Lenacapavir: An Overview

D.Nagavalli[1], P.Nanthagopal[2]
[1]*M.Pharm, Ph.D., Professor & H.O.D, Department of Pharmaceutical Chemistry, Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamil Nadu, India*
[2]*Department of Pharmaceutical Chemistry, Adhiparasakthi College of Pharmacy, Melmaruvathur, Kancheepuram District, The Tamilnadu Dr.M.G.R Medical university Chennai-28,Melmaruvathur-603319,Tamil Nadu, India*

Abstract – Lenacapavir was approved for medical use in European Union in August-2022, Lenacapavir is the first of a new class of drugs called "Capsid inhibitors to be FDA-approved for treating HIV/AIDS. Lenacapavir a new type of antiretroviral medication for adult patients living with Human Immunodeficiency Virus type-1(HIV-1), who's HIV Infections cannot be successfully treated with other available treatments due to resistance, intolerance considerations. Lenacapavir works by blocking the HIV-1 virus' protein shell (the Capsid) .Lenacapvir, in combination with other antiretroviral(s), is indicated for the treatment of multidrug-resistant human immunodeficiency virus type-1 (HIV-1)-Infection. Lenacapvir first formulation Oral Tablets and Subcutaneous injection-form at trade Name-(Sunlenac), Lenacapavir -is achieved in HIV RNA suppression .Lenacapvir is a long- acting, potent inhibitor of the HIV Capsid protein. Lenacapavir binds directly to HIV-capsid in a pocket between capsid protein subunits in hexamers.Treatement of emergent resistance to lenacapvir has been reported in the phase 2/3 CAPELLA trail evaluating Lenacapvir for HIV treatment. Combination antiretroviral therapy-suppression HIV-1 replication and increase CD $^{4+}$ cell counts.

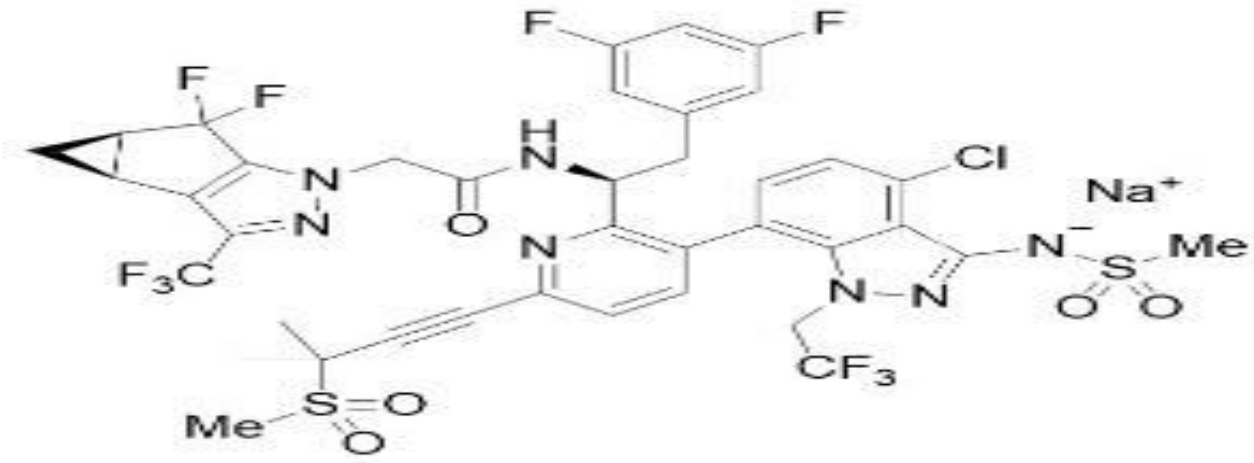
Key Words: Lenacapavir, Capsid-Inhibitor, HIV-1, Anti-Retroviral agent, SUNLENCA.

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a pathogenic retrovirus that infects cells of the human immune system and, if left untreated, can result in Acquired Immunodeficiency Syndrome (AIDS). An estimated 38 million people are infected worldwide and, since the epidemic began in the early 1980s, approximately 33 million people have died from HIV-related deaths. Combination antiretroviral therapy (cART) currently provides effective viral suppression for most patients, but concerns including drug resistance and adverse drug events provide a powerful motivation for investigation into new mechanisms to treat HIV-1 infection.

DRUG PROFILE

SUNLENCA- tablets and SUNLENCA -injection contain Lenacapavir sodium, a capsid inhibitor.



Figer-1-Lenacapavir Sodium

The chemical name of Lenacapavir Sodium is: Sodium (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)(methylsulfonyl)amide.

Lenacapavir sodium has a Molecular Formula - C39H31ClF10N7NaO5S2,

Molecular Weight - 990.3 g/mole.

Solubility: Lenacapavir sodium is a light yellow to yellow solid and is practically insoluble in water.

PH – 3.3

PKa- 6.69

Property Name	Property Value
Molecular Weight	968.3
XLogP3-AA	6.4
Hydrogen Bond Donor Count	2
Hydrogen Bond Acceptor Count	19
Rotatable Bond Count	13
Exact Mass	967.1435188
Monoisotopic Mass	967.1435188
Topological Polar Surface Area	175 Å²
Heavy Atom Count	64
Formal Charge	0
Complexity	2040
Isotope Atom Count	0
Defined Atom Stereocenter Count	3
Undefined Atom Stereocenter Count	0

STORAGE: Stored at room temperature, keep tablets in blister pack, keep injections vial stoppers are not made with neutral rubber latex. Store at 20 °C – 25 °C (68 °F – 77 °F), excursions permitted to 15 °C – 30°C (59 °F – 86 °F). Order to protect from Light.

- Store Lenacapavir tablets at room temperature, 68°F to 77°F (20°C to 25°C).
- Keep Lenacapavir tablets in their original blister pack. The blister pack is packaged with a small packet of drying agent (called a desiccant); do not remove it. The desiccant protects the medicine from moisture.
- Do not use Lenacapavir if the original seal over the blister pack opening is broken or missing.
- Throw away Lenacapavir that is no longer needed or expired (out of date). Follow (FDA guidelines) on how to safely dispose of unused medicine.
- Keep Lenacapavir and all medicines out of reach of children.

HIV- Capsid:

The mechanism of HIV-infection involves the transport and integration of the viral genome into the DNA of the host cell. This process involves both viral and cellular proteins which reveres transcribe the viral RNA to double-standard DNA and incorporate the viral DNA into the Host cell genome.

