NEW DRUG APPROVAL

Brand Name	Sunlenca®
Generic Name	lenacapavir
Drug Manufacturer	Gilead Sciences, Inc

New Drug Approval

FDA approval date: December 22, 2022

Review designation: Priority

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 215973, 215974

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

HIV (human immunodeficiency virus) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment.

If left untreated, HIV can lead to the disease AIDS (acquired immunodeficiency syndrome).

A subset of people living with HIV (PLHIV) are heavily treatment experienced (HTE) and have limited remaining antiretroviral therapy (ART) options due to resistance, intolerance, and potential interactions with concomitant medications.

Prevalence of HTE was variable across definitions, but all estimates suggest that HTE patients make up a small sub-set of the general HIV population in the United States.

- Approximately 1.2 million people in the U.S. have HIV. About 13 percent of them don't know it and need testing.
- HIV continues to have a disproportionate impact on certain populations, particularly racial and ethnic minorities and gay, bisexual, and other men who have sex with men.
- In 2019, an estimated 34,800 new HIV infections occurred in the U.S.
- New HIV infections declined 8% from 37,800 in 2015 to 34,800 in 2019, after a period of general stability.
- In 2020, 30,635 people received an HIV diagnosis in the U.S. and 6 dependent areas—a 17% decrease from the prior year, likely due to the impact of the COVID-19 pandemic on HIV prevention, testing, and care-related services.

Efficacy

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 log 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 log HIV-1 RNA decline compared to the screening visit or after cohort 1 reached its planned sample size.

In the 14-day functional monotherapy 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 virologic activity of Sunlenca®. After the functional monotherapy 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 $\log_{10}$ 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/mm^3 (range: 6 to 827). 75% of subjects had $CD4^+$ cell counts below 200 cells/mm^3. 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 $\log_{10}$ copies/mL (range: 1.3 to 5.7). 19% of subjects had baseline viral loads greater than 100,00 copies/mL. The mean baseline $CD4^+$ cell count was 258 cells/mm^3 (range: 3 to 1296). 53% of subjects had $CD4^+$ cell counts below 200 cells/mm^3. 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 $\log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. The results of the primary endpoint analysis are shown in Table 1.

Table 1: Proportion of Subjects Achieving a ≥ 0.5 log10 Decrease in Viral Load at the End of the Functional Monotherapy Period in the CAPELLA Trial (Cohort 1)

	Sunlenca® (N=24)	Placebo (N=12)
Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load	87.5%	16.7%
Treatment Difference (95% CI)	70.8% (34.9% to 90.0%) [a]	

[a] $p < 0.0001$

The results at Weeks 26 and 52 are provided in Table 2 and Table 3.

Table 2: Virologic Outcomes (HIV-1 RNA < 50 copies/mL) at Weeks 26[a] and 52[b] with Sunlenca® plus OBR in the CAPELLA Trial (Cohort 1)

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

OBR = optimized background regimen

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

Table 3: Virologic Outcomes (HIV-1 RNA < 50 copies/mL) by Baseline Covariates at Weeks 26[a] and 52[b] with Sunlenca® plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca® plus OBR (N=36)	
	Week 26	Week 52
Age (Years)		
< 50	100% (9/9)	89% (8/9)
≥ 50	74% (20/27)	81% (22/27)
Gender		
Male	77% (20/26)	77% (20/26)
Female	90% (9/10)	100% (10/10)
Race		
Black	81% (13/16)	75% (12/16)
Non-Black	84% (16/19)	89% (17/19)
Baseline plasma viral load (copies/mL)		
≤ 100,000	86% (25/29)	86% (25/29)

> 100,000	57% (4/7)	71% (5/7)
Baseline CD4⁺ (cells/mm³)		
< 200	78% (21/27)	78% (21/27)
≥ 200	89% (8/9)	100% (9/9)
Baseline INSTI resistance profile		
With INSTI resistance	85% (23/27)	81% (22/27)
Without INSTI resistance	63% (5/8)	88% (7/8)
Number of fully active ARV agents in the OBR		
0	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)
≥ 2	81% (13/16)	94% (15/16)
Use of DTG and/or DRV in the OBR		
With DTG and DRV	83% (10/12)	83% (10/12)
With DTG, without DRV	83% (5/6)	83% (5/6)
Without DTG, with DRV	78% (7/9)	89% (8/9)
Without DTG or DRV	78% (7/9)	78% (7/9)

ARV = antiretroviral; DRV=darunavir; DTG=dolutegravir; INSTI = integrase strand-transfer inhibitor; OBR = optimized background regimen;

a. Week 26 window was between Days 184 and 232 (inclusive).
b. Week 52 window was between Days 324 and 414 (inclusive).

In cohort 1, at Weeks 26 and 52, the mean change from baseline in CD4⁺ cell count was 81 cells/mm³ (range: -101 to 522) and 82 cells/mm³ (range: -194 to 467), respectively.

In cohort 2, at Week 26 and 52, 81% (29/36) and 72% (26/36) of patients achieved HIV1 RNA < 50 copies/mL, respectively, and the mean change from baseline in CD4⁺ cell count was 97 cells/mm³ (range: -103 to 459) and 113 cells/mm³ (range: -124 to 405), respectively.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence greater than or equal to 3%, all grades) are nausea and injection site reactions.

WARNINGS & PRECAUTIONS

- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- Residual concentrations of lenacapavir may remain in systemic circulation for up to 12 months or longer. Counsel patients regarding the dosing schedule; non-adherence could lead to loss of virologic response and development of resistance.
- May increase exposure and risk of adverse reactions to drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of Sunlenca®.
- If discontinued, initiate an alternative, fully suppressive antiretroviral regimen where possible no later than 28 weeks after the final injection of Sunlenca®. If virologic failure occurs, switch to an alternative regimen if possible.
- Injection site reactions may occur, and nodules and indurations may be persistent.

CONTRAINDICATIONS

Concomitant administration of Sunlenca® is contraindicated with strong CYP3A inducers.

Clinical Pharmacology

MECHANISMS OF ACTION

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

Dose & Administration

ADULTS

- Recommended dosage – Initiation with one of two options followed by once every 6-months maintenance dosing. Tablets may be taken without regard to food.

Table 4: Dosing

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 tablet)
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 the date of the last injection +/-2 weeks.	

- Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue Sunlenca®, restart initiation from Day 1, using either Option 1 or Option 2.
- Two 1.5 mL subcutaneous injections are required for complete dose.

PEDIATRICS

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

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustment required.

HEPATIC IMPAIRMENT

No dosage adjustment required.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 300 mg
Injection: 463.5 mg/1.5 mL (309 mg/mL) in single-dose vials.