GILEAD | Medical Information

Sunlenca® (lenacapavir) Treatment-Emergent Resistance

This document is in response to your request for information regarding Sunlenca® (lenacapavir [LEN]) and treatment-emergent resistance.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

Summary

Product Labeling[1]

LEN, an HIV-1 CA inhibitor, in combination with other ARV(s), is indicated for the treatment of HIV-1 infection in HTE adults with multidrug resistant HIV-1 whose current ARV regimen is failing due to resistance, intolerance, or safety considerations.

Residual concentrations of LEN may remain in the systemic circulation for prolonged periods (up to 12 months or longer after the last SUBQ 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 virologic response and development of resistance.

Clinical Data on Treatment-Emergent Resistance to LEN

In the phase 2/3 CAPELLA study of HTE PWH, LEN resistance emerged in 14/72 participants through Week 156. All participants were at high risk of treatment-emergent LEN resistance due to either inadequate adherence to their OBR (n=10) or lack of fully active ARVs in their OBR (n=4).[2]

In the phase 2 CALIBRATE study in ARV-naive PWH, 3/157 participants on a LEN-containing regimen developed LEN RAMs through Week 80.[3] Two of these participants had suspected incomplete adherence.[4]

Clinical Data on Treatment-Emergent Resistance to LEN

CAPELLA: LEN in HTE PWH

Study design and baseline resistance analysis

CAPELLA (NCT04150068) is an ongoing, global, phase 2/3, placebo-controlled clinical study evaluating oral LEN followed by SUBQ LEN in combination with an OBR in HTE PWH

with multidrug resistance. The study enrolled participants who had resistance to ≥2 ARVs in ≥3 of the 4 main ARV classes: NRTIs, NNRTIs, PIs, and INSTIs.[5]

Baseline resistance at screening was assessed using genotypic and phenotypic assays or historical data provided by the investigators. Baseline HIV-1 CA genotypic and phenotypic analyses were also performed.[6] At baseline, no RAMs associated with LEN resistance were found in the 62 participants with available data.[7]

Table 1. CAPELLA Study: Baseline Resistance to NRTI, NNRTI, INSTI, and PI Classes[8]

Key ARV Classes, n (%)		LEN (N=72)
Known resistance to ≥2 drugs in class	NRTI	71 (99)
	NNRTI	70 (97)
	PI	58 (81)
	INSTI	50 (69)
Resistance to all four major ARV classes		33 (46)

Post-baseline resistance analyses

Post-baseline resistance analyses were conducted in participants with virologic failure (confirmed HIV-1 RNA ≥50 c/mL and <1-$\log_{10}$ decrease in HIV-1 RNA from LEN initiation; assessed at Week 4), virologic rebound (confirmed HIV-1 RNA ≥50 c/mL after achieving HIV-1 RNA <50 c/mL or >1-$\log_{10}$ increase from nadir), or HIV-1 RNA ≥50 c/mL at their last visit.[6]

Through Week 104, 27 participants were included in the resistance analysis population, and LEN RAMs emerged in 14 of these participants (Table 2). All were at high risk of emergent LEN resistance due to inadequate OBR adherence (n=10) or lack of fully active drugs in OBR (n=4).[6]

Table 2. CAPELLA Study: Treatment-Emergent LEN Resistance Through Week 104[6]

	LEN (N=72)
Participants who met criteria for resistance testing, n (%)	27 (38)
Treatment-emergent LEN resistance, n (%)	14 (19)
Q67H/K/N	8 (11)
K70H/N/R/S	7 (10)
M66I	6 (8)
T107A/C/N/S[a]	6 (8)
A105S/T	5 (7)
N74D/H/K	5 (7)
No treatment-emergent LEN resistance, n (%)	13 (18)

[a]One participant developed a T107A polymorphism in CA (0.6-fold change vs wild type), and 1 participant developed a T107S polymorphism in CA (1.3-fold change vs wild type); neither participant lost susceptibility to LEN and was, therefore, counted in the "no LEN resistance" category, whereas the mutations were included in the T107 category.