The Capsid surrounding the viral RNA, Nucleocapsids, Reverse transcriptase, Integrate plays a key role in the infection process. The capsid is composed of Amino-and Carboxyl-terminal domains that form hexametric and pentameric rings. This is ring assemble to form a cone-shaped structure surrounding the viral RNA and proteins. Upon entering the Cytoplasm of a host cell, the capsid an unfolding process that releases the viral RNA and Proteins into the cell.

The uncoating process in highly ordered multistep process in which the capsid is weaken and most or all capsid proteins are removed from the shell. Upsetting this process can have downstream effects that significantly reduce the infectivity of the virus. Because of this, capsid uncoating is a favorable target for antiretroviral medicines.

HIV-1 Capsid-Inhibitor:

In the management of HIV/AIDS, HIV-Capsid inhibitors are Antiretroviral medicines a class of drugs

that interfere with HIV-capsid, a protein shell that protects HIV- genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stage of the viral life cycle. It inhibits HIV-1 replication by acting at a late step to disrupt proper assembly of the mature viral capsid, without altering Gag processing. C 1 inactive at the time of virus infection of target cells.
Eg: Lenacapavir Sodium.

FORMULATION OF LENACAPAVIR :(SUNLENCA)

SUNLENCA tablets are for oral administration. Each film-coated tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium) and the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and poloxamer 407. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
SUNLENCA injection is for subcutaneous administration. Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium) as a sterile, preservative-free, clear, yellow solution and the following inactive ingredients: 896.3 mg of polyethylene glycol 300 (as solvent) and water for injection. The apparent pH range of the injection is 9.0–10.2.

What Sunlenca contains:
The active substance is lenacapavir. Each tablet contains Lenacapavir sodium equivalent to 300 mg lenacapavir. The other ingredients are Tablet core Mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), copovidone, magnesium stearate (E572), poloxamer (Sunlenca contains sodium).
Film-coating Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172), iron oxide red (E172).

MODES OF ACTION

As mentioned previously, Lenacapavir is involved in treatment of AIDS, long acting HIV-1 Inhibitor. It doesso by acting on various pathways and genetic. Signaling systems involved in Capsid inhibitor – Lenacapavir is a long-acting, potent inhibitor of the HIV capsid protein with in-vitro activity against viral strains resistant to other Anti-Retro-Viral classes. By targeting HIV capsid, lenacapvir interferes with multiple early- to late-stage processes of the viral life cycle: Lenacapavir binds directly to HIV capsid in a pocket between capsid protein subunit hexamers. Lenacapavir interferes with the functioning of Gag/Gag-pol and reduces capsid protein subunit production. Lenacapavir functions by binding to the hydrophobic pocket formed by two neighboring protein subunits in the capsid shell. This bond stabilizes the capsid structure and inhibits the functionally disassembly of the capsid in infected cells. These include capsid –mediated nuclear uptake of protein degration complexes, virion production and proper capsid core formation. Virus produced in the presence of Lenacapavir displays improperly shaped capsids that can enter new target cells but cannot replicate.

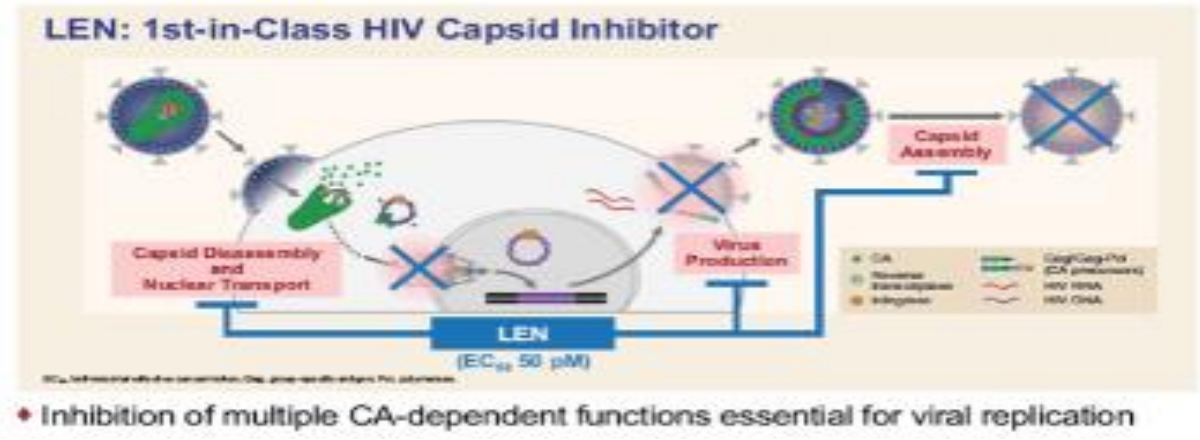
HIV-1 co-opts various host factors during its replicative cycle, including during host cell entry, nuclear integration, replication, and virion assembly. Following the initial fusion with the host cell membrane, the viral capsid is released into the host cell cytoplasm. The capsid comprises approximately 250 hexamers and exactly 12 pentamers, each composed of monomeric capsid proteins (CA). Each CA monomer has an N-terminal and C-terminal domain (NTD/CTD) and offers an interaction surface for host cell machinery. Several important protein-protein interaction interfaces occur between CA monomers in the assembled multimers; the binding constants of these proteins are substantially lower for assembled multimers than individual capsid monomers. To facilitate HIV-1 genomic integration, the capsid must cross the nuclear envelope, for which it utilizes the nuclear pore complex (NPC). Two host proteins shown to be essential for capsid nuclear entry that directly bind to the capsid are cleavage and polyadenylation specificity factor subunit 6 (CPSF6) and nucleoporin 153 (Nup153, an NPC protein present on the nucleoplasm face of the complex). Both proteins bind the same

