Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Sunlenca

Active ingredient: Lenacapavir sodium

Sponsor: Gilead Sciences Pty Ltd

January 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ARV	Antiretroviral
ASA	Australia-specific annex
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{inf}	Area under the concentration versus time curve from time zero to infinity
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
COVID-19	Coronavirus disease 2019
DDI	Drug-drug interaction
DLP	Data lock point
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ER_{AUC}	Exposure ratio based on AUC
FDA	Food and Drug Administration (United States)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ISR	Injection site reaction
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OBR	Optimised background regimen
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetic
popPK	Population pharmacokinetic
RMP	Risk management plan
SC	Subcutaneous
TEAE	Treatment-emergent adverse event

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum plasma concentration
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Sunlenca
Active ingredient:	Lenacapavir sodium
Decision:	Approved
Date of decision:	23 March 2023
Date of entry into ARTG:	27 March 2023
ARTG numbers:	386895 392350
¡ *Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Gilead Sciences Pty Ltd Level 6, 417 St Kilda Road Melbourne VIC 3004
Dose forms:	Solution for injection Film coated tablets
Strengths:	463.5 mg/1.5 mL solution 300 mg tablets
Containers:	Vial Blister pack
Pack sizes:	2 vials 5 tablets
Approved therapeutic use for the current submission:	*Sunlenca, in combination with other antiretrovirals, is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.*
Routes of administration:	Subcutaneous injection Oral
Dosage:	Sunlenca should be prescribed by physicians experienced in the treatment of HIV. Prior to starting Sunlenca, the healthcare professional should carefully select patients who agree to the required injection schedule. To help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses, the healthcare professional should also

counsel patients about the importance of adherence to both the scheduled dosing visits and the optimised background regimen.

The recommended Sunlenca treatment regimen in adults consists of an initiation dosing period (oral tablets and subcutaneous injections) and once every 6-months maintenance dosing (subcutaneous injections).

If Sunlenca is discontinued, it is essential to adopt an alternative, fully suppressive antiretroviral regimen where possible, no later than 28 weeks after the final injection of Sunlenca.

Initiation:

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.

Oral tablets can be taken with or without food.

Maintenance:

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).

For further information regarding dosage, refer to the Product Information.

Pregnancy category: B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Gilead Sciences Pty Ltd (the sponsor) to register Sunlenca (lenacapavir sodium) as 309 mg/mL solution for injection in vials, and as 300 mg tablets in blister packs, for the following proposed indication:[1]

> *Sunlenca, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and paediatric patients weighing at least 35 kg with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.*

Human immunodeficiency virus (HIV) is a retrovirus that primarily targets immune effector cells in humans, mainly cluster of differentiation 4 positive (CD4+) lymphocytes. There is currently no cure available for HIV infection, which if left untreated can ultimately lead to the development of acquired immunodeficiency syndrome (AIDS). The incidence of newly diagnosed human immunodeficiency virus type 1 (HIV-1) infection in Australia in 2021 was 552 cases.[2]

The development and introduction of highly effective antiretroviral therapy (ART) has improved the lives of HIV-infected individuals. The currently available treatment regimens (combination ART) reduce disease morbidity and mortality. However, a subset of people with HIV continue to experience virologic and immunologic failure especially heavily treatment experienced people with HIV. Drug-associated toxicity, tolerability problems, and poor adherence are other factors affecting long-term therapy.

Heavily treatment experienced people with HIV with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve sustained viral suppression. However, the goal of plasma HIV RNA suppression remains. An ART regimen change is usually indicated and tailored to the patient based on ART history and drug resistance testing. Usually, this involves a new combination of conventionally used ART therapies, for example, nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors and integrase strand transfer inhibitors (INSTIs). Therapies specifically considered for heavily treatment experienced people with HIV include chemokine receptor 5 (CCR5) antagonists, fusion inhibitors, attachment inhibitors and post-attachment inhibitors:

- ibalizumab (not registered in the ARTG), a monoclonal humanised antibody post-attachment inhibitor, that targets CD4 cell receptors to prevent HIV entry
- fostemsavir, an attachment inhibitor that selectively inhibits the interaction between HIV and cellular CD4 receptors, and thereby preventing viral entry into the host cells
- maraviroc, a CCR5 antagonist that selectively binds to CCR5, preventing CCR5-tropic HIV from entering cells. However, its use is limited as many treatment-experienced people with HIV do not have CCR5-tropic HIV, but instead CXCR4-tropic HIV or mixed-tropic HIV
- enfuvirtide, a fusion inhibitor of the structural rearrangement of the HIV-1 glycoprotein 41, binding to this protein and blocking fusion between the viral and target cell membranes preventing viral RNA from entering the cell.

Lenacapavir is a novel, first-in-class, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein subunits. Lenacapavir inhibits HIV-1 replication by

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] Accessed October 2023 at HIV | Kirby Institute (unsw.edu.au)

interfering with multiple, essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA, virus assembly, and capsid core formation.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in the Europe Union, Canada and the United States of America (USA). The following table summarises these submissions and provides the approved indications.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	30 July 2021	Approved on 17 August 2022	*Sunlenca injection, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.* *Sunlenca tablet, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen, for oral loading prior to administration of long-acting lenacapavir injection.*
Canada	31 March 2022	Approved on 2 November 2022	*Sunlenca (lenacapavir), in combination with other antiretroviral(s), 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.*

Region	Submission date	Status	Approved indications
United States of America	27 June 2022	Approved on 22 December 2022	*Sunlenca, in combination with other antiretroviral(s), 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.*

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the priority registration process.

Table 2: Timeline for Submission PM-2022-00982-1-2

Description	Date
Priority determination	2 February 2022
Submission dossier accepted and first round evaluation commenced	2 May 2022
Second round evaluation completed	19 January 2023
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice[3]	3 January 2023
Sponsor's pre-Advisory Committee response	18 January 2023
Advisory Committee meeting	3 February 2023
Registration decision (Outcome)	23 March 2023
Administrative activities and registration in the ARTG completed	27 March 2023
Number of working days from submission dossier acceptance to registration decision*	139

*Target timeframe for priority submissions is 150 working days from acceptance for evaluation to the decision.

[3] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who approved the medicine under section 25 of the Act.

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

Committee for Medicinal Products for Human Use (CHMP): Guideline on the clinical development of medicinal products for the treatment of HIV infection. EMEA/CPMP/EWP/633/02 Rev. 3.

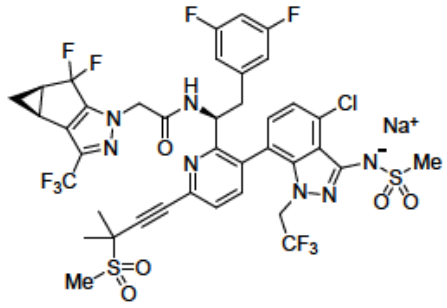
European Agency for the Evaluation of Medicinal Products. Committee For Proprietary Medicinal Products (CPMP): Points to Consider on Application With 1. Meta-Analyses; 2. One Pivotal Study. CPMP/EWP/2330/99.

Quality

Drug substance

The molecular formula of lenacapavir sodium is $C_{39}H_{31}ClF_{10}N_7NaO_5S_2$ and its chemical structure is shown in Figure 1. The drug substance has 3 stereogenic centres with defined configuration and is produced as a single stereoisomer of an interconvertible mixture of 2 atropisomers. Form I, II, and III are the solvent-free crystalline forms of lenacapavir sodium that have been isolated in laboratory studies. Form I is the designated drug substance, and the manufacturing process is designed to produce this form.

Figure 1. Chemical structure of lenacapavir sodium



Total impurities are consistent with specified impurity levels and are satisfactory. Satisfactory specifications have been provided for all reagents, solvents, raw materials, and auxiliary materials.

The data support the proposed retest period of 36 months for the drug substance stored in the container closure system indicated at 30°C.

Drug products

Solution for injection

The solution for injection is packaged in a 3 mL clear glass vial and is supplied as a kit containing 2 vials and co-packaged with items to deliver the dose: 2 disposable 3 mL syringes, 2 injection safety needles, and 2 vial transfer spikes. These components are included separately in the ARTG.

All excipients are pharmacopeial, non-novel, and are not of human or animal origin.

The provided data support a shelf life of 24 months when stored below 30°C. The proposed storage condition protect from light is appropriate given the results of the forced degradation studies.

Film coated tablet

The film coated tablets are packaged in pack size of 5 tablets in a polyvinyl chloride/aluminium blister fitted between 2 paperboard cards and further packaged in a sealed aluminium laminated pouch with silica gel desiccant.

As lenacapavir is a BCS Class IV compound,[4] formulation of lenacapavir as an amorphous spray-dried dispersion was determined to be the most appropriate strategy to improve its pharmacokinetic performance.

All the excipients except for the film-coat material are of a pharmacopeial quality. The components of the film-coat material have been provided and each comply with an acceptable quality standard. The mannitol content in the tablet would result in a daily dose of less than 2 g, therefore a warning for sugar alcohols is not required, in accordance with *Therapeutic Goods Order No. 91 - Standard for labels of prescription and related medicines.* The stability studies demonstrate chemical compatibility of the drug substance with the excipients.

The storage condition 'Store in Original Container' is appropriate.

Only 18 months long-term stability has been provided. Therefore, the data support a shelf life of 30 months when packaged in the primary container-closure system and stored below 30°C.

Conclusion

Approval for registration of the proposed lenacapavir products is recommended from a pharmaceutical chemistry perspective. No specific condition of registration was proposed.

Nonclinical

Dossier

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals.[5] The overall quality of the dossier was high with all pivotal safety studies conducted under Good Laboratory Practice conditions. The exposures in the submitted toxicity studies were adequate to establish the safety profile of lenacapavir.

Mechanism of action and resistance

In vitro, lenacapavir binds at the interface formed between 2 adjacent HIV-1 capsid protein monomers with nanomolar affinity (dissociation constant (K_D) = 1.4 nM) and interferes with viral replication and infectivity by disrupting capsid-mediated nuclear uptake of HIV-1 proviral DNA, capsid assembly, and capsid protein formation with the effective concentration giving 50% inhibition of virus replication within expected clinical plasma concentrations. Lenacapavir did not affect HIV-1 entry into host cells.

[4] The Biopharmaceutics Classification System (BCS) is a guidance for predicting intestinal drug absorption provided by the US Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

[5] European Medicines Agency. ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. EMA/CPMP/ICH/286/1995.

Several amino acid substitutions in viral capsid sequence, either single or in dual combinations, conferring various degree of resistance to lenacapavir (up to more than 5000-fold) compared to the wild-type HIV-1 were identified and include HIV-1 capsid genotypes L56I, M66I, Q67H, K70N, N74D/S, T107N and N57H.

Lenacapavir was tested against a panel of 87 receptors, ion channels and transporters. Based on the clinical maximum plasma concentration (C_{max}) and the distribution pattern of [^{14}C]lenacapavir sodium derived radioactivity in rats no effects are predicted at clinically relevant concentrations.