There were no new cases of LEN resistance between Weeks 104 and 156. Two participants who had previously detected resistance developed additional mutations: 1 participant had emergence of K70R+T107N with existing Q67H (reduction in LEN susceptibility from 4.5- to 85-fold of wild-type), and 1 participant had emergence of T107T/N with existing K70N+N74K (no LEN susceptibility data for triple mutant).[2]

Despite the emergence of LEN resistance through Week 156, 5 participants were resuppressed while continuing LEN treatment; OBR was changed in 2 participants and unchanged in 3 participants. Six of 9 participants, who were not resuppressed, continued

study treatment (2 participants returned to their baseline viral load; mean log reduction for the 4 participants who did not return to baseline viral load: -1.64), and 3 participants discontinued LEN due to death, investigator's discretion due to non-compliance, and loss to follow-up (each, n=1).[2]

Safety results[2]

A safety analysis was not conducted in the subgroup of participants with treatment-emergent LEN resistance. Overall, the median (IQR) duration of follow-up on LEN was 165 (146–178) weeks. The most common treatment-emergent AEs that occurred in ≥15% of participants, excluding ISRs and COVID-19, were diarrhea (n=15), nausea (n=14), urinary tract infections (n=12), and cough (n=12).

Most ISRs (97.2%) reported through Week 156 were Grade 1 or 2, and the frequency of ISRs decreased over time. No Grade 4 ISRs were reported. Grade 1 ISRs of injection site nodules led to study discontinuation in 2 participants. The median (IQR) duration of localized ISRs were the following: swelling, 8 (4–15) days; erythema, 5 (3–8) days; pain, 3 (2–5) days; nodules, 288 (155–548) days; and induration, 190 (67–410) days.

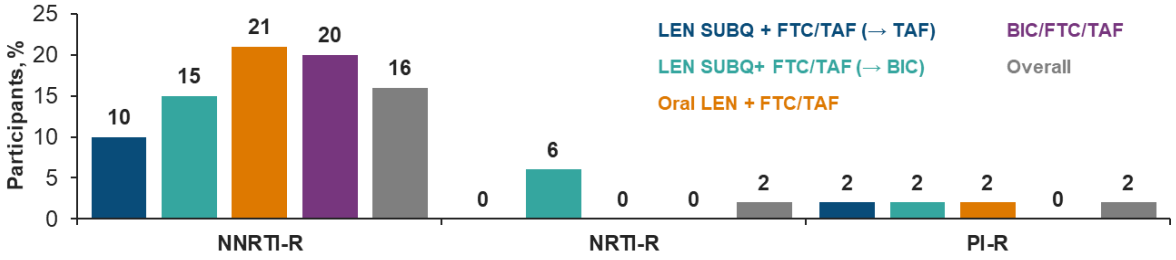
CALIBRATE: LEN in ARV-Naive PWH

Study design and baseline resistance analysis

CALIBRATE was a phase 2, randomized, open-label, active-controlled clinical study that evaluated the safety and efficacy of LEN in combination with other ARVs compared with BIC/FTC/TAF in ARV-naive PWH. A total of 182 PWH were randomized to one of four treatment arms: participants received SUBQ LEN every 6 months in combination with FTC/TAF→TAF (n=52) or FTC/TAF→BIC (n=53), oral LEN in combination with FTC/TAF (n=52), or oral BIC/FTC/TAF in the active control group (n=25).[4]

Baseline resistance was assessed by population genotyping at screening. Baseline HIV-1 CA genotypic and phenotypic analyses were also performed at study entry.[4] NNRTI RAMs were the most common at baseline (Figure 1) and primarily included K103N/S and E138A/G/K/Q/R. The NRTI RAMs primarily consisted of thymidine analogue mutations. There were no LEN or INSTI RAMs detected at baseline.[9]

Figure 1. CALIBRATE Study: Baseline Resistance Substitutions[9]



Post-baseline resistance analyses

Resistance analyses were performed if participants had suboptimal virologic response (confirmed HIV-1 RNA ≥50 c/mL and a <1-$\log_{10}$ decrease from Day 1 at Week 10), virologic rebound (confirmed HIV-1 RNA ≥50 c/mL after achieving HIV-1 RNA <50 c/mL or >1-$\log_{10}$ increase in HIV-1 RNA from the nadir), or HIV-1 RNA ≥50 c/mL at last visit.[9]

At Week 80, 7 participants met the criteria for resistance testing; 3 of these participants had emergent LEN resistance (Table 3). Of the 3 participants with emergent LEN resistance, 2 had suspected incomplete adherence to coadministered ARVs.[3,4]

Table 2. CALIBRATE Study: Resistance Population at Week 80[3]

	SUBQ LEN + FTC/TAF (→TAF) (n=52)	SUBQ LEN + FTC/TAF (→BIC) (n=53)	Oral LEN + FTC/TAF (n=52)	BIC/FTC/ TAF (n=25)
Met criteria for resistance testing, n	2	1	3	1
Emergent LEN resistance, n	1	1	1	0
Q67H	1	1	1	0
K70R	1	1	1	0