phenylalanine-glycine binding pocket between the NTD and CTD of neighbouring CA monomers in multimeric CA assemblies. Lenacapavir contains a difluorobenzyl ring that occupies the same binding pocket as CPSF6/Nup153, overlapping with the benzyl group of F321 in CPSF6 and F1417 in Nup153 in the overlayed structures. Crystal structures of Lenacapavir bound to CA hexamers reveal that six Lenacapavir molecules bind to each hexamer, establishing extensive hydrophobic interactions, two cation-π interactions, and seven hydrogen bonds, contacting ~2,000 Å2 of buried protein surface area. Strong binding of Lenacapavir, therefore competitively interrupts capsid interactions with CPSF6 and Nup153. _In vitro_ HIV-1 replication inhibition experiments in a variety of cell lines show EC50 values of ~12-314 pM, with greater efficacy against early steps over later steps. At very low concentrations (0.5 nM), Lenacapavir inhibits viral nuclear entry, while at higher concentrations (5-50 nM), it additionally inhibits viral DNA synthesis and reverse transcription. As CPSF6 and Nup153 are essential for nuclear entry, it is likely that Lenacapavir binding inhibits these interactions and blocks capsid nuclear entry. Lenacapavir may have additional effects beyond blocking interactions with host cell factors. Lenacapavir increases the rate and extent of CA assembly, dramatically extends the lifetime of assembled CA structures, even at high salt concentrations, and alters assembled capsid morphology. The stabilizing concentration is ~1:1, closely mimicking the observed binding stoichiometry to isolated CA hexamers. Further analysis suggests that Lenacapavir binding alters intra- and inter-hexamer interactions, altering the structure and stability of the resulting assemblies. Serial passage of HIV-1 in increasing concentrations of Lenacapavir resulted in the appearance of major resistance mutations Q67H and N74D, which remain sensitive to other antiretroviral drugs. Extended passage resulted in the additional mutations L56I, M66I, K70N, N74S, and T107N. All identified resistance mutations map to the Lenacapavir binding site, and all but the Q67H variant show reduced replication capacity _in vitro_. Additional studies have shown no Lenacapavir resistance in variants associated with resistance to other antiretroviral or naturally occurring polymorphisms, suggesting a very low potential for cross-resistance in combination therapy.

MICROBIOLOGY

Mechanism of Action:

Lenacapavir is multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid proteins (p24) subunits in hexamers. Surface Plasmon resonance sensograms showed dose-dependent and storable binding of lenacapavir to cross-linked wild-type capsid hexamer with an equilibrium binding constant (KD) of 1.4 n M. Lenacapavir inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid –mediated nuclear uptake of HIV-1 prodigal DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-pol functioning , reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).



Antiviral Activity in Cell Culture:
Lenacapavir has antiviral activity that is specific to human immune deficiency virus (HIV-1) and (HIV-2). The antiviral activity of lenacapavir against laboratory and clinical isolates of HIV-1 was assessed in T-lymphoblastic cell lines, PBMCs, primary monocyte/macrophage s cells, and $CD4^+$ T-Lymphocytes with EC50- values ranging from 30 to 190 p M. Lenacapavir displayed antiviral activity in cell culture against all HIV-1 groups(M,N,O), Including subtype A, A1,AE, AG,B,BF,C,D,E,F,G with EC-50 values ranging from 20 and 160 p M. The median EC50 values for subtype B isolates (n=8) was 40 pM. A lenacapavir was 15-to 25 – fold less active against HIV-2 isolates relative to HIV-1. In a study of lenacapavir in combination with representative from the major classes of antiretroviral agents (INSTIs, NNRTIs, and Pls), no antagonism of antiviral activity was observed.

Type of Medication- HIV capsid inhibitor
• Indication- Treatment of HIV-1 in combination with other antiretroviral medications in heavily treatment-experienced adults with multidrug resistant HIV

PHARMACODYNAMIC

Lenacapavir is an antiviral drug with an extend pharmacokinetic profile. Lenacapavir works against the HIV-1 Virus. Single subcutaneous doses >100mg in healthy persons resulted in plasma concentration exceeding the 95% effective concentration (EC_{95}) for > 12 weeks while doses >300 mg exceeded the EC_{95} for >24 weeks. Single subcutaneous doses of 20-450 mg resulted in a mean maximum log_{10} –transform reduction in plasma HIV-1 RNA of 1.35-2.20 by the 9^{th} day post-injection. Exposure-Response In CAPELLA, oral loading doses (600 mg on Day 1 and Day 2, 300 mg on Day 8) followed by subcutaneous doses (927 mg every 6 months starting on Day 15) of SUNLENCA in heavily treatment-experienced subjects with multiclass resistant HIV-1, efficacy outcomes (change in plasma HIV-1 RNA from Day 1 to Day 14, and percentage of subjects with HIV-1 RNA less than 50 copies/mL at Week 26) were similar across the range of observed lenacapavir exposures. Lenacapavir is an antiviral drug with an extended pharmacokinetic profile. Lenacapavir works against the HIV-1 virus by inhibiting viral replication: it interferes with a number of essential steps of the viral lifecycle, including viral uptake, assembly, and release. Single subcutaneous doses ≥100 mg in healthy volunteers resulted in plasma concentrations exceeding the 95% effective concentration (EC95) for ≥12 weeks while doses ≥300 mg exceeded the EC95 for ≥24 weeks. In treatment-naive HIV-1-infected patients, a single subcutaneous dose of 20-450 mg resulted in a mean maximum log10-transformed reduction in plasma HIV-1 RNA of 1.35-2.20 by the ninth-day post-injection

Cardiac Electrophysiology: At supratherapeutic exposures of lenacapavir (9-fold higher than the therapeutic exposures of SUNLENCA), SUNLENCA does not prolong the QTcF interval to any clinically relevant extent.

Preclinical safety data:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development. Lenacapavir was not mutagenic or clastogenic in conventional genotoxicity assays. Lenacapavir was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 300 mg/kg/dose once every 13 weeks, which resulted in exposures approximately 60 times the exposure in humans at the recommended human dose. A 2-year rat carcinogenicity study is ongoing. In offspring from rat and rabbit dams treated with lenacapavir during pregnancy, there were no toxicologically significant effects on developmental endpoints. In rats, male and female fertility was not affected at lenacapavir exposures up to 8 times the human exposure at the recommended human dose (RHD). In rats and rabbits, embryofoetal development was not affected at exposures up to 21 and 172 times the human exposure, respectively, at the RHD. In rats, pre- and postnatal development was not affected at exposures up to 7 times the human exposure at the RHD. Transfer of lenacapavir from maternal to neonatal rats was observed in a prenatal and postnatal development study, but it is not known whether the transport occurred via the placenta or the milk; therefore the potential for lenacapavir to pass into the placenta or be excreted into milk in humans is not known.

CLINICAL STUDIES

The efficacy and safety of SUNLENCA in HIV-1 infected, heavily treatment-experienced subjects with multidrug resistance is based on 52-week data from CAPELLA, a randomized, placebo-controlled, double-blind, multicenter trial (NCT 04150068).