Safety pharmacology

In vitro lenacapavir displayed negligible toxicity against HIV-1 permissible human cells and other cell types. *In vitro* lenacapavir did not display anti-viral activity against hepatitis C virus (HCV) or human rhinovirus serotype 16 and had very low activity against hepatitis B virus (HBV) and respiratory syncytial virus.

Safety pharmacology studies assessed effects on the cardiovascular, central nervous and respiratory systems. No adverse effects were seen on the cardiovascular system or central nervous system function in respective 2-month repeat dose studies in dogs or rats with plasma C_{max} lenacapavir that was 20 to 48 times the clinical C_{max}. In rats, following a single subcutaneous (SC) lenacapavir administration a slightly increased tidal volume and a slightly reduced mean respiration rate were noted at approximately 20 times the clinical C_{max}. However, these outcomes were of minor magnitude and not statistically significant. Furthermore, no respiratory effects were observed at approximately 7 times the clinical C_{max}. Consequently, no cardiovascular, central nervous system or respiratory effects are predicted at clinical concentrations of lenacapavir.

In animals and humans, lenacapavir bioavailability was moderate to high following SC administration, and low following oral administration, likely due its low permeability and efflux by P-glycoprotein (P-gp). Following SC administration, lenacapavir was absorbed slowly, had a substantially longer terminal half-life than following intravenous (IV) administration, and displayed a sustained drug release at all administered doses in rats and dogs. Accumulation of lenacapavir was observed after daily oral doses in rats and dogs and after multiple monthly SC doses in dogs. No meaningful sex differences were observed in pharmacokinetic analysis. Lenacapavir exists as a mixture of atropisomers 'LEN.1' and 'LEN.2', and their ratio was not influenced by plasma binding proteins or enzymes *in vitro*. The extent of protein binding was high (at least 98.5%) in mice, rats, dogs, monkeys and humans. In rats, lenacapavir-related radioactivity was widely distributed to most tissues and was cleared from all tissues by 56 days post-dose. The highest concentration of radioactivity was found in the liver, kidney, pancreas, fat, small intestine, adrenal gland and stomach (there was minimal distribution to the brain and testis, consistent with lenacapavir being a substrate of P-gp). Lenacapavir was detected in rat pups via milk and/or placental transfer. In rats, dogs and humans, the major route of elimination was excretion as intact lenacapavir in the bile and intestinal secretion (by P-gp), and to a smaller

extent through metabolism by CYP3A (oxidation)[6] and/or UGT1A1 (glucuronidation)[7]. All human metabolites (accounting for less than 3% each in plasma and excreta) were observed in nonclinical species.

Drug-drug interactions

Lenacapavir is a substrate of P-gp, and P-gp mediated excretion is a major elimination pathway. Thus, plasma lenacapavir concentrations may be altered by P-gp inhibitors or inducers. Lenacapavir time-dependently inhibits of CYP3A but is not predicted to be an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K. Lenacapavir is not predicted to cause drug interactions through CYP induction. Based on *in vitro* data, an interaction with OATP1B1 is considered possible (the ratio of the half maximal inhibitory concentration (IC_{50}) to the unbound hepatic inlet concentration is 25 or less). However, a clinical drug interaction study using oral administration revealed no significant effects of lenacapavir on pharmacokinetics of an OATP substrate, pitavastatin.

Toxicity

Lenacapavir had a low order of acute oral toxicity in rats and dogs. Repeat-dose toxicity studies were conducted in rats and dogs by the oral (for 4 weeks) and SC (for 26 weeks in rats and 9 months in dogs) routes. Maximum exposures (area under the concentration versus time curve (AUC)) to lenacapavir following oral or SC dosing were generally high multiples of the clinical AUC, reaching over 30 in the pivotal studies in rats and dogs. Repeated oral dosing with lenacapavir did not cause systemic adverse effects at doses up to 10 mg/kg/day (exposure ratio based on AUC (ER_{AUC}) of 22) in rats, and 30 mg/kg/day (ER_{AUC} 59) in dogs. In rats, no systemic adverse effects were observed after repeated SC dosing with lenacapavir (ER_{AUC} 32 or less). In dogs, SC administration of lenacapavir at very high doses (at ER_{AUC} over 60) caused clinical signs suggestive of hepatobiliary degeneration (vacuolar hepatocyte and bile duct epithelial degeneration, bile pigment, and/or oval cell/bile ductule hyperplasia), as well as microscopic findings in the kidney (tubule degeneration and/or dilatation, and/or pigment), and/or stomach (mucosa degeneration/atrophy). Due to the high relative exposures at which they were observed, these effects are not expected to be of clinical significance.

Effects were observed at the local injection site (that is, chronic granulomatous inflammation reaction) in mice, rats, dogs and rabbits. This foreign body host response, due to the subcutaneous depot of lenacapavir, occurred even at formulation concentrations lower than that of the proposed clinical formulation. Injection site reactions are expected clinically and are documented in the Product Information.

Lenacapavir was not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in human lymphocytes). Lenacapavir was not clastogenic in rats. No treatment related increase in tumour

[6] Cytochrome P450 (CYP) enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for a large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[7] UGT (Uridine diphosphate glucuronosyltransferase), OATP (organic anion transporting polypeptide), OAT (organic anion transporter), OCT (organic cation transporter), MATE (multidrug and toxin extrusion protein), and BCRP (breast cancer resistance protein) are examples of enzymes or transporters involved in drug metabolism.

incidence was observed in a short-term carcinogenicity study in transgenic mice. A long-term carcinogenicity study is in progress.

Fertility and embryofetal development

Fertility was unaffected in male and female rats treated with lenacapavir SC at exposure levels 7.5 (male) and 5.5 (female) times the clinical AUC. There were no adverse effects on embryofetal development when lenacapavir was administered during the period of organogenesis to rats (at 17 times the predicted human exposure at the proposed clinical dose) or rabbits (at 135 times the predicted human exposure). There were no adverse effects on postnatal development in rats (ER_{AUC} 5.3). Lenacapavir-related radioactivity was distributed to nursing pups via either milk or placental transfer (maternal to pup concentration ratios were between 5 and 6).

Pregnancy category

The Pregnancy Category proposed by the sponsor (B1) is appropriate.[8] Lenacapavir is not teratogenic.

Conclusions

The pharmacology studies support the use of lenacapavir for the proposed indication. Secondary pharmacodynamics and safety pharmacology studies with lenacapavir did not raise safety concerns.

Lenacapavir is a moderate inhibitor of CYP3A and may inhibit the hepatic uptake transporter OATP1B1.

The combined animal safety studies revealed chronic granulomatous inflammation reaction at the SC injection site. Effects on the liver are considered to be of low concern in humans as they occurred at very high systemic exposure in animals.

The toxicity of lenacapavir in combination with other drugs was not investigated in nonclinical studies. There are no toxicity studies in juvenile animals to support its use in children.

No specific condition of registration was proposed.

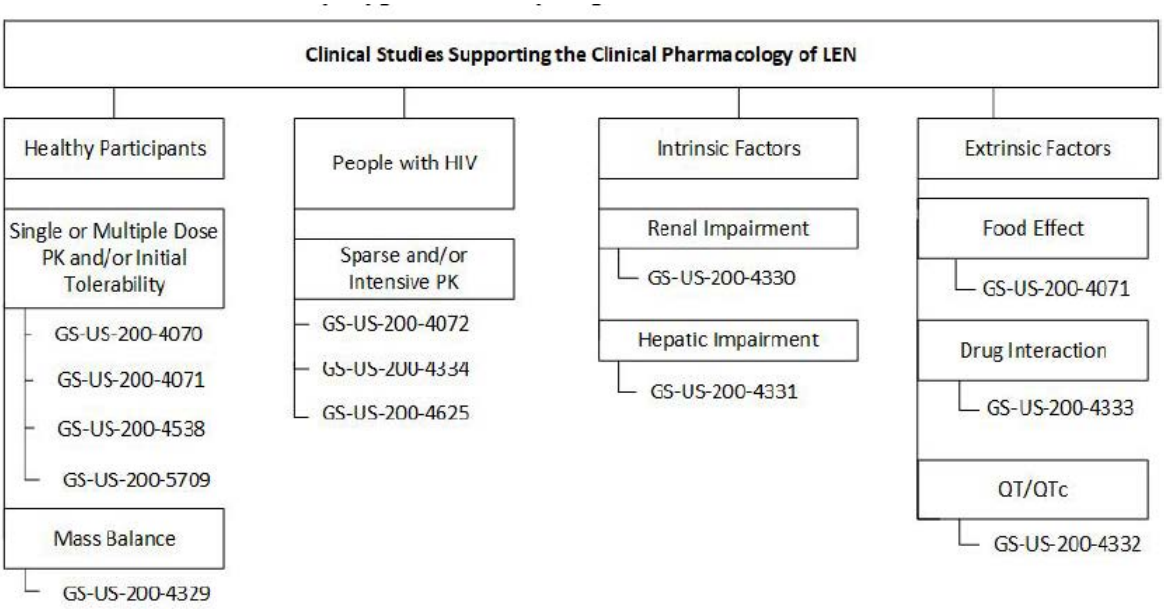
Clinical

Summary of clinical studies

The clinical dossier consisted of 12 studies, as shown in Figure 2. In addition, a single population pharmacokinetics (popPK) study investigated lenacapavir pharmacokinetics (PK) in healthy subjects and patients with HIV, based on the results from 7 studies.

[8] Definition of the Australian category B1 for prescribing medicines in pregnancy: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Figure 2: Overview of clinical pharmacology studies



LEN = lenacapavir; PK = pharmacokinetics

Pharmacokinetics

Absorption

Following a single oral tablet dose of 300 mg lenacapavir, the median time to maximum concentration (T_{max}) was 4.0 hours (fasted). Following SC lenacapavir dosing the median T_{max} ranged from 77 days to 84 days.

The absolute bioavailability of oral or subcutaneous administration compared with intravenous lenacapavir was not directly determined but estimated after dose correction to be 10% for oral lenacapavir (300 mg dosing) (Studies 4071 and 4329), and 100% for SC lenacapavir (Studies 4538 and 4329).

Following a single oral tablet dose of 300 mg lenacapavir to healthy subjects, the median T_{max} under fasted conditions and following a low-fat and high-fat meal occurred at 4.0 hours, 5.0 hours and 6.0 hours, respectively. Food status is unlikely to have a clinically significant effect on lenacapavir exposure.

Distribution

Following a single oral dose of lenacapavir 300 mg tablets under fed conditions, the apparent volume of distribution was 19,597 L.[9]

Following a single oral dose of single SC injection of 927 mg lenacapavir sodium solution, the apparent volume of distribution ranged from 9,495 L to 11,675 L.