One participant in the SUBQ LEN + FTC/TAF→BIC group developed FTC RAM M184I/V at Week 2 before LEN RAMs (Q67H + K70R) and reverse transcriptase RAMs (M184M/I), which were detected at Week 10. This pattern of mutation emergence suggested incomplete adherence to FTC/TAF preceding emergent LEN resistance.[4] LEN plasma concentrations were consistently within the target range, and FTC and tenofovir concentrations were consistent with expected pharmacokinetics. After a switch to AZT/3TC + TDF + DTG at Week 22, the participant achieved virologic suppression after Week 28.[4,9]

The second participant with treatment-emergent LEN resistance was in the oral LEN + FTC/TAF group and had a LEN RAM (Q67H) detected at Week 54 and subsequent detection of K70R. Pill counts and plasma drug concentrations for LEN and TAF suggested incomplete adherence.[3]

The third participant with emergent LEN resistance was in the SUBQ LEN + FTC/TAF→TAF group and developed LEN RAMs (Q67H+K70R) at Week 80.[3]

Safety results[3]

A safety analysis was not conducted in the subgroup of participants with treatment-emergent LEN resistance. Through Week 80, the most common AEs (excluding ISRs) in ≥10% of participants included headache, nausea, COVID-19, syphilis, influenza, and diarrhea. No participants discontinued LEN treatment due to a non-ISR AE.

Most ISRs reported through Week 80 were mild to moderate, and 1 participant experienced a Grade 3 nodule. Four participants discontinued LEN due to Grade 1 ISRs: induration after the first dose (n=2), induration after the third dose (n=1), and erythema and swelling after the second dose (n=1).

References

1. Enclosed, Gilead Sciences Inc. SUNLENCA® (lenacapavir) tablets, for oral use. SUNLENCA® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.
2. Ogbuagu O, McGowan JP, Stapleton A, et al. Long-Acting Subcutaneous Lenacapavir in People With Multi-Drug-Resistant HIV-1: 3-Year Results of the CAPELLA Study.[Presentation #155]. Paper presented at: IDWeek 2024; October 16-19, 2024; Los Angeles, CA.
3. Hagins D, Koenig E, Safran R, et al. Long-Acting Lenacapavir in a Combination Regimen for Treatment Naïve PWH: Week 80 [Poster 522]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 19-22 February, 2023; Seattle, WA.
4. Gupta SK, Berhe M, Crofoot G, et al. Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-

label, active-controlled, phase 2 trial [main article + supplementary]. *Lancet HIV.* 2023;10(1):e15-e23.
5. Ogbuagu O, Molina JM, Chetchotisakd P, et al. Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People with Multidrug-Resistant HIV-1: Week 104 Results of a Phase 2/3 Trial. *Clin Infect Dis.* 2025;80(3):566-574.
6. Margot NA, Jogiraju V, Pennetzdorfer N, et al. Resistance Analyses in Heavily Treatment-Experienced People with HIV Treated with the Novel HIV Capsid Inhibitor Lenacapavir After 2 years. *J Infect Dis.* 2025;231:1239–1245.
7. Margot NA, Naik V, VanderVeen L, et al. Resistance Analyses in Highly Treatment-Experienced People With Human Immunodeficiency Virus (HIV) Treated With the Novel Capsid HIV Inhibitor Lenacapavir. *J Infect Dis.* 2022;226(11):1985-1991.
8. Ogbuagu O, Molina JM, Chetchotisakd P, et al. Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People with Multidrug-Resistant HIV-1: Week 104 Results of a Phase 2/3 Trial [Supplementary Appendix]. *Clin Infect Dis.* 2025;80(3):566-574.
9. VanderVeen LA, Margot N, Naik V, Dvory-Sobol H, Rhee MS, Callebaut C. Resistance Analysis of Long-Acting Lenacapavirin Treatment-Naïve People With HIV at 54 Weeks [Poster EPB239]. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.

Abbreviations

3TC=lamivudine
AE=adverse event
ARV=antiretroviral
AZT=zidovudine
BIC=bictegravir
c/mL=copies/mL
CA=capsid
DTG=dolutegravir
FTC=emtricitabine
HTE=heavily treatment-experienced
INSTI=integrase strand transfer inhibitor
ISR=injection site reaction
LEN=lenacapavir
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OBR=optimized background regimen
PI=protease inhibitor
PWH=people with HIV
RAM=resistance-associated mutation
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Sunlenca US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers, and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.