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

The trial was composed of two cohorts. Subjects were enrolled into the randomized cohort (cohort 1, N=36) if they had a < 0.5 log10 HIV-1 RNA decline compared to the screening visit. Subjects were enrolled into the non-randomized cohort (cohort 2, N=36) if they had a ≥ 0.5 log10 HIV-1 RNA decline compared to the screening visit or after cohort 1 reached its planned sample size.

In the 14-day functional mono therapy period, subjects in cohort 1 were randomized in a 2:1 ratio in a blinded fashion to receive either SUNLENCA or placebo, while continuing their failing regimen. This period was to establish the virology activity of SUNLENCA. After the functional mono therapy period, subjects who had received SUNLENCA continued on SUNLENCA along with an optimized background regimen (OBR); subjects who had received placebo during this period initiated SUNLENCA along with an OBR.

Subjects in cohort 1 had a mean age of 52 years (range: 24 to 71), 72% were male, 46% were White, 46% were Black, and 9% were Asian. 29% percent of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.3 log10 copies/mL (range: 2.3 to 5.4). 19% of subjects had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 161 cells/mm3 (range: 6 to 827). 75% of subjects had CD4+ cell counts below 200 cells/mm3. The mean number of years since subjects first started HIV treatment was 24 years (range: 7 to 33); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 1 to 7). The percentage of subjects in the randomized cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 97%, 94%, 78% and 75%, respectively. In cohort 1, 53% of subjects had no fully active agents, 31% had 1 fully active agent, and 17% had 2 or more fully active agents within their initial failing regimen, including 6% of subjects were who were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

Subjects in cohort 2 initiated SUNLENCA and an OBR on Day 1

Subjects in cohort 2 had a mean age of 48 years (range: 23 to 78), 78% were male, 36% were White, 31% were Black, 33% were Asian, and 14% of subjects identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.1 log10 copies/mL (range: 1.3 to 5.7). 19% of subjects had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 258 cells/mm3 (range: 3 to 1296). 53% of subjects had CD4+ cell counts below 200 cells/mm3. The mean number of years since subjects first started HIV treatment was 19 years (range: 3 to 35); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 2 to 7). The percentage of subjects in the non-randomized cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 100%, 100%, 83% and 64%, respectively. In cohort 2, 31% of subjects had no fully active agents, 42% had 1 fully active agent, and 28% had 2 or more fully active agents within their initial failing regimen, including 6% of subjects who were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

The primary efficacy endpoint was the proportion of subjects in cohort 1 achieving ≥ 0.5 log10 copies/mL reduction from baseline in HIV-1 RNA at the end of the functional mono therapy period. The results of the primary endpoint analysis. Background: Patients with multidrug-resistant human immunodeficiency virus type 1 (HIV-1) infection have limited treatment options. Lenacapavir is a first-in-class capsid inhibitor that showed substantial antiviral activity in a phase 1b study.

Methods: In this phase 3 trial, we enrolled patients with multidrug-resistant HIV-1 infection in two

cohorts, according to the change in the plasma HIV-1 RNA level between the screening and cohort-selection visits. In cohort 1, patients were first randomly assigned in a 2:1 ratio to receive oral lenacapavir or placebo in addition to their failing therapy for 14 days; during the maintenance period, starting on day 15, patients in the lenacapavir group received subcutaneous lenacapavir once every 6 months, and those in the placebo group received oral lenacapavir, followed by subcutaneous lenacapavir; both groups also received optimized background therapy. In cohort 2, all the patients received open-label oral lenacapavir with optimized background therapy on days 1 through 14; subcutaneous lenacapavir was then administered once every 6 months starting on day 15. The primary end point was the percentage of patients in cohort 1 who had a decrease of at least 0.5 log10 copies per milliliter in the viral load by day 15; a key secondary end point was a viral load of less than 50 copies per milliliter at week 26.

Results: A total of 72 patients were enrolled, with 36 in each cohort. In cohort 1, a decrease of at least 0.5 log10 copies per milliliter in the viral load by day 15 was observed in 21 of 24 patients (88%) in the lenacapavir group and in 2 of 12 patients (17%) in the placebo group (absolute difference, 71 percentage points; 95% confidence interval, 35 to 90). At week 26, a viral load of less than 50 copies per milliliter was reported in 81% of the patients in cohort 1 and in 83% in cohort 2, with a least-squares mean increase in the CD4+ count of 75 and 104 cells per cubic millimeter, respectively. No serious adverse events related to lenacapavir were identified. In both cohorts, lenacapavir-related capsid substitutions that were associated with decreased susceptibility developed in 8 patients during the maintenance period (6 with M66I substitutions).

Conclusions: In patients with multidrug-resistant HIV-1 infection, those who received lenacapavir had a greater reduction from baseline in viral load than those who received placebo. (Funded by Gilead Sciences; CAPELLA ClinicalTrials.gov number, NCT04150068.).

Risk Summary:
There are insufficient human data on the use of SUNLENCA during pregnancy to inform a drug-associated risk of birth defects and miscarriage. In animal reproduction studies, no adverse developmental effects were observed when lenacapavir was administered to rats and rabbits at exposures (AUC) ≥16 times the exposure in humans at the recommended human dose (RHD) of SUNLENCA (see Data).
The background risk of major birth defects and miscarriage for the indicated population is unknown. The background rate of major birth defects in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) is 2.7%. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15 to 20%.

Animal Data: Lenacapavir was administered intravenously to pregnant rabbits (up to 20 mg/kg/day on gestation days (GD) 7 to 19), orally to rats (up to 300 mg/kg/day on GD 6 to 17), and subcutaneously to rats (up to 300 mg/kg on GD 6). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at exposures (AUC) approximately 16 times (rats) and 39 times (rabbits) the exposure in humans at the RHD of SUNLENCA.

NONCLINICAL TOXICOLOGY

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

Lenacapavir was not carcinogenic in a 6-month rasH2 transgenic mouse study in males or females at doses of up to 300 mg/kg/dose once every 13 weeks. A 2-year rat carcinogenicity study is ongoing.

Mutagenesis

Lenacapavir was not mutagenic in a battery of *in vitro* and *in vivo* genotoxicity assays, including microbial mutagenesis, chromosome aberration in human peripheral blood lymphocytes, and in *in vivo* rat micronucleus assays.