Lenacapavir is highly bound to plasma proteins. Its plasma protein binding was approximately 99.8% in subjects with normal hepatic function. Mean whole blood-to-plasma concentration ratios following a radioactive dose of lenacapavir ranged from 0.500 to 0.695 through to 336 hours post-dose, indicating low association between radioactivity and red blood cells.

[9] Apparent volume of distribution during the terminal phase after non-intravenous administration.

Metabolism

Following a single dose of [^{14}C]lenacapavir, 76% of the total radioactivity was recovered from faeces and less than 1% from urine. Unchanged lenacapavir was 68.8% and 32.9% of circulating total radioactivity, in plasma and of faeces, respectively. As the primary circulating form of lenacapavir is unchanged drug, genetic polymorphisms in CYP enzymes or transporters are unlikely to significantly affect the plasma PKs of lenacapavir.

Metabolism was via oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation and glutathione conjugation, involving CYP3A and UGT1A1.

Three circulating metabolites that represented greater than 1% of circulating activity were identified in plasma. None of these metabolites accounted for 10% or more of plasma drug-related exposure.

Excretion and elimination

The median half-life after administration ranged from 10 days to 12 days (after oral administration) and 8 weeks to 12 weeks (after SC administration). The mean apparent clearance was 55 L/h (oral) and 4.2 L/h (SC).

Following a single 300 mg oral tablet dose of lenacapavir to healthy subjects, lenacapavir apparent oral clearance ranged from approximately 41 L/h to 52 L/h, whereas, following a single SC administration of 927 mg lenacapavir sodium mean apparent oral clearance was approximately 4.2 L/h.

Dose proportionality

Following single doses of 50 mg, 300 mg, 900 mg and 1800 mg of lenacapavir oral tablets, increases in lenacapavir AUC and C_{max} values were less than dose proportional.

Following single SC administrations of the lenacapavir free acid suspension at doses of 30 mg, 100 mg, 300 mg or 450 mg, lenacapavir exposure increased in a dose proportional manner. Moreover, at doses of 100 mg or greater, mean lenacapavir plasma concentrations exceeded the 95% effective concentration for wild-type HIV-1 (3.87 ng/mL), as determined in MT-4 cells, for at least 12 weeks.

Following 2 days of oral tablet dosing with 600 mg lenacapavir, mean lenacapavir C_{max} approximately doubled following Day 1 dosing (22 ng/mL) compared to Day 2 dosing (40.4 ng/mL) and T_{max} increased from 4 h to 6 h.

Following 10 days of once daily dosing with lenacapavir oral capsules containing either 30 mg or 100 mg, steady state lenacapavir exposure was not achieved; however, consistent with the $t_{1/2}$, the mean lenacapavir C_{max} and area under the concentration versus time curve from time zero to 24 hours (AUC_{0-24}) were at least 10-fold higher than those after a single dose.

Accumulation

Following a single intravenous dose of [^{14}C]lenacapavir 20 mg to healthy male participants, 75.9% of the dose was recovered in faeces and 0.24% in urine.

Intra-individual and inter-individual variability

The inter-individual values for clearance, peripheral volume of distribution, oral first-order absorption rate constant, SC first-order transit absorption rate constant, and SC bioavailability relative to intravenous, were 44%, 85%, 78%, 32% and 39%, respectively. A combined additive

and proportional error model was used to characterise residual variability, which had values of 0.025 ng/mL and 27% of the coefficient of variation, respectively.

Pharmacokinetics in the target population

As in healthy subjects, lenacapavir PKs following SC administration of the suspension formulation to people with HIV were characterised by prolonged exposure, with measurable plasma concentrations for at least 32 weeks following doses of 150 mg, 450 mg and 750 mg. The median $t_{1/2}$ across doses ranged between approximately 36 days and 45 days. Moreover, lenacapavir C_{max} and area under the concentration versus time curve from time zero to infinity (AUC_{inf}) increased in a dose proportional manner across the range of doses evaluated. By contrast, the popPK analysis indicated that lenacapavir clearance and peripheral volume of distribution were 30.4% and 133% higher in healthy subjects than in people with HIV.

Pharmacokinetics in special populations

Hepatic impairment: Lenacapavir AUC_{inf} and C_{max} were 47% and 161%, respectively, higher in the moderately impaired subjects than in participants with normal hepatic function, respectively. lenacapavir PKs have not been evaluated in subjects with severe hepatic impairment.

Renal impairment: Lenacapavir C_{max} and AUC_{inf} were increased by 162% and 84%, respectively, in participants with severe renal impairment compared matched healthy controls. lenacapavir PKs were not studied in patients with end-stage renal disease or undergoing dialysis.

Age: PopPK analyses indicated at the 5th and 95th percentiles of age, lenacapavir clearance was 12.2% higher and 11.9% lower, respectively. A change in exposure (−39.7 to +19.9%) for participants aged 50 years or older was not considered clinically meaningful and no dose adjustment is recommended.

Elderly: There appears to be no clinically meaningful differences in participants aged 65 years to 78 years (n = 5) compared with participants aged under 65 years (n = 155), but the sample size was too small for definite conclusions.

Biological sex: Lenacapavir clearance was 20.4% lower in female than in male subjects, but given the rather low effect on exposure, a dose adjustment based on sex is not required.

Weight: PopPK analyses identified that body weight was a significant covariate on lenacapavir clearance, volume of the central compartment, peripheral volume of distribution, and compartmental clearance, such that at the 90th percentiles of possible body weights following oral dosing, lenacapavir exposure was up to 23.5% and up to 32% lower respectively, whereas, following SC administration, lenacapavir exposure was up to 20.3% higher and up to 28.8% lower, respectively.

Ethnicity: No impact of ethnicity on lenacapavir PK was identified.

Population pharmacokinetics data

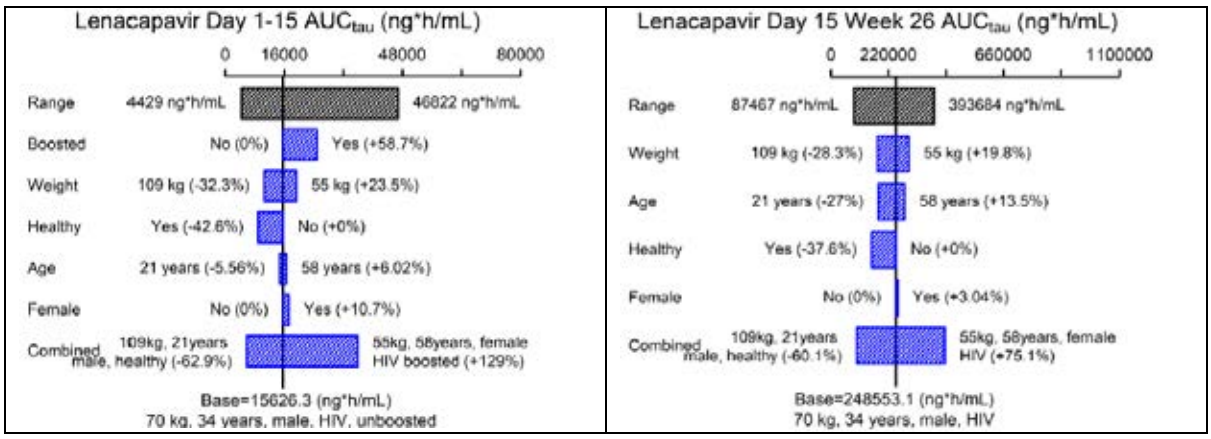
Population pharmacokinetic (popPK) data were provided by Study CTRA-2021-1054 lenacapavir PopPK.

The final lenacapavir model was a 2-compartment model with first-order absorption after oral administration, parallel direct (first-order) and transit compartment absorption after SC administration, and first-order elimination from the central compartment.

Based on the popPK study results, dose appeared to affect oral bioavailability. Boosters (cobicistat/ritonavir) increased oral bioavailability by 58.7%. Age and dose appeared to affect clearance. Healthy volunteers had higher clearance (30.4% increase) and peripheral volume of

distribution (133% increase) compared to patients with HIV, and female participants were found to have lower clearance (20.4% decrease) compared to male participants. Weight also affected lenacapavir exposures (ranging from approximately −32.3% to +23.5% for subjects at the 5th and 95th weight percentiles, respectively).

Figure 3: PopPK Study CTRA-2021-1054 Sensitivity plot: effect of covariates on lenacapavir AUC over the dosing interval on Days 1 to 15 (Oral Loading Portion) (left figure) and on Day 15 Week 26 (SC Administration) (right figure)



Pharmacodynamics (PD)

Efficacy results analysis

The effect of SC lenacapavir on HIV-1 RNA through Day 10 was dose dependent across the range of 20 mg to 750 mg. The mean maximum reductions in HIV-1 RNA from baseline through Day 10 following single SC doses of 20 mg, 50 mg, 150 mg, 450 mg and 750 mg doses of lenacapavir suspension were −1.35, −1.79, −1.76, −2.20 and −2.26 $\log_{10}$ copies/mL, respectively, whereas the corresponding value for placebo was −0.17 $\log_{10}$ copies/mL. Three participants achieved HIV-1 RNA below 50 copies/mL by Day 10 (1 participant in each of the lenacapavir 50 mg, 450 mg and 750 mg groups). No participant in the other lenacapavir or placebo groups ever achieved HIV-1 RNA below 50 copies/mL by Day 10.

Cardiac safety

Lenacapavir is unlikely to have any clinically significant adverse effects on QTc interval or other electrocardiogram (ECG) parameters following supratherapeutic doses.[10]

Resistance

In treatment-naive subjects, the emergence of treatment resistant mutations was 0.6% in subjects administered either SC or oral lenacapavir. By contrast in a population of Heavily treatment experienced subjects, 11.1% developed treatment resistance through Week 26. Overall, in this population, the most common mutation was M66I, which is associated with a mean decrease in lenacapavir susceptibility of 234-fold, when compared with wild-type.

Maximum effect modelling suggests that mean lenacapavir concentrations of 12.6 ng/mL and higher will provide near maximal (94%) anti-viral activity.

[10] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave on an electrocardiogram. The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

Drug-drug interactions

Lenacapavir is a substrate of P-gp. Oral dosing with 600 mg lenacapavir twice daily inhibits both P-gp and BCRP transporters as well as CYP3A, as co-administration of lenacapavir resulted in 32%, 31% and 259% increases in the AUC_{inf} values for tenofovir alafenamide, rosuvastatin and midazolam, respectively. Lenacapavir did not appear to inhibit OATP transporters.

Co-administration of lenacapavir with the following led to the corresponding changes in lenacapavir AUC_{inf}:

- strong CYP3A4 inhibitor, voriconazole: 41% increase
- strong CYP3A4 and P-gp inhibitor, cobicistat: 128% increase
- strong CYP3A inhibitor and P-gp inducer, darunavir plus cobicistat: 94% increase
- strong CYP3A4, P-gp and UGT1A1 inhibitor, atazanavir plus cobicistat: 321% increase
- strong CYP3A4, P-gp and UGT1A1 inducer, rifampin: 84% decrease
- moderate CYP3A4 and P-gp inducer, efavirenz: 56% decrease.

