was not affected at lenacapavir exposures up to 5 times the human exposure at the recommended human dose. In rats and rabbits, embryofoetal development was not affected at exposures up to 13 and 108 times the human exposure, respectively, at the recommended human dose. In rats, pre- and postnatal development was not affected at exposures up to 4 times the human exposure at the recommended human dose.
In a pre- and postnatal developmental study, the transfer of lenacapavir from dams to neonatal rats was observed. However, it is not known whether the transfer occurred via the placenta or milk; therefore, it is not known whether lenacapavir may pass into the placenta or breast milk in humans.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicinal product after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Keep out of reach of children.
Do not store above 30°C.
Store in the original packaging in order to protect from light (solution for injection) or moisture (film-coated tablets).

Shelf life in the syringe

As soon as the solution has been drawn into the syringe, for microbiological reasons, the product should be used immediately.

Instructions for handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For an illustrated instructions for administration of Sunlenca injection, see the instructions for use card in the pack.

Authorisation number

68385, 68386 (Swissmedic)

Packs

Sunlenca, solution for injection: 1x 2 [A]
Sunlenca injection is packaged in a dosing kit containing:

- 2 single-use clear glass vials of Sunlenca, each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir. Vials are sealed with an elastomeric closure and aluminum overseal with flip off cap;
- 2 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, 12.7 mm).

Sunlenca 300 mg, film-coated tablets: 1x 5 [A]
Sunlenca tablets are packaged in a blister pack containing:

- 5 tablets of Sunlenca, each containing 300 mg of lenacapavir, in a clear blister film sealed to a foil lidding material. The blister card, which is fitted between child-resistant sealed paperboard cards, is packaged with silica gel dessicant in a sealed flexible laminated pouch.

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

Date of revision of the text

February 2023

The following information is intended for healthcare professionals only:

Instructions for Use Sunlenca 463.5 mg solution for injection

Your pack contains

2 vials	

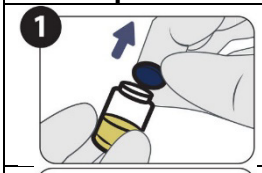
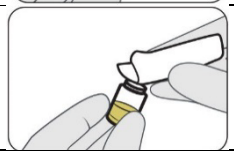
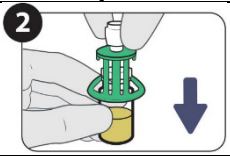
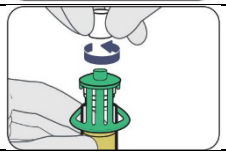
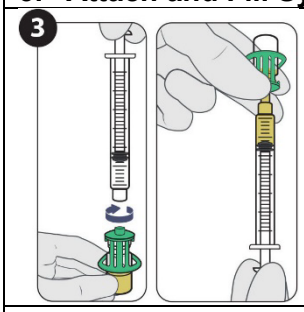
2 vial access devices	
2 syringes	
2 injection needles	

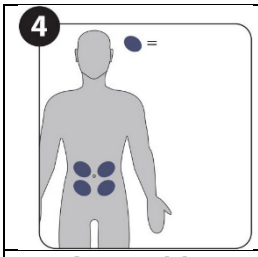
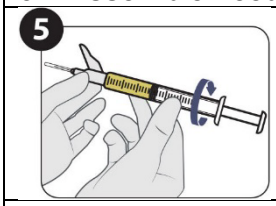
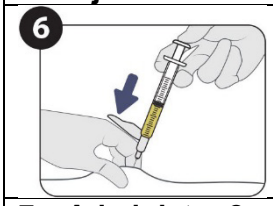
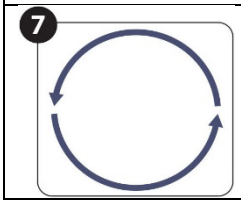
All the components are for single use.

A complete dose requires **two 1.5 mL injections.** The use of **the vial access device** is required.

Make sure that:

- Vial contains a **yellow-to-brown solution** with **no particles**
- Contents are **not damaged**
- Product is **not expired**

1. Prepare Vial	
	Remove cap.
	Clean vial stopper with alcohol wipe.
2. Prepare Vial Access Device	
	Push down.
	Twist off.
3. Attach and Fill Syringe	
	• Attach syringe and inject 1.5 mL of air into vial. • Flip upside down and withdraw all contents.
4. Prepare an Injection Site on Patient's Abdomen	

	Injection site options (at least 5 cm from navel).
5. Assemble needle and Syringe	
	Attach Injection Needle and Prime to 1.5 mL.
6. Inject Dose	
	Inject 1.5 mL of Sunlenca subcutaneously.
7. Administer 2nd Injection	
	Repeat steps for 2nd injection **at new injection site.**