Impairment of Fertility: There were no effects on fertility, mating performance or early embryonic development when Lenacapavir was administered to rats at systemic exposures (AUC) 5 times the exposure to humans at the RHD of SUNLENCA

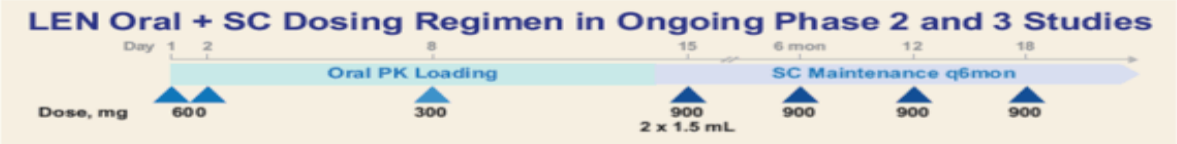
LEN Safety Summary: Blinded Data*

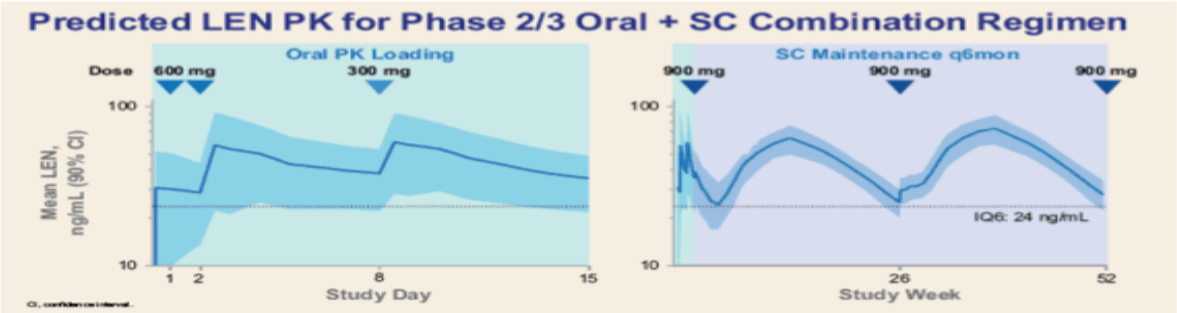
AEs: ≥5 Participants, n (%)	LEN 300 mg or PBO (1 x 1.0 mL) n=10	LEN 900 mg or PBO (3 x 1.0 mL) n=10	LEN 900 mg or PBO (2 x 1.5 mL) n=10	Overall N=30
Injection-site induration	3 (30)	8 (80)	10 (100)	21 (70)
Injection-site pain	0	6 (60)	8 (80)	14 (47)
Injection-site erythema	1 (10)	5 (50)	4 (40)	10 (33)
Headache	3 (30)	4 (40)	3 (30)	10 (33)
Injection-site swelling	0	4 (40)	4 (40)	8 (27)
Injection-site nodule	2 (20)	3 (30)	0	5 (17)

- Overall, LEN was well tolerated
- No serious or Grade 2, 3, or 4 AEs related to study drug
- No AEs leading to discontinuation
- Injection-site reactions were common (80%), but all were mild (Grade 1) and mostly lasted only a few days; induration and nodules were generally detectable only by clinicians and lasted several weeks
- 7 participants (23%) had Grade 3 or 4 laboratory abnormalities; none were clinically relevant

Simulations Supporting Phase 2/3 LEN Dosing Regimen

- Based on observed antiviral activity,[3] the mean LEN target concentration is 24 ng/mL, corresponding to a mean IQ ≥6 (range 6.2–20.3)
- The new LEN 300-mg/mL SC injection formulation exhibits a slow initial release necessitating an oral PK loading regimen prior to the first injection
- PK simulations were performed using single-dose oral LEN tablet PK[5] and SC injection PK from the present study
- The regimen was predicted to achieve target concentrations within a few days of initiation of dosing and maintain them with a 26-wk (6-mon) dosing interval





PHARMACOKINETIC

Specific Populations: There were no clinically significant differences in the pharmacokinetics of lenacapavir based on age (18 to 78 years), sex, ethnicity (Hispanic or non-Hispanic), race (white, black, Asian or other), body weight (41.4 to 164 kg), severe renal impairment (creatinine clearance of 15 to less than 30 mL per minute, estimated by Cockroft-Gault method), or moderate hepatic impairment (Child-Pugh Class B). The effect of end-stage renal disease (including dialysis), or severe hepatic impairment (Child-Pugh Class C), on the pharmacokinetics of lenacapavir is unknown. As lenacapavir is greater than 98.5% protein bound, dialysis is not expected to alter exposures of lenacapavir [see Use in Specific Populations.

ABSORPTION:

Following subcutaneous administration, Lenacapavir, with peak plasma concentrations occurring at 84-days post-dose. Absolute

bioavailability following oral administration is low, approximately 6 to 10%. T_{max} after oral administration is about four hours. The mean steady-state C_{max}(%CV) is 97.2(70.3) ng/mL following oral and subcutaneous administration. Lenacapavir exposures ($AUC_{tau,}$ Cmax and C_{trough}) were 29%to 84%.

VOLUME OF DISTRIBUTION:
The steady state volume of distribution was 976 L in heavily treatment –experienced patient with an HIV-1 infection.

PROTEIN BINDING:
In-vitro, Lenacapavir is approximately 99.8% bound to plasma proteins.

METABOLISM:
Metabolism played a lesser role in lenacapavir elimination. It undergoes CYP3A4- and UGT1A1-mediated oxidation, N-dealkylation, hydrogenation, amide, hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation. Contraindicated to give with strong CYP3A inducers.

ROUTE OF ELIMINATION:
Following a single intravenous dose of radiolabelled-lenacapavir in healthy subjects, 76% of the total radioactivity was recovered from feces and less than 1% from urine. Unchanged lenacapavir was the predominant moiety in plasma (69%) and feces (33%).

HALF-LIFE:
The medicine half-life ranged from 10 to 12days following oral administration, and 8 to 12 weeks following subcutaneous administration.

CLEARANCE:
Lenacapavir clearance was 3.62 L/h in heavily treatment.

TOXICITY:
There is limited information available regarding the acute toxicity and overdose of lenacapavir. If overdose occurs the patient must be monitored for sign or symptoms of adverse reactions. Treatment of overdose with Lenacapavir consist of general supportive measures including monitoring of vital sign as well as observation of the clinical status of the patient. As Lenacapavir is highly protein bound, it is unlikely to be significantly removed by dialysis.