Co-administration of the acid reducing agent famotidine did not result in clinically significant changes in lenacapavir PK.

Table 3: Study GS-US-200-4333 Effect of oral lenacapavir 600 mg on the pharmacokinetics of co-administered drugs in healthy participants (pharmacokinetic analysis set)

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

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

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

b value is AUC_{last}

Table 4: Study GS-US-200-4333 Effect of co-administered drugs on the pharmacokinetics of oral lenacapavir 300 mg in healthy participants (pharmacokinetic analysis set)

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

CYP = cytochrome P450 enzyme; FAM = famotidine; GLSM = geometric least-squares mean; H2RA = histamine 2 receptor antagonist; LEN = lenacapavir; P-gp = P-glycoprotein; PK = pharmacokinetics; UGT = uridine diphosphate glucuronosyltransferase

a Famotidine was administered 2 hours before LEN

Dose finding

Dose selection for the pivotal study was supported by results from following studies:

- PK and safety data from the Phase Ib proof-of-concept study (GS-US-200-4072) in treatment-naive and treatment-experienced but capsid inhibitor-naive people with HIV
- PK and safety data from the 2 Phase I studies in healthy participants (Studies GS-US-200-4538 and GS-US-200-4071).

Dosing

In the main 2 efficacy studies in the dossier, the selected dosing regimen consisted of a 14-day oral lead-in period (oral lenacapavir 600 mg on Days 1 and 2, oral lenacapavir 300 mg on Day 8), followed by SC lenacapavir injection 927 mg on Day 15 and every 26 weeks.

The sponsor states that this regimen was mainly to enable assessment of the contribution of lenacapavir to the efficacy of an otherwise failing regimen, and an assessment of safety and tolerability of lenacapavir prior to administration of SC lenacapavir injection.

However, the sponsor proposes a simplified dosing regimen which differs from the clinical trial 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 26 weeks.

The sponsor claims that that population PK model simulations showed that this simplified regimen yielded a comparable lenacapavir PK profile to that of the Phase II and II/III dosing regimen, and that a 4-week dosing window around the injection time (26 ± 2 weeks since the last dose) is appropriate.

Efficacy

The efficacy and safety of Sunlenca is mainly assessed from data from pivotal Phase III Study GS-US-200-4625 (CAPELLA). This study evaluated Sunlenca in the target population, heavily

treatment experienced adults with HIV aged 18 years and older with multidrug resistance (MDR).

Additional supportive data are also provided from supportive study GS-US-200-4334. This study evaluated Sunlenca in a population of treatment-naive people with HIV.

Pivotal Phase III Study GS-US-200-4625 (CAPELLA)

Design

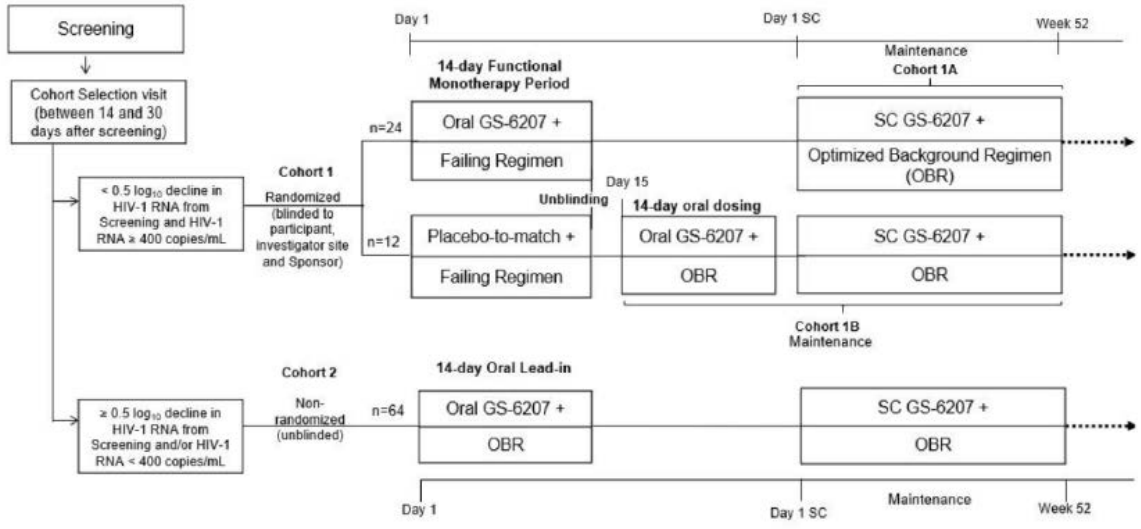
A pivotal, ongoing, Phase II/III, randomised, double-blind (Functional Monotherapy Period only) or open-label, multi-centre (31 centres in 9 countries (26 week report) or 42 centres in 11 countries (52 week report)), parallel-group, placebo-controlled study to assess the anti-viral activity, efficacy and safety of lenacapavir with an optimised background regimen (OBR) in 72 adults with HIV aged 18 years and older with MDR (to at least 2 antiretroviral [ARV] medications from each of at least 3 of the 4 main classes) who are failing their current regimen (defined as plasma HIV-1 RNA of 400 copies/mL and higher).

The duration of the study and treatment is at least 54 weeks with the option to continue and receive SC lenacapavir every 26 weeks with study visits at Weeks 62, 78, 88, 104, 114 and 130.

The study period was from 21 November 2019 (first participant screened) to 28 September 2021 (date of last visit at Week 52 for last-enrolled participant). The study is ongoing.

The primary objective was to evaluate the anti-viral activity of lenacapavir (lenacapavir; GS-6207) administered as an add-on to a failing regimen (functional monotherapy) for people with HIV with multidrug resistance. The secondary objective was to evaluate the safety and efficacy of lenacapavir in combination with an OBR at Weeks 26 and 52.

Figure 4: Study GS-US-200-4625 (CAPELLA) Study design schema



GS-6207 = lenacapavir; OBR = optimized background regimen; SC = subcutaneous
Eligible participants were enrolled into Cohort 2 if Cohort 1 was fully enrolled.

Key inclusion criteria

- Age 18 years and older (all sites) or aged 12 years and older and at least 35 kg (North America and Dominican Republic).
- Receiving a stable failing ARV regimen for more than 8 weeks before screening and willing to continue the regimen until Day 1 (or a failing regimen until Day 14 for Cohort 1).
- HIV-1 RNA of 400 copies/mL or higher at screening.

- Resistance to at least 2 ARVs from each of at least 3 of the 4 main classes (resistance to emtricitabine or lamivudine with the M184V/I mutation not eligible).
- Had 2 or less fully active ARVs remaining from the 4 main classes.

Key exclusion criteria

- Within 30 days prior to screening: opportunistic illness requiring acute therapy; active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungals; active tuberculosis; acute hepatitis.
- Untreated or newly treated (less than 3 months prior to screening) HBV infection.
- HCV antibody positive and HCV RNA greater than lower limit of quantification.
- History of or current clinical decompensated liver cirrhosis.
- Concomitant (or within 3 months prior to screening) immunosuppressant therapies, hydroxyurea, foscarnet, radiation, or cytotoxic chemotherapeutic agents without prior approval.
- Active malignancy requiring acute therapy (except local cutaneous Kaposi's sarcoma).
- Clinically significant abnormal ECG at screening.
- Laboratory values at screening: estimated glomerular filtration rate (eGFR) below or equal to 50 mL/min; alanine aminotransferase (ALT) more than 5-fold upper level of normal; direct bilirubin more than 1.5-fold upper level of normal; platelets below 50,000/mm^3; haemoglobin below 8.0 g/dL (4.96 mmol/L).

Randomisation

Randomisation was conducted using an interactive web response system on the day of the screening visit. The details of the randomisation method are not entirely clear and may have involved block randomisation rather than simple randomisation.

Treatment assignments were blinded to the sponsor, participants, investigators, and study staff. Functional monotherapy of lenacapavir was assessed while participants continued their failing regimen. After each participant completed the Functional Monotherapy Period, the participant's treatment assignment was unblinded.

Treatments

Cohort 1: Eligible participants with a less than 0.5 $\log_{10}$ HIV-1 RNA decline compared with the screening visit and HIV-1 RNA of 400 copies/mL or higher at the cohort-selection visit were randomised in a 2:1 ratio into Cohort 1A or Cohort 1B.

Cohort 2: Participants were enrolled into Cohort 2, if Cohort 1 had been fully enrolled or if they did not meet the criteria for Cohort 1 (that is, HIV-1 RNA decline of 0.5 $\log_{10}$ copies/mL or more compared with the screening visit or HIV-1 RNA less than 400 copies/mL at the cohort-selection visit).

Treatments for each cohort are shown below.

Table 5: Study GS-US-200-4623 (CAPELLA) Treatment by cohort

	Cohort 1A (n = 24†)	Cohort 1B (n = 12†)	Cohort 2 (n = 36†)
Functional Monotherapy Period	Oral lenacapavir 600 mg on Days 1 and 2 and 300 mg on Day 8 + failing regimen	Placebo on Days 1, 2, and 8 + failing regimen	---
Oral Lead-in Period	---	---	Oral lenacapavir 600 mg on Days 1 and 2 and 300 mg on Day 8 + OBR
Maintenance Period	---	Oral lenacapavir 600 mg on Days 15 and 16 and 300 mg on Day 22	---
	SC lenacapavir injection 927 mg on Day 1* SC and every 6 months (26 weeks) thereafter + OBR	SC lenacapavir injection 927 mg on Day 1* SC and every 6 months (26 weeks) thereafter + OBR	SC lenacapavir injection 927 mg on Day 1 SC* and every 6 months (26 weeks) thereafter + OBR

Abbreviations: n = number of participants; OBR = optimised background regimen; SC = subcutaneous.

*SC Day 1 was 14 days after the first dose of oral lenacapavir

†Planned numbers

Participants were to be treated for at least 54 weeks and, if successful, given the option to continue with the treatment of SC lenacapavir 927 mg every 6 months (26 weeks) while continuing their OBR.

Baseline characteristics

In Cohort 1, demographic baseline characteristics were generally similar between the lenacapavir and placebo groups. The majority of participants were male (72.2%), White (45.7%) or Black (45.7%). The median age was 54 years (range: 24-71 years).

The baseline disease characteristics were generally consistent with the profile of the heavily treatment experienced population, with a median number of prior ARV medications of 9 (range: 2-24), and 75% of participants with CD4 cell count less than 200 cells/µL.

There were some differences observed between the lenacapavir and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage, with the patients assigned to placebo typically having less favorable disease markers on average.

The most common prior ARV medications were as follows: INSTI (97.2%), NRTI (94.4%), NNRTI (88.9%), and protease inhibitors (83.3%). Known resistance proportions to 2 or more drug classes were: NRTI (97.2%), NNRTI (94.4%), protease inhibitors (77.8%), and INSTI (75.0%).

The median number of ARVs in the failing regimen was 3 (range: 1 to 7). The median number of ARVs in the OBR was 4 (range: 2 to 7). Six of 36 (16.7%) participants continued their failing regimens as OBRs. The proportion of patients by the number of fully active agents OBR agents were: 16.7% (no fully active agent), 38.9% (1 fully active ARV agent), 25.0% (2 fully active ARV agents), and 19.4% (3 or more fully active ARV agents).

In Cohort 2, the majority of participants were male (77.8%), White (36.1%) or Asian (33.3%), and not Hispanic or Latino (86.1%). The median age was 49 years (range: 23-78 years).

The baseline disease characteristics, prior ARVs, and resistance characteristics for Cohort 2 were generally consistent with the profile of the heavily treatment experienced population.

Magnitude of the treatment effect and its clinical significance

Primary endpoint

The proportion of participants in Cohort 1 achieving 0.5 log_{10} copies/ml or greater reduction from baseline in HIV-1 RNA at the end of Functional Monotherapy Period is shown below.

Table 6: Study GS-US-200-4625 (CAPELLA) Primary endpoint results

	Cohort 1		**Lenacapavir versus Placebo**	
	Lenacapavir (N = 24)	Placebo (N = 12)	P value	Proportional Difference (95% CI)
Number and proportion of participants achieving a reduction in HIV-1 RNA of at least 0.5 log_{10} copies/mL from baseline	21 (87.5%)	2 (16.7%)	<0.0001	71.8% (34.9% to 90.0%)

Primary endpoint sensitivity analyses

Due to lower baseline HIV-1 RNA levels in the lenacapavir group compared to placebo, a post-hoc analysis of the primary efficacy endpoint with adjustment for baseline HIV-1 RNA (using rank analysis of covariance) had the following result: 87.5% versus 16.7%, p = 0.0003.

To address a baseline CD4 cell count imbalance, post-hoc analyses in participants with comparable or clinically relevant CD4 cell counts retained a statistically significant difference between groups:

- Participants with the 12 lowest baseline CD4 cell count counts in each group (median 98.5 cells/µL (lenacapavir) and 84.5 cells/µL (placebo)): 83.3% (10 of 12 participants) versus 16.7% (2 of 12 participants); treatment difference: 66.7%; 95% confidence interval (CI) 25.2%, 90.5%; p = 0.0008.
- Baseline CD4 cell count under 200 cells/µL: 87.5% (14 of 16 participants) versus 9.1 (1 of 11 participants); treatment difference: 78.4% (95% CI: 39%, 95%; p < 0.0001.

Primary endpoint per protocol analysis set results

Primary endpoint per protocol results were similar compared to the full analysis set: 87.5% (21 of 24 participants) versus 9.1% (1 of 11 participants); treatment difference: 78.4% (95% CI: 44.6%, 93.9%; p < 0.0001).

Secondary endpoints

The secondary endpoint was the proportion of participants in Cohort 1 with plasma HIV-1 RNA under 50 copies/mL and under 200 copies/mL at Week 26 and Week 52 of treatment, based on the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm.[11]

[11] Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry (fda.gov)

At Week 26, the proportions of participants in Cohort 1 with HIV-1 RNA under 50 copies/mL and under 200 copies/mL were 80.6% (29 of 36 participants) and 88.9% (32 of 36 participants), respectively (Table 7)

At Week 52, the proportions of participants in Cohort 1 with HIV-1 RNA under 50 copies/mL and under 200 copies/mL were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively (Table 8).

Table 7: Study GS-US-200-4625 (CAPELLA) Main secondary endpoint results at Week 26

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 6)	Total (N = 42)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	8 (66.7%)	29 (80.6%)	4 (66.7%)	33 (78.6%)
95% CI	67.6% to 97.3%	34.9% to 90.1%	64.0% to 91.8%	22.3% to 95.7%	63.2% to 89.7%
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	23 (95.8%)	9 (75.0%)	32 (88.9%)	4 (66.7%)	36 (85.7%)
95% CI	78.9% to 99.9%	42.8% to 94.5%	73.9% to 96.9%	22.3% to 95.7%	71.5% to 94.6%

Table 8: Study GS-US-200-4625 (CAPELLA) Main secondary endpoint results at Week 52

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 9)	Total (N = 45)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	9 (75.0%)	30 (83.3%)	5 (55.6%)	35 (77.8%)
95% CI	67.6% to 97.3%	42.8% to 94.5%	67.2% to 93.6%	21.2% to 86.3%	62.9% to 88.8%
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	22 (91.7%)	9 (75.0%)	31 (86.1%)	6 (66.7%)	37 (82.2%)
95% CI	73.0% to 99.0%	42.8% to 94.5%	70.5% to 95.3%	29.9% to 92.5%	67.9% to 92.0%

Subgroup analyses

The proportion of participants with HIV 1 RNA under 50 copies/mL at Week 26 using the US FDA-defined snapshot algorithm based on the full analysis set was numerically higher in participants aged under 50 years, in female patients, patients with baseline CD4 cell count of 200 cells/µL or more, and patients with baseline viral load of 100,000 copies/mL or less.

At Week 52, the proportion was numerically higher in patients that were female, non-black, and patients with baseline CD4 cell count of 200 cells/µL or more, and patients with baseline viral load of 100,000 copies/mL or less.

Study GS-US-200-4334 (CALIBRATE)

Design

Study GS-US-200-4334 is a Phase II, ongoing, randomised, open-label, multi-centre (41 centres in 2 countries), parallel-group, active-controlled study to assess the efficacy and safety of

GS-6207 (lenacapavir) in combination with other retroviral agents in 182 adult treatment-naïve people with HIV aged 18 years and older.

Treatment-naive people with HIV who met all eligibility criteria were randomised in a 2:2:2:1 ratio to 1 of the 4 treatment groups (Figure 4). Randomisation was stratified by HIV-1 RNA level (100,000 copies/mL and less, or over 100,000 copies/mL) at screening.

The study was conducted from 22 November 2019 to 26 March 2021 (last patient observation for interim report).

The primary objective was to evaluate efficacy of lenacapavir-containing regimens in people with HIV determined by proportion of participants with HIV-1 RNA less than 50 copies/mL at Week 54.

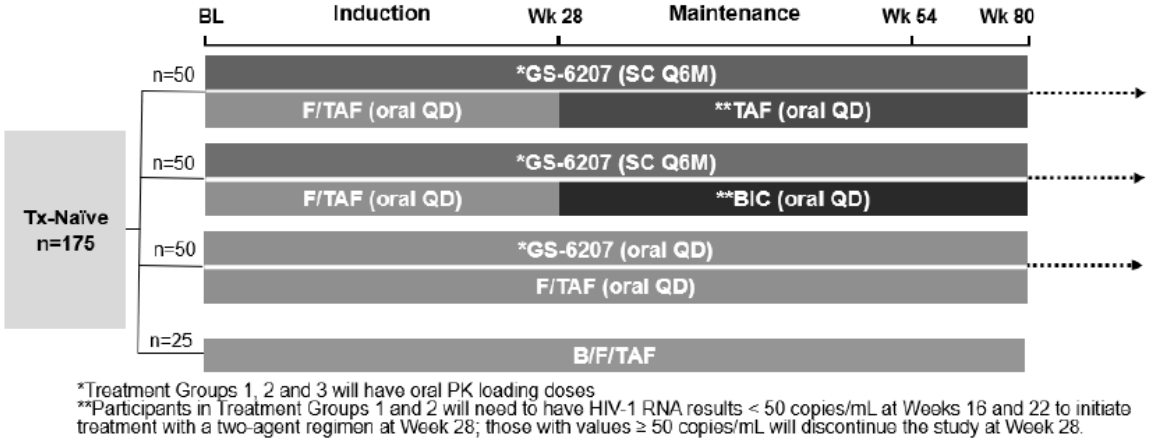
Key inclusion criteria

- Age 18 years and older
- ARV naïve
- plasma HIV-1 RNA of 200 copies/mL and greater
- plasma CD4 cell count of 200 cells/μL and greater
- negative serum pregnancy test.

Key exclusion criteria

- Opportunistic illness requiring acute therapy, active serious infections, acute hepatitis within 30 days prior to screening
- active tuberculosis
- HBV infection
- HCV antibody positive and HCV RNA greater than lower limit of quantification
- history of or current clinical decompensated liver cirrhosis
- immunosuppressant therapies
- acute therapy for malignancy (except local cutaneous Kaposi sarcoma)
- abnormal ECG or certain laboratory values
- prior lenacapavir use/exposure
- use or planned use of exclusionary medications.

Figure 5: Study GS-US-200-4334 (CALIBRATE) Study design schema



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

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BL = baseline; F/TAF = emtricitabine/tenofovir alafenamide; GS-6207 = lenacapavir; PK = pharmacokinetic(s); Q6M = every 6 months; QD = once daily; SC = subcutaneous; TAF = tenofovir alafenamide; Tx = treatment; Wk x = Week x

Study treatments

The study treatments are summarised in the table below.

Table 9: Study GS-US-200-4334 Study treatments

Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily TAF 25 mg[a]
2	Induction (Day 1 through Week 27)	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and 300 mg (1 × 300-mg tablet) on Day 8 • Oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[a] • SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) on Day 15
	Maintenance (Weeks 28 through 80)	• SC LEN injection 927 mg (309 mg/mL; 2 × 1.5 mL) at Week 28 and every 6 months (26 weeks) thereafter • Oral daily BIC 75 mg[a]
3	Day 1 through Week 80	• Oral LEN 600 mg (2 × 300-mg tablets) on Days 1 and 2 and oral daily LEN 50 mg (1 × 50-mg tablet) from Day 3 onwards • Oral daily DVY (F/TAF 200/25 mg)
4	Day 1 through Week 80	• Oral daily BVY (B/F/TAF 50/200/25 mg)

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir;
BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy);
DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide

a Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28.

All study drugs were administered without regard to food.

Participants were treated for at least 80 weeks. At Week 80, participants in Treatment Group 4 will complete the study. Participants willing to continue the study beyond Week 80 in Treatment Groups 1 and 2 will continue to receive SC lenacapavir 927 mg every 6 months (26 weeks) from Week 80 onwards and participants in Treatment Group 3 will continue to receive oral lenacapavir 50 mg (daily) from Week 80.

The baseline demographic characteristics were similar across the treatment groups. Most patients were male (93.4%) and cisgender (92.3%). Participants included people who were Black (52.2%) and Hispanic (45%). The median age was 29 years (range: 19-72 years).

The baseline disease characteristics were similar across the treatment groups. The median baseline HIV-1 RNA value was 4.37 (first quartile 3.86; third quartile 4.74) $\log_{10}$ copies/mL, and the median baseline CD4 cell count was 437 (first quartile 332; third quartile 599) cells/µL. Most of the 182 patients had HIV-1 RNA of 100,000 copies/mL and less (85.2%) and a CD4 cell count range of at least 350 cells/µL up to 500 cells/µL (31.9%) or 500 cells/µL and above (37.4%).