Pharmacokinetic Properties of Lenacapavir

		Oral	Subcutaneous
Absorption			
% Absolute bioavailability		6 to 10	100 *
T_{max} †		4 hours	77 to 84 days ‡
Effect of Food			
Effect of low-fat meal (relative to fasting) §	AUC_{inf} ratio	98.6 (58.2,167.2)	-
	C_{max} ratio	115.8 (55.4, 242.1)	-
Effect of high-fat meal (relative to fasting) ¶	AUC_{inf} ratio	115.2 (72.0, 184.5)	-
	C_{max} ratio	145.2 (77.9, 270.5)	-
Distribution			
Apparent volume of distribution (Vd/F, L)		19240	9500 to 11700
% bound to human plasma proteins		>98.5	
Blood-to-plasma ratio		0.5 to 0.7 #	
Elimination			
$t_{1/2}$		10 to 12 days	8 to 12 weeks
Clearance (mean apparent clearance, L/h)		55	4.2
% of dose of unchanged drug in plasma **		69	

EFFICANCY AND SAFETY

Efficacy of Lenacapavir-(SUNLENCA)- was demonstrated in HIV-1 infected, heavily treatment-experienced subjects with multidrug resistance participating in a 52-weeks, randomized, placebo-controlled, double-blind, multicenter trial. The primary efficacy endpoint was the proportion of subjects in cohort 1 achieving > 0.5 $\log_{10}$ /mL reduction from baseline in HIV-1 RNA at the end of the functional mono therapy period.

WARNINGS AND PRECAUTIONS

IMMUNE RECONSTITUTION SYNDROME

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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

LONG-ACTING PROPERTIES AND POTENTIAL ASSOCIATED RISKS WITH SUNLENCA

Residual concentrations of lenacapavir may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer after the last subcutaneous dose). It is important to counsel patients that maintenance dosing by injection is required every 6 months, because missed doses or non-adherence to injections could lead to loss of virology response and development of resistance.

Lenacapavir, a moderate CYP3A inhibitor, may increase the exposure to, and therefore potential risk of adverse reactions from, drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of SUNLENCA [see Drug Interactions and Clinical Pharmacology.

If SUNLENCA is discontinued, to minimize the potential risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral regimen where possible no later than 28 weeks after the final injection of SUNLENCA. If virology failure occurs during treatment, switch the patient to an alternative regimen if possible.

INJECTION SITE REACTIONS

Administration of SUNLENCA may result in local injection site reactions (ISRs). If clinically significant ISRs occur, evaluate and institute appropriate therapy and follow-up.

Manifestations of ISRs may include swelling, pain, erythema, nodule, induration, pruritus, extravasation or mass. Nodules and indurations at the injection site may take longer to resolve than other ISRs. In clinical studies, after a median follow-up of 553 days, 30% of nodules and 13% of indurations (in 10% and 1% of subjects, respectively) associated with the first injections of SUNLENCA had not fully resolved. Measurements and qualitative assessments of ISRs were not routinely reported. Where described, the majority of the injection site nodules and indurations were palpable but not visible, and had a maximum size of approximately 1 to 4 cm .

The mechanism driving the persistence of injection site nodules and indurations in some patients is not fully understood, but based on available data, they may be related to the presence of the subcutaneous drug depot. In some patients who had a skin biopsy performed of an injection site nodule or induration, dermatopathology revealed foreign body inflammation or granulomatous response.

PEDIATRIC USE

The safety and effectiveness of SUNLENCA have not been established in pediatric patients.

GERIATRIC USE

Clinical studies of SUNLENCA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

RENAL IMPAIRMENT

No dosage adjustment of SUNLENCA is recommended in patients with mild, moderate or severe renal impairment (estimated creatinine clearance greater than or equal to 15 mL per minute). SUNLENCA has not been studied in patients with

ESRD (estimated creatinine clearance less than 15 mL per minute)

HEPATIC IMPAIRMENT

No dosage adjustment of SUNLENCA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. SUNLENCA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)

THERAPEUTIC APPLICATION

Treat HIV-1 infection in adults:

• Who have received HIV-1 medicines in the past, who have HIV-1 virus that is resistant to many HIV-1 medicines, and

• Whose current HIV-1 medicines are failing? Your HIV-1 medicines may be failing because the HIV-1 medicines are Not working or no longer work, you are not able to tolerate the side effects, or there are safety reasons why you cannot take them.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

It is not known if SUNLENCA is safe and effective in children.

INTERACTIONS OF LENACAPAVIR

Sometimes, one medication can interfere with the effects of another. Specialists refer to this as drug interaction.

Drugs that may interact with Lencapavir include Trusted Source: The following should not be taken with lenacapavir because they generally reduce levels of Lenacapavir.

- Efavirenz
- Etravirine
- Nevirapine
- Atazanavir
- Rifampicin
- Rifabutin
- Carbamazepine
- Phenytoin
- Oxcarbazepine
- Phenobarbital

The following drugs can be increased by Lencapavir. So used at lower dose.

- Sildenafil(viagra)
- Dextromethasone
- Cortisone
- Dioxin, midazolam, triazolam, lovastatin, simvastatin.
- Ergotamine.

CHEMISTRY OF LENACAPAVIR

Input

SMILES: O=C(Cn1nc(c2c1C(F)(F)[C@H]1[C@@H]2C1)C(F)(F)F)N[C@H](c1nc(C#CC(S(=O)(=O)C)(C)C)ccc1c1ccc(c2c1n(nc2NS(=O)(=O)C)CC(F)(F)F)Cl)Cc1cc(F)cc(c1)F