Of the 249 participants who were screened, 183 were randomised and 182 received at least one dose of study drug. Incidence of premature discontinuation was numerically higher in the SC lenacapavir total group (13.3%; 14 of 105 participants) and oral lenacapavir group (5.8%; 3 of 52 participants) compared to the reference bictegravir/emtricitabine/tenofovir alafenamide group (0%).

Magnitude of the treatment effect and its clinical significance

Endpoints

The primary endpoint was the proportion of patients with HIV-1 RNA less than 50 copies/mL at Week 54 (US FDA-defined snapshot algorithm). The results were similar (and not statistically significantly different) in each treatment group:

- 90.4% SC lenacapavir + [emtricitabine/tenofovir alafenamide → tenofovir alafenamide (see Figure 5)
- 84.9% for SC lenacapavir + [emtricitabine/tenofovir alafenamide → bictegravir]
- 84.6% for Oral lenacapavir + emtricitabine/tenofovir alafenamide
- 92.0% for bictegravir/emtricitabine/tenofovir alafenamide
- 87.6% for SC lenacapavir total
- 86.6% for lenacapavir total.

The secondary endpoints of this study were the proportion of participants with HIV-1 RNA less than 50 copies/mL at Weeks 28, 38, and 80 as determined by the US FDA-defined snapshot algorithm and the change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell count at Weeks 28, 38, 54, and 80. These results were generally supportive of the primary endpoint results.

Table 10: Study GS-US-200-4334 Primary endpoint results: Virology outcome at Week 54 (HIV-1 RNA cut-off at 50 copies/mL, snapshot algorithm) (full analysis set)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (= 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
HIV-1 RNA < 50 copies/mL	47 (90.4%)	45 (84.9%)	44 (84.6%)	23 (92.0%)	92 (87.6%)	136 (86.6%)
HIV-1 RNA ≥ 50 copies/mL	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
HIV-1 RNA ≥ 50 copies/mL in Week 54 Window	0	0	3 (5.8%)	0	0	3 (1.9%)
Discontinued Study Drug Due to Lack of Efficacy	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥ 50 copies/mL	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
No Virologic Data in Week 54 Window	3 (5.8%)	6 (11.3%)	5 (9.6%)	2 (8.0%)	9 (8.6%)	14 (8.9%)
Discontinued Study Drug Due to AE/Death	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	3 (5.8%)	4 (7.5%)	4 (7.7%)	1 (4.0%)	7 (6.7%)	11 (7.0%)
Missing Data During Window but on Study Drug	0	0	1 (1.9%)	1 (4.0%)	0	1 (0.6%)
LEN vs. BVY						
P-value	0.7178	0.3900	0.3797		0.5109	0.4340
Diff in Percentage (95% CI)	−2.6% (−18.4% to 13.2%)	−7.1% (−23.4% to 9.3%)	−7.2% (−23.5% to 9.1%)		−4.7% (−19.2% to 9.7%)	−5.6% (−19.5% to 8.4%)

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); CMH = Cochran-Mantel-Haenszel; Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MH = Mantel-Haenszel; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
The Week 54 window was between Days 323 and 413 (inclusive).
* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
The difference in percentage of participant with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group, and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).
P-value was from the CMH tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

The proportion of patients in the subgroups by age (younger than 50 years, or 50 years and older), sex (male and female), and race (Black and non-Black) with HIV-1 RNA less than 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm were similar to the overall results. However, the small size and imbalance of participant numbers within each subgroup preclude definite conclusions.

Safety

Exposure

Pivotal Study GS-US-200-4625 (CAPELLA): By week 52, a total of 72 Cohort 1 and 2 patients received oral lenacapavir: 72 received SC lenacapavir on Day 1, 70 (Cohort 1 and 2: 36 and 34 patients, respectively) received a second dose at Week 26, and 36 patients (34 and 2 patients) received a third dose at Week 52. The median duration was 484 days (first quartile 411; third quartile 559) and 317 days (first quartile 267; third quartile 352) for Cohorts 1 and 2, respectively.

Study GS-US-200-4334: By Week 54, 89.2% of patients in the lenacapavir total group (140 of 157 participants) and 96.0% in the bictegravir/emtricitabine/tenofovir alafenamide group (24 of 25 participants) had been exposed to study drug for at least 54 weeks.

With regard to exposure of at least 12 months, only approximately 176 patients have been exposed to lenacapavir, and only 36 of these participants were in the actual target population.

There were no paediatric safety (or efficacy) data.

In the Phase I studies, 365 healthy participants received lenacapavir (short-term).

Adverse event overview

Study GS-US-200-4334

The proportion of participants who had any AE by Week 28 was similar in the lenacapavir total (86.6%; 136 of 157 participants) and bictegravir/emtricitabine/tenofovir alafenamide (84.0%; 21 of 25 participants) groups. The percentages of participants with Grade 3 or higher AEs were also similar between the lenacapavir total (7%; 11 of 157 participants) and bictegravir/emtricitabine/tenofovir alafenamide (5.1%; 8 of 25 participants) groups. Serious AEs occurred only in the lenacapavir total group (5.1%, 8 participants), but none were considered related to study drug.

The 3 most commonly reported AEs (reported in at least 5% of participants overall) by treatment group were as follows:

- lenacapavir total (n = 157), excluding ISRs: headache (11.5%), nausea (10.8%), and lymphadenopathy (7.6%)
- SC lenacapavir total (n = 105), only ISRs: injection site swelling (22.9%), injection site erythema (21.0%), and injection site pain (each 21.0%)
- Oral lenacapavir + emtricitabine/tenofovir alafenamide (n = 52): headache (13.5%), nausea, lymphadenopathy, diarrhea, back pain, and urinary tract infection (each 7.7%)
- bictegravir/emtricitabine/tenofovir alafenamide (n = 25): syphilis, insomnia, and weight increased (each 12.0%).

Similar percentages of participants in the lenacapavir total (n = 157) and bictegravir/emtricitabine/tenofovir alafenamide (n = 25) groups had any AE by Week 54 (lenacapavir total 87.9%; bictegravir/emtricitabine/tenofovir alafenamide 84.0%). The percentages of participants with Grade 3 or higher AEs were also similar between the lenacapavir total and bictegravir/emtricitabine/tenofovir alafenamide groups (lenacapavir total 8.3%; bictegravir/emtricitabine/tenofovir alafenamide 8.0%).

Treatment related adverse event (adverse drug reaction) overview

Pivotal Study GS-US-200-4625 (CAPELLA)

Functional Monotherapy Period: For Cohort 1, the percentages of participants who experienced adverse events (AEs) were slightly higher in the lenacapavir group (37.5%; 9 of 24 participants) compared to placebo (25.0%; 3 of 12 participants); see Table 11, which uses MedDRA Preferred Terms.[12]

[12] The Medical Dictionary for Regulatory Activities (MedDRA) is a standardised international medical terminology, developed as a project of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which can be used for regulatory communication and evaluation of data pertaining to medicinal products for human use. As a result, MedDRA is designed for use in the registration, documentation and safety monitoring of medicinal products through all phases of the development cycle (that is, from clinical trials to post-marketing surveillance).
'Preferred Terms' are single concepts for symptoms, signs, disease diagnoses, therapeutic indications, investigations, surgical or medical procedures, and medical, social or family history characteristics. There are over 20,000 Preferred Terms.

Table 11: Study GS-US-200-4625 (CAPELLA) Cohort 1 treatment-emergent adverse events by preferred term in at least 5% of participants (Functional Monotherapy Period) (safety analysis set)

	LEN (N = 24)	Placebo (N = 12)
Number (%) of Participants With Any Treatment-Emergent Adverse Event	9 (37.5%)	3 (25.0%)
Nausea	3 (12.5%)	0
Diarrhoea	1 (4.2%)	1 (8.3%)
Abscess limb	0	1 (8.3%)
Neck pain	0	1 (8.3%)
Thrombocytopenia	0	1 (8.3%)
Vomiting	0	1 (8.3%)

Week 26 analysis

- The majority (91.7%; 66 of 72) of patients who received lenacapavir in Cohorts 1 and 2 experienced AEs.
- Adverse events (most Grade 1 or 2)[13] reported in at least 5% of participants were all injection site reactions (ISRs) including injection site swelling (29.2%; 21 of 72), injection site erythema (26.4%; 19 of 72) and injection site pain (25.0%; 18 of 72).
- Grade 3 or higher AEs were experienced by 13.9% in Cohort 1 and 22.2% in Cohort 2.

Week 52 analysis

- The majority (93.1%; 67 of 72) of patients who received lenacapavir in Cohorts 1 and 2 experienced at least one AE. Three additional patients had Grade 3 or higher AEs and 16 new terms of Grade 3 or higher AEs were reported.
- The most common treatment-emergent adverse events (TEAEs) reported were ISRs including injection site pain (37.5%), swelling (33.3%), erythema (27.8%) and nodule (25.0%). Typically, ISRs occurred most after the first SC dose and less following the second and third SC doses at Week 26 and 52.

Pivotal Study GS-US-200-4625 (CAPELLA)

Functional Monotherapy Period

The proportion of participants with treatment-related AEs was higher in the lenacapavir group (16.7%, 4 of 24 participants) compared to placebo (8.3%, 1 of 12 participants).

Week 26 analysis

- Of the 91.7% (66 of 72 participants) who experienced treatment-related AEs, ISRs was reported most commonly.
- Three patients had Grade 3 ISRs attributed to enfuvirtide. Four patients had Grade 3 or higher AEs considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and hepatic function abnormal (1 participant each).

[13] Severity grades were defined by the US National Institutes of Health Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017). In general: Grade 1 = mild event; Grade 2 = moderate event; Grade 3 = severe event; Grade 4 = potentially life-threatening event; Grade 5 = death.

Week 52 analysis

- Two-thirds (66.7%; 48 of 72 participants) experienced treatment-related AEs (lower than at Week 26 due to reduction in ISRs with time). The most common events were injection site pain and injection site swelling (30.6%), injection site erythema (25.0%), and injection site nodule (23.6%).

Study GS-US-200-4334

Week 54 analysis

Adverse events related to the study drug occurred more frequently in the SC lenacapavir total group (compared to Oral lenacapavir + emtricitabine/tenofovir alafenamide; or bictegravir/emtricitabine/tenofovir alafenamide) and consisted mainly of ISRs (SC lenacapavir total 58.1% [61 of 105 participants], Oral lenacapavir + emtricitabine/tenofovir alafenamide 15.4% [8 of 52 participants], and bictegravir/emtricitabine/tenofovir alafenamide 16.0% [4 of 25 participants]). For lenacapavir total, 34.4% (54 of 157 participants) had treatment-related AEs.

In the SC lenacapavir group, 44.8% of participants (47 of 105) had treatment-related AEs, mainly due to ISRs including injection site swelling (18.1%; 19 of 105), erythema (16.2%; 17 of 105), and pain (15.2%; 16 of 105). Treatment-related AEs excluding ISRs included nausea (4.5%; 7 of 157), diarrhoea (2.5%; 4 of 157), fatigue, and headache (each 1.9%; 3 of 157).

Treatment-related AEs in the Oral lenacapavir + emtricitabine/tenofovir alafenamide (13.5%; 7 of 52 participants) included nausea (3.8%; 2 of 52), diarrhoea (3.8%; 2 of 52), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, overdose, and hot flush (each 1.9%; one patient).

With the exception of one patient (1.0%; 1 of 105 participants) in the SC lenacapavir total group with a Grade 3 AE related to study drug (injection site nodule), none of these events were Grade 3 or higher.

Deaths

Pivotal Study GS-US-200-4625 (CAPELLA)

Functional Monotherapy Period

No death was reported in either the lenacapavir or placebo group.

Week 26 analysis

One patient in Cohort 2 died during in the study, experiencing an AE of cancer, which was considered not related to the study drug.

Week 52 analysis

There were no additional deaths beyond Week 26.

Study GS-US-200-4334

No death was reported in this study.

Serious adverse events

Pivotal Study GS-US-200-4625 (CAPELLA)

Functional Monotherapy Period

No serious adverse events (SAEs) or AEs leading to discontinuation of study drug, or Grade 3 or higher AEs, were reported in either the lenacapavir or placebo group.

Week 26 analysis

Four patients (5.6%) (2 in each cohort) experienced SAEs. None of the SAEs were reported in more than 1 patient and all SAEs were considered not related to study drug.

Week 52 analysis

Four additional participants experienced SAEs: 2 with COVID-19; 1 with septic shock, renal impairment, shock; 1 with pneumonia. Two patients who previously experienced SAEs experienced additional SAEs of anal squamous cell carcinoma, impaired healing, anal cancer (1 patient), and angina pectoris (1 patient).

Study GS-US-200-4334

By Week 28, SAEs occurred in 5.1% of participants (8 of 157) (lenacapavir total) group and no patient in the bictegravir/emtricitabine/tenofovir alafenamide group. None were considered related to the study drugs. By Week 52, SAEs had occurred in 6.4% of participants (10 of 157). None were considered related to the study drugs.

Discontinuations

Pivotal Study GS-US-200-4625 (CAPELLA)

There were no discontinuations due to AEs in the Functional Monotherapy Period or by Week 26. One patient (1.4%) discontinued the study drug due to an AE after Week 26.

Study GS-US-200-4334

Adverse events that led to a premature discontinuation of the study drug occurred in 3 participants (2.9%) in the SC lenacapavir total group and no participants in the other treatment groups.

Adverse events of special interest

Liver function and liver toxicity: There were no clinically relevant changes from baseline in ALT, aspartate aminotransferase (AST) or alkaline phosphatase. In study GS-US-200-4334, Grade 3 or higher laboratory abnormalities in the lenacapavir total group included high ALT (1.3%; 2 of 157 participants), high AST (2.5%; 4 of 157 participants) and hyperbilirubinemia (0.6%; 1 of 157 participants). For all participants, Grade 3 or higher laboratory abnormalities either improved or returned to normal.

In CAPELLA, one participant (2.8%) experienced a Grade 3 increase in ALT and a Grade 4 increase in AST, reported as an AE of immune reconstitution inflammatory syndrome (IRIS), even though potentially related to HBV infection.

Renal function and renal toxicity: There were no clinically relevant changes in serum creatinine and eGFR. In CAPELLA: Grade 3 increased creatinine (6.9%; 5 of 72 participants), Grade 3 low creatinine clearance or eGFR (9.7%; 9 of 72) and Grade 4 increased creatinine (1.4%; 1 of 72) either improved or returned to normal for most patients. In GS-US-200-4334, the following occurred: Grade 3 high creatinine in 1.9% (3 of 157 participants) and 4% (1 of 25 participants)

in the lenacapavir total and bictegravir/emtricitabine/tenofovir alafenamide groups, respectively; low creatinine clearance or eGFR in 3.8% (6 of 157 participants) and 8% (2 of 25), in the lenacapavir total and bictegravir/emtricitabine/tenofovir alafenamide groups, respectively.

Haematology and haematological toxicity: No clinically relevant changes were reported.

Electrocardiograph findings and cardiovascular safety: No clinically relevant changes in ECG were reported.

Immunogenicity and immunological events: No AEs matching Preferred Terms in a relevant Standardised MedDRA Query were SAEs and none resulted in study drug discontinuation.

Serious skin reactions: Mild rash and injections site reactions were reported, but there were no reports of any serious skin reactions.

Other clinical chemistry: Most participants in the Functional Monotherapy Period of CAPELLA, 75.0% (18 of 24 participants) (lenacapavir) and 75.0% (9 of 12 participants) (placebo) had at least one graded laboratory abnormality (most were Grade 1 or 2). Grade 3 abnormalities occurred in 12.5% in the lenacapavir group (increased creatinine, hyperglycaemia [non-fasting], and increased lipase) and in 0% for placebo. No Grade 4 abnormalities occurred. In the Week 26 and Week 52 analyses, 91.7% (66 of 72 participants) and 97.2% (70 of 72) had at least one graded laboratory abnormality (most were Grade 1 or 2).

None of the abnormalities were considered clinically relevant. All were transient, improved on subsequent visits despite continued study drug exposure, or patients had underlying conditions such as diabetes. No Grade 3 or higher increase in creatine kinase or creatine kinase-associated AEs such as rhabdomyolysis occurred.

Study GS-US-200-4334 showed a similar pattern, but in the Phase I Study GS-US-200-4329, there was one creatine kinase Grade 4 event in an intravenous lenacapavir group participant who had a rhabdomyolysis SAE considered related to study drug.

Resistance

In CAPELLA, 29% of patients (21 of 72) met the criteria for resistance analyses through Week 52 (HIV-1 RNA at least 50 copies/mL at confirmed virologic failure [suboptimal virologic response at Week 4, virologic rebound, or viraemia at last visit]). These patients were analysed for lenacapavir-associated mutation emergence:

- 11.1% (8 of 72) had lenacapavir-associated capsid mutations
- 8.3% (6 of 72) had a M66I capsid mutation (alone or in combination with other lenacapavir-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 capsid.

There were no emergent resistance mutations to components of the OBR.

In Study GS-US-200-4334 until Week 54, 1.3% of participants (2 of 157) who received oral or SC lenacapavir had lenacapavir-associated mutation (Q67H, Q67H + K70R), but the much lower proportion compared to CAPELLA is likely due to the treatment-naive population.

Safety in special populations

Age, sex, ethnicity: In CAPELLA, TEAEs in the All Lenacapavir Analysis was not affected by age (under 50 years; 50 years and older), sex, race (Black and non-Black) and region (US and non-US), but the interpretation was limited by small sample sizes in some subgroups.

Pregnancy and lactation: Pregnant and lactating women were excluded from all lenacapavir clinical studies. Animal studies do not indicate direct or indirect harmful effects with regard to pregnancy, embryonal and fetal development, parturition, or postnatal development. No pregnancies were reported in the submitted studies. Safety of lenacapavir in lactating women has not been evaluated.

Safety related to drug-drug interactions and other interactions

Hormonal contraceptives: No formal drug-drug interaction (DDI) studies between lenacapavir and hormonal contraceptives have been conducted.

Safety in DDI in Study GS-US-200-4333: The study investigated some potential lenacapavir DDIs using a wide range of probe drugs. Most of the AEs, across all treatment cohorts, were Grade 1 or Grade 2 in severity and no Grade 4 AEs were reported. Grade 3 AEs were experienced by:

- 1 participant (3%) who was administered rosuvastatin+lenacapavir in Cohort 11 (AE of transaminases increased, considered related to lenacapavir; this participant had a Grade 1 laboratory abnormality of ALT increased prior to receiving lenacapavir)
- 8 participants (32%) receiving atazanavir/ cobicistat in Cohort 7 and 5 participants (20%) receiving atazanavir/ cobicistat + lenacapavir in Cohort 7. Most of the Grade 3 AEs in Cohort 7 were hyperbilirubinemia and were considered to be related to atazanavir/cobicistat.

Eight participants had AEs that led to premature discontinuation of study drug (3 permanently), of which only one AE was considered related to lenacapavir treatment (Grade 3 AE of transaminases increased); the other 7 participants had AEs that were either related to study drugs other than lenacapavir or not related to any study drug. No SAEs or deaths were reported during the study.

Post marketing experience

No data available.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are presented in Table 12. The TGA may request an updated risk management plan (RMP) at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 12: Summary of safety concerns

Safety concern		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	*Nil*				
Important potential risks	Viral resistance due to unintended monotherapy	ü	-	ü	-
Missing information	Long-term safety information	ü	ü†	-	-

Safety concern		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
	Safety in pregnancy and lactation	ü*	ü‡	ü	-
	Safety in patients less than 18 years of age	ü	ü§	ü	-

*Follow-up questionnaire (Australia-specific annex (ASA) only)

† Studies GS-US-200-4625 and GS-US-200-4334

‡ Antiretroviral pregnancy registry

§ Planned Study GS-US-563-5958

The safety specification is satisfactory from an RMP perspective. Routine and additional pharmacovigilance activities are proposed.

Routine pharmacovigilance activities include a follow-up questionnaire for pregnancy (ASA only). Additional pharmacovigilance activities include 2 studies (GS-US-200-4625 and GS-US-200-4334) that will provide information regarding long term safety and a planned study (GS-US-563-5958) that will provide further information regarding safety in patients 18 years and younger. In addition, there is an antiretroviral pregnancy register. This is acceptable.

Routine risk minimisation activities only are proposed. This is acceptable as patients will be under specialist supervision, the dosing and administration is uncomplicated and the side effects manageable with routine risk minimisation activities.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

Risk-benefit analysis

Delegate's considerations

Efficacy

In CAPELLA, lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in heavily treatment experienced people with HIV.

With regard to the primary endpoint, the proportion of participants in Cohort 1 achieving at least 0.5 $\log_{10}$ copies/ml reduction from baseline in HIV-1 RNA at the end of Functional Monotherapy Period was 87.5% (lenacapavir) versus 16.7% (placebo) ($p < 0.0001$).

Efficacy was also observed in patients with a potentially suboptimal OBR (for example, low overall susceptibility score, nil or one fully active agent, INSTI resistance, no dolutegravir or darunavir) indicating a clinically meaningful contribution of lenacapavir.

The secondary endpoint results were generally consistent with the primary endpoint showing clinically meaningful improvements in CD4 cell counts and reductions in viral load. At Week 26, the proportion of participants in Cohort 1 with HIV-1 RNA less than 50 copies/mL and less than

200 copies/mL were 80.6% (29 of 36 participants) and 88.9% (32 of 36 participants), respectively. At Week 52, the proportion of participants in Cohort 1 with HIV-1 RNA less than 50 copies/mL and less than 200 copies/mL were 83.3% (30 of 36 participants) and 86.1% (31 of 36 participants), respectively. Efficacy data beyond Week 52 are not available.