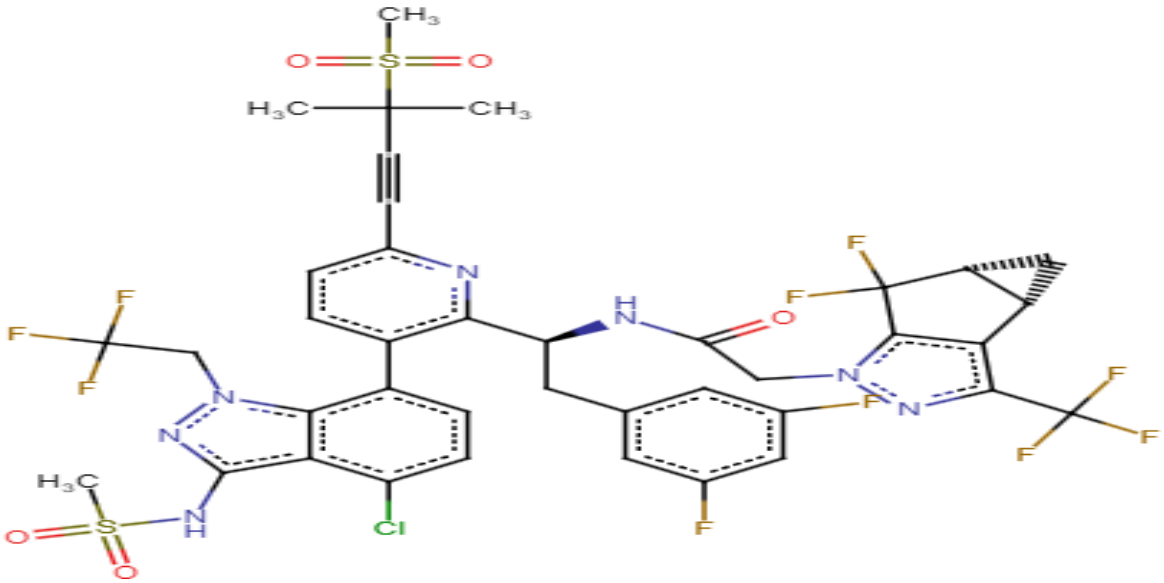


Fig: Lenacapavir @ Swiss ADME.

Bioactivity Comments:
Picomolar concentrations of GS-6207 produced antiviral activity against all of the HIV-1 subtypes that were tested. The EC_{50} is 105 pM in MT-4 cells infected with HIV-1, and 32 pM in primary human $CD4^+$ T cells. GS-6207 is highly stable *in vivo*, and sustains antiviral activity for more than 6 months, and is activate against HIV-1 variants that are resistant to current drug classes.

PHYSIO-CHEMICAL PROPERTIES (MOL-inspiration)

Hydrogen bond acceptors	10
Hydrogen bond donors	2
Rotatable bonds	14
Topological polar surface area	174.7
Molecular weight	967.14
XLogP	8.17
No. Lipinski's rules broken	2

SIDE EFFECT'S

Lenacapvir signs of an allergic reaction-hives, difficult breathing, swelling face, lips, tongue, throat. Common side effects of lenacapavir–bruising, swelling, warmth, redness, oozing, bleeding-given injection. Nausea,anxiety,tremors, weight loss, puffy eyes, enlarged thyroid, muscle pain, rash, loss of menstrual periods, loss of appetite, irregular heartbeats,

MEDICAL USES
Lenacapavir is used primarily to treat HIV/AIDS. (This medicine will not cure HIV infection), It works by lowering the amount of HIV in blood and help the immune system. It is a potent inhibitor of HIV-Capsid.

DOSE
Lenacapavir is started by Adult taking a 600mg oral tablet on day-1 and 2. This is followed by a 300 mg tablet on day-8. Then, on day-15, the recommended standard adult dose in one subcutaneous injection (927 mg) every six months. Lenacapavir can be given with or without food.

Lenacapavir Dosing Schedule

Lenacapavir Dosing Schedule	
Initiation Option 1	
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) + 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Initiation Option 2	
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablets)
Day 15	927 mg by subcutaneous injection (2 x 1.5 mL injections)
Maintenance	
927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) from date of the last injection +/-2 weeks	
Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue lenacapavir, restart initiation from Day 1, using either Option 1 or Option 2	

MARKATED: (SUNLENCA)-Lenacapavir.
Lenacapavir (Preparations- Oral: 300 mg tablets
- Subcutaneous injection: 463.5 mg/1.5 mL vial.

Cross-Resistance:
The antiviral activity in cell culture of lenacapavir was determined against a broad spectrum of HIV-1 site-directed mutants and patient-derived HIV-1 isolates

with resistance to the four main classes of anti-retroviral agents (INSTI, NNRTI, NRTI, and PI; n=58), as well as to viruses resistant to the gp120-directed attachment inhibitor fostemsavir, the CD4+-directed post-attachment inhibitor ibalizumab, the CCR5 co-receptor antagonist maraviroc, and the gp41 fusion inhibitor enfuvirtide (n=42). These data indicated that lenacapavir remained fully active against all variants tested, thereby demonstrating a non-overlapping resistance profile. In addition, the antiviral activity of lenacapavir in patient isolates was unaffected by the presence of naturally occurring Gag polymorphisms and substitutions at protease cleavage sites.

Resistance:
In Cell Culture- HIV-1 variants with reduced susceptibility to lenacapavir have been selected in cell culture. Resistance selections with lenacapavir identified 7 substitutions in capsid: L56I, M66I, Q67H, K70N, N74D/S, and T107N singly or in dual combination that conferred 4- to >3,226-fold reduced phenotypic susceptibility to lenacapavir relative to wild-type (WT) virus. The M66I substitution alone or in combination conferred >3,226-fold decreased susceptibility to lenacapavir in a single-cycle infectivity assay; substitutions Q67H and T107N, conferred 4- to 6.3-fold decreased susceptibility; K70N, N74D and Q67H/N74S conferred 22- to 32-fold decreased susceptibility; and L56I conferred 239-fold decreased susceptibility.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information). If SUNLENCA is discontinued, advise patients that SUNLENCA may remain in the body and affect certain other drugs for up to 9 months after receiving their last injection.

Immune Reconstitution Syndrome:
Advice patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started.

Adherence to SUNLENCA :(LENACAPAVIR)
Counsel patients about the importance of continued medication adherence and scheduled visits to maintain viral suppression and to reduce risk of loss of virology response and development of resistance. Advice patients to contact their healthcare provider immediately if they stop taking SUNLENCA or any other drug in their antiretroviral regimen.

Injection Site Reactions:
Inform patients that injection site reactions (ISRs), such as swelling, pain, erythema, nodule, induration, pruritus, extravasation or mass, may occur. Nodules and indurations at the injection site may take longer to resolve than other ISRs and may be persistent. Instruct patients when to contact their healthcare provider about these reactions.

Pregnancy Registry:
Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant individuals exposed to SUNLENCA.

Lactation: Instruct individuals with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk.

Risk Summary:
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.
It is not known whether SUNLENCA is present in human breast milk, affects human milk production, or has effects on the breastfed infant. After administration to pregnant rats, lenacapavir was detected in the plasma of nursing rat pups, without effects on these nursing pups (see Data).
Because of the potential for 1) HIV transmission (in HIV-negative infants); 2) developing viral resistance (in HIV-positive infants); and 3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving SUNLENCA.

Do not stop taking Sunlenca tablets without talking to your doctor. Stopping Sunlenca can seriously affect how future HIV treatments work.

Recent advances:

Effect of Other Drugs on Lenacapavir:

Coadministered Drug	Dose of Coadministered Drug (mg)	Mean Ratio of Lenacapavir Pharmacokinetic Parameters (90% CI); No effect = 1.00	
		C_{max}	AUC
Cobicistat (fed) (Inhibitor of CYP3A [strong] and P-gp)	150 once daily	2.10 (1.62, 2.72)	2.28 (1.75, 2.96)
Darunavir / cobicistat (fed) (Inhibitor of CYP3A [strong] and inhibitor and inducer of P-gp)	800/150 once daily	2.30 (1.79, 2.95)	1.94 (1.50, 2.52)
Voriconazole (fasted) (Inhibitor of CYP3A [strong])	400 twice daily, 200 twice daily ‡	1.09 (0.81, 1.47)	1.41 (1.10, 1.81)
Atazanavir / cobicistat (fed) (Inhibitor of CYP3A [strong] and UGT1A1 and P-gp)	300/150 once daily	6.60 (4.99, 8.73)	4.21 (3.19, 5.57)
Rifampin (fasted) (Inducer of CYP3A [strong] and P-gp and UGT)	600 once daily	0.45 (0.34, 0.60)	0.16 (0.12, 0.20)
Efavirenz (fasted) (Inducer of CYP3A [moderate] and P-gp)	600 once daily	0.64 (0.45, 0.92)	0.44 (0.32, 0.59)
Famotidine (2 hours before, fasted)	40 once daily	1.01 (0.75, 1.34)	1.28 (1.00, 1.63)

* Single dose of lenacapavir 300 mg administered orally.

† All interaction studies conducted in subjects without HIV-1.

‡ 400 mg loading dose twice daily for a day, followed by 200 mg maintenance dose twice daily.

CONCLUSIO N

Lenacapavir is a drug which provide HIV-1 treatment. A first-in- class HIV-1 Capsid inhibitor condition Lenacapvir is usually superior. This means that Lenacapvir provides more potent with a degree of HIV-1 virus infection treatment that physicians feel worthwhile. Interpretation: “Lenacapavir warrants further investigation as a potential antiretroviral used orally and as injection in combination with other antiretroviral drugs.”

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REFERENCE

[1] National Institute of Allergy and Infectious Diseases (NIAID). NIAID ChemDB, HIV Drugs in Development. Accessed January 9, 2023.

[2] American Medical Association (AMA) website. Statement on a nonproprietary name adopted by the USAN council: lenacapavir. Accessed January 9, 2023.

[3] Gilead Sciences. A Phase 3, double-blinded, multicenter, randomized study to evaluate safety and efficacy of twice yearly long-acting subcutaneous lenacapavir, and daily oral emtricitabine/tenofovir alafenamide for pre-exposure prophylaxis in adolescent girls and young women at risk of HIV infection. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Registered on August 2, 2021. NLM Identifier: NCT04994509. Accessed January 9, 2023

[4] Gilead Sciences. A Phase 3, double-blind, multicenter, randomized study to evaluate the efficacy and safety of subcutaneous twice yearly

long acting lenacapavir for HIV pre-exposure prophylaxis in cisgender men, transgender women, transgender men, and gender non-binary people ≥ 16 years of age who have sex with partners assigned male at birth and are at risk for HIV infection. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Registered on May 28, 2021. NLM Identifier: NCT04925752. Accessed January 9, 2023.

[5] Oh KS, Han E. A comparison of medication adherence and viral suppression in antiretroviral treatment-naive patients with HIV/AIDS depending on the drug formulary. PLoS ONE. 2021; 16(1): e0245185. - DOI - PubMed - PMC

[6] Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. PLoS Med. 2016; 13(11): e1002183. - DOI - PubMed - PMC

[7] Gilead Sciences: Press release, dated December 22, 2022. Sunlenca® (lenacapavir) receives FDA approval as a first-in-class, twice-yearly treatment option for people living with multi-drug resistant HIV. Accessed January 9, 2023.

[8] Gilead Sciences Inc. Lenacapavir (Sunlenca®): EU summary of product characteristics. 2022. https://ema.europa.eu/. Accessed 21 Sep 2022.

[9] Gilead Sciences Inc. Gilead announces first regulatory approval for Sunlenca® (lenacapavir), the only twice-yearly HIV treatment option [media release]. 22 Aug 2022. https://www.gilead.com...

[10] Zhuang S, Torbett BE: Interactions of HIV-1 Capsid with Host Factors and Their Implications for Developing Novel Therapeutics. Viruses. 2021 Mar 5; 13(3). Pii: v13030417. Doi: 10.3390/v13030417.

[11] Singh K, Gallazzi F, Hill KJ, Burke DH, Lange MJ, Quinn TP, Neogi U, Sonnerborg A: GS-CA Compounds: First-In-Class HIV-1 Capsid Inhibitors Covering Multiple Grounds. Front Microbiol. 2019 Jun 20; 10:1227. Doi: 10.3389/fmicb.2019.01227. eCollection 2019.

[12] Margot N, Ram R, Rhee M, Callebaut C: Absence of Lenacapavir (GS-6207) Phenotypic Resistance in HIV Gag Cleavage Site Mutants and in Isolates with Resistance to Existing Drug Classes. Antimicrob Agents Chemother. 2021 Feb 17; 65(3). pii: AAC.02057-20. Doi: 10.1128/AAC.02057-20. Print 2021 Feb 17.

[13] Highleyman L (15 March 2021). "Lenacapavir Shows Promise for Long-Acting HIV Treatment and Prevention". *POZ*. Archived from the original on 19 July 2021. Retrieved 15 March 2021.

[14] https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf.

[15] https://www.ema.europa.eu/en/medicines/human/EPAR/sunlenca.

[16] Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature*, 584 (7822): 614-618. [PMID:32612233]

[17] Thenin-Houssier S, Valente ST. (2016) HIV-1 Capsid Inhibitors as Antiretroviral Agents. Curr HIV Res, 14 (3): 270-82. [PMID: 26957201]