The results were generally robust and consistent in the primary full analysis set and in the sensitivity analyses.

Lenacapavir showed anti-viral activity in heavily treatment experienced patients with MDR with no current evidence for cross-resistance.

Supportive evidence of efficacy was provided by the ongoing Study GS-US-200-4334 in adult treatment-naive people with HIV, that is, not conducted in the target population for the proposed indication.

The validity of the rather favourable results from the trial program (in particular the efficacy results in the ongoing CAPELLA trial) has to be carefully considered due to quite a number of limitations outlined further below.

Safety

From the available data, the overall safety profile of lenacapavir appears favourable, but the total number of exposed patients (in particular in the target population) and the total exposure time is rather small. Based on this, uncommon adverse reactions are unlikely to emerge.

Lenacapavir is a first-in-class new chemical entity and there is no experience with other products in this class that may be able to inform the safety profile.

The most common AEs reported in the lenacapavir-treated patients were injection site reactions (ISRs) including injection site pain, swelling, erythema and nodule. The incidence reported ISRs was highest after the first SC dose and lower following the second and third SC doses at Week 26 and 52.

Common non-ISR AEs were headache, nausea and lymphadenopathy. In CAPELLA, 37.5% versus 25% of patients had a TEAE in the placebo-controlled phase. Nausea was reported by 12.5% (3 of 24 participants, compared to none on placebo. It may be assumed that this is in relation to the oral formulation and may not be applicable to the SC formulation, but in the supportive Study GS-US-200-4334 nausea occurred in 14.3% (SC lenacapavir) versus 10.8% (lenacapavir total) versus 4% (bictegravir/emtricitabine/tenofovir alafenamide).

One participant (2.8%) experienced a Grade 3 increase in ALT and a Grade 4 increase in AST, reported as an AE of immune reconstitution inflammatory syndrome (IRIS), even though potentially related to HBV infection.

In the Phase I Study GS-US-200-4329, there was one creatine kinase Grade 4 event in an intravenous lenacapavir group participant who had a rhabdomyolysis SAE considered related to study drug by the sponsor.

The safety profile of lenacapavir, and in particular the TEAEs of unclear aetiology need to be monitored with pharmacovigilance activities and reported in periodic safety update reports.

Routine pharmacovigilance activities include a follow-up questionnaire for pregnancy. Additional pharmacovigilance activities include the 2 efficacy studies (GS-US-200-4625 (CAPELLA) and GS-US-200-4334) that will provide information regarding long term safety, a planned study (GS-US-563-5958) that will provide further information regarding safety in patients aged 18 years and younger, and an antiretroviral pregnancy register.

Resistance

In CAPELLA, 29% (21 of 72) of patients met the criteria for resistance analyses: 11.1% (8 of 72) had lenacapavir-associated capsid mutations. Of these, 8.3 % (6 of 72) had a M66I CA mutation (alone or in combination with other lenacapavir-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. There were no emergent resistance mutations to components of the OBR.

In Study GS-US-200-4334 until Week 54, 1.3% (2 of 157) of participants who received oral or SC lenacapavir had lenacapavir-associated mutation (Q67H, Q67H + K70R), but the much lower proportion compared to CAPELLA is likely due to the treatment-naive population.

Clinical practice and patient considerations

A simple dosing regimen is more likely to facilitate compliance. A 6-monthly regimen compared to daily dosing may contribute to this.

Sunlenca, if registered, would provide an additional option in the armamentarium to treat people with HIV who have a multidrug resistant HIV-1 infection.

Deficiencies of the data

The validity of the rather favourable results from the trial program (in particular the efficacy results in the ongoing CAPELLA trial) has to be carefully considered due to quite a number of limitations.

Single pivotal trial: The clinical trial program only consisted of one study in the target population, namely the pivotal CAPELLA trial in people with HIV aged 18 years and older with multidrug resistance infection. A second study in the target population would have been advantageous.

Target population: Only the CAPELLA study enrolled patients in the target population. Given the different baseline characteristics of ART-naive people with HIV in Study GS-US-200-4334, the efficacy data are only supportive. The same applies to the safety data observed in ART-naive people with HIV in study GS-US-200-4334 and pooled studies GS-US-200-4538 and GS-US-200-5709 in healthy subjects, as these studies were not conducted in the target patient population.

Sample size: A larger sample size in the pivotal trial would have been advantageous, especially given potential imbalances in the cohorts (for example, with regard to baseline disease characteristics) which may have introduced biases, even though the relevant post-hoc analyses did not provide evidence for this.

The total number of exposed patients (in particular in the target population) and the total exposure time was rather small. Based on this, uncommon adverse reactions are unlikely to emerge. No clinically meaningful conclusions can be made with regard to safety in certain subgroups or certain special populations.

It is noted that the final clinical study reports for Studies GS-US-200-4625 (CAPELLA) and GS-US-200-4334 will contain a safety-exposure analysis, for example, to assess safety in patients with moderate to severe renal and hepatic impairment.

Ongoing trials and longer-term efficacy and safety: The pivotal and the supportive studies are still ongoing. Only Week 52 and Week 54 results, respectively, were available in the dossier. Longer-term data would be useful to determine whether the favourable efficacy is sustained, and to add data to the safety database.

Paediatric population: No paediatric data were submitted in the current dossier. No patients under the age of 18 years were part of the clinical studies (including the clinical pharmacology studies), even though CAPELLA allowed patients aged 12 years and above, but no participant aged 12 to 17 years was enrolled.

There is an agreed Paediatric Investigation Plan for the EMA (referenced in the RMP submitted in Australia) which includes:

- the development of an oral formulation for use in patients from 2 years to less than 12 years
- a dedicated clinical study (GS-US-563-5958) in patients from 2 years to less than 18 years of age with HIV infection, who are virologically suppressed
- the development of a population pharmacokinetics model in the adult population to predict lenacapavir exposures in heavily treatment experienced people with HIV, and in virologically suppressed paediatric subjects from 2 years to less than 18 years of age to support lenacapavir paediatric dosing
- an analysis of similarity in exposure-response relationship to support the extrapolation of efficacy of lenacapavir in children and adolescents from 6 years to less than 18 years of age.

The popPK study CTRA-2021-1054 undertook simulations of lenacapavir exposure in patients aged 12 years up to 18 years and weighing at least 35 kg, and concluded that the simulated paediatric exposures were sufficiently similar to corresponding adult exposures. The popPK source studies did not contain any clinical paediatric PK data, and the results could not have been compared to actual PK data. The simulations appear to have used the American National Health and Nutrition Examination Survey (NHANES) data, but it is not clear which variables were used to inform the simulation (for example, weight).

No specific justification for the proposed paediatric indication has been provided other than a justification based on the popPK study results. It appears that factors other than simulated PK results were not considered. No clinical efficacy or safety data (including developmental data) are available.

Patients aged 65 years or older: Only limited clinical data are available and conclusions on a potential age-related risk of adverse events cannot be made at this stage.

Pregnant/lactating women: No clinical data are available.

Other: Data on co-infection status (for example, with HCV) appear not to have been captured. No formal drug-drug interaction studies with hormonal contraceptives have been conducted. No formal clinical studies for withdrawal or rebound effects of lenacapavir were conducted. The effect of lenacapavir on ability to drive/operate machinery has not been evaluated.

Proposed action

Lenacapavir has demonstrated efficacy in heavily treatment experienced people with HIV with multidrug resistance and appears to have a reasonable safety profile. There are various limitations including the small sample size and lack of longer-term data.

While a decision is yet to be made, at this stage I am inclined to approve the registration of the product, but only for a more restrictive indication.

At this stage, there are insufficient data available to justify a HIV-1 indication of Sunlenca in a population aged below 18 years, in particular for a first-in-class new chemical entity in the context of a single pivotal study which is ongoing and included no paediatric patients. It is noted that the sponsor is undertaking a study in paediatric patients which will inform the efficacy and safety in children.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Can the ACM comment on whether there are sufficient data to register Sunlenca?

The ACM advised that the efficacy and safety data are sufficient to introduce the medicine to meet unmet need for heavily treatment experienced adults.

Efficacy was demonstrated in the pivotal study in patients with multidrug resistant HIV-1 and in the supporting study in naive patients. The ACM noted the small cohort and limited follow-up (approximately 1 year).

The ACM noted that the proposed dosing protocol in the Product Information (prior to sponsor revision) was not tested in the pivotal study but appears to be a practical approach that is unlikely to affect efficacy. However, this proposed dosing schedule for Sunlenca did not have an oral lead-in period prior to administration of the long-acting injection. A potential advantage of the dosing regimen used in the pivotal clinical trial is the ability to assess tolerability to Sunlenca during the oral lead-in period. If not tolerated, treatment cessation of Sunlenca would be possible prior to administration of the long-acting injection. This may be important in the context of a long pharmacokinetic tail, and in the context of preventing the development of resistance.

2. Can the ACM comment on the sponsor-proposed indication wording including the proposed paediatric indication?

The ACM noted that while the study plan for CAPELLA allowed for patients aged 12 to 17 years, none of the recruited 72 patients were in this age group.

The ACM was uncertain that the population pharmacokinetics model of the slow release of lenacapavir from the site of subcutaneous administration (peak plasma concentrations occurring 77 to 84 days postdose in adults) could be extrapolated to adolescents.

The ACM noted that the European Medicines Agency approval includes a Paediatric Investigation Plan, which includes:

- the development of an oral formulation for use in patients from 2 years to less than 12 years
- a dedicated clinical study (GS-US-563-5958) in patients from 2 years to less than 18 years of age with HIV infection, who are virologically suppressed.

The Delegate informed the ACM that subsequent to the pre-ACM response the sponsor had agreed to remove paediatric use from the proposed indication.

3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM noted that the Product Information directs that Sunlenca should be prescribed by physicians experienced in the treatment of HIV. The ACM supported this approach.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Sunlenca, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults weighing at least 35 kg with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Sunlenca (lenacapavir sodium) as 309 mg/mL solution for injection in vials, and as 300 mg tablets in blister packs, indicated for:

Sunlenca, in combination with other antiretrovirals, is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.

Specific conditions of registration applying to these goods

- Sunlenca (lenacapavir sodium) is to be included in the Black Triangle Scheme. The PI and CMI for Sunlenca must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Sunlenca EU Risk Management Plan (version 0.1, dated 19 July 2021, data lock point 1 April 2021), with Australia-specific annex (version 0.2, dated June 2022), included with submission PM-2022-00982-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than 3 years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Revision 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- The final clinical study report for Study GS-US-200-4625 (CAPELLA) should be submitted to the TGA, once available.
- The final clinical study report for Study GS-US-200-4334 (CALIBRATE) should be submitted to the TGA, once available.

Attachment 1. Product Information

The PI for Sunlenca approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #