# Sunlenca® (lenacapavir)
# Use in Treatment-Naïve Individuals

This document is in response to your request for information regarding the use of Sunlenca® (lenacapavir [LEN]) in treatment-naïve (TN) individuals with HIV-1 infection. LEN is not approved by any regulatory authority for use in TN individuals.

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

Clinical Study of LEN in TN PWH

In the phase 2 CALIBRATE study in TN PWH, 87% of participants in the pooled LEN group who received either SUBQ LEN + FTC/TAF→TAF, SUBQ LEN + FTC/TAF→BIC, or oral LEN + FTC/TAF achieved and maintained virologic suppression at Week 54,[2] and high rates of virologic suppression were maintained through Week 80.[3,4]

- At Week 80, 4 participants had emergent LEN resistance.[3,4] Two of these participants had suspected incomplete adherence.[2,4]
- ISRs were the most commonly reported AEs, were mostly Grade 1 or 2 in severity, and resulted in discontinuation of LEN in 4 participants.[3]
- The most common non-ISR AEs in participants receiving LEN included influenza, headache, and COVID-19. There were no treatment-related SAEs.[4]


## Clinical Study of LEN in TN PWH

### CALIBRATE: LEN in TN PWH

#### Study design and demographics

CALIBRATE was a randomized, open-label, active-controlled phase 2 study (NCT04143594) that evaluated the safety and efficacy of LEN in combination with other ARVs compared with BIC/FTC/TAF in ARV-naïve PWH. A total of 182 PWH were randomized to one of four treatment arms, and participants received SUBQ LEN every 6 months in combination with FTC/TAF→TAF (TG1) or FTC/TAF→BIC (TG2), oral LEN in combination with FTC/TAF

(TG3), or oral BIC/FTC/TAF in the active control group (TG4; Figure 1).[2]

The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 54.[3] Secondary endpoints included the proportion of participants with plasma HIV-1 RNA <50 c/mL at Weeks 28, 38, and 80 and the change in $log_{10}$ HIV-1 RNA and CD4+ cell counts from baseline to Weeks 28, 38, 54, and 80. Baseline demographics and characteristics were similar among the four treatment groups (Table 1).

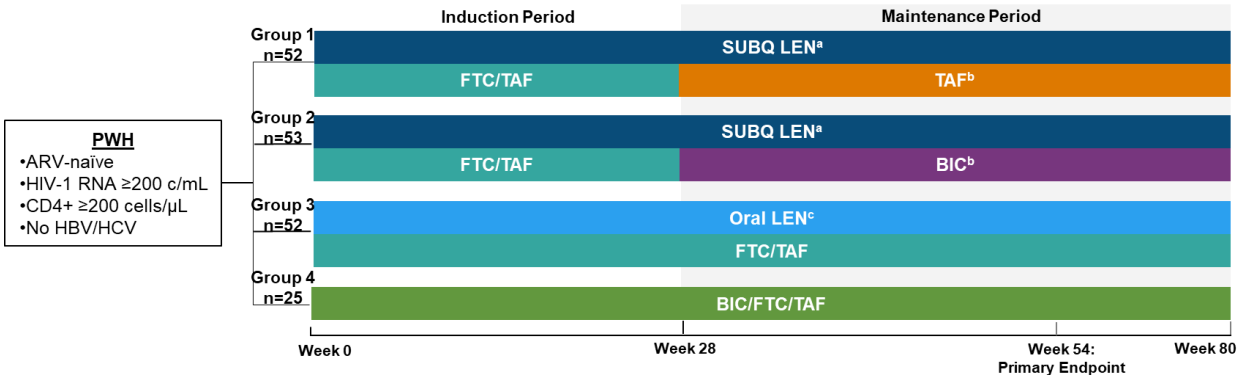



**Figure 1. CALIBRATE: Study Design[2,4,5]**

[a]The LEN dosing schedule included an oral initiation phase (Day 1: 600 mg; Day 2: 600 mg; Day 8: 300 mg), followed by SUBQ LEN 927 mg on Day 15 and every 26 weeks thereafter.
[b]Participants were required to have HIV-1 RNA <50 c/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28. Those with HIV-1 RNA ≥50 c/mL discontinued the study at Week 28.
[c]The oral LEN dosing schedule was as follows: 600 mg on Day 1, 600 mg on Day 2, and 50 mg daily starting on Day 3.
Note: FTC/TAF (200/25 mg), TAF (25 mg), BIC (75 mg), and BIC/FTC/TAF (50/200/25 mg) are administered as daily oral doses.

**Table 1. CALIBRATE Study: Key Baseline Demographics and Disease Characteristics[2,4,5]**

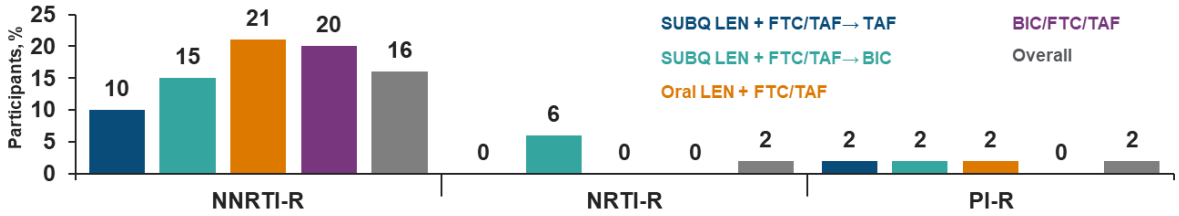
| Key Demographics and Characteristics | | SUBQ LEN + FTC/TAF→TAF (n=52) | SUBQ LEN + FTC/TAF→BIC (n=53) | Oral LEN + FTC/TAF (n=52) | BIC/FTC/TAF (n=25) |
|---|---|---|---|---|---|
| Age, median (range), years | | 31 (26–40) | 28 (24–33) | 28 (24–36) | 29 (26–33) |
| Male sex at birth, n (%) | | 47 (90) | 52 (98) | 46 (89) | 25 (100) |
| Race, n (%) | Asian | 1 (2) | 0 | 1 (2) | 0 |
| | Black | 24 (46) | 24 (45) | 31 (60) | 16 (64) |
| | White | 23 (44) | 28 (53) | 19 (37) | 8 (32) |
| | Other | 4 (8) | 1 (2) | 1 (2) | 1 (4) |
| HIV-1 RNA | Median (range[a]), $log_{10}$ c/mL | 4.3 (3.8–4.6) | 4.3 (4.0–4.7) | 4.5 (3.8–4.8) | 4.4 (4.1–4.8) |
| | >100,000 c/mL, n (%) | 5 (10) | 9 (17) | 9 (17) | 4 (16) |
| CD4 cell count, median (range[a]), cells/µL | | 404 (320–599) | 450 (332–599) | 409 (301–600) | 482 (393–527) |
| Distribution <200 cells/µL, n (%) | | 0 | 1 (2)[b] | 3 (6)[b] | 0 |

[a] IQR (interquartile ratio)
[b]All participants met inclusion criteria and had CD4 counts >200 at screening, which then decreased to <200 at Day 1.

### *Baseline resistance*

No LEN RAMs were detected at baseline. NNRTI-R was the most common resistance substitution observed (Figure 2) and primarily included K103N/S and E138A/G/K/Q/R. The NRTI-R mutations primarily consisted of thymidine analogue mutations.[6]

**Figure 2. CALIBRATE Study: Baseline Resistance Substitutions[6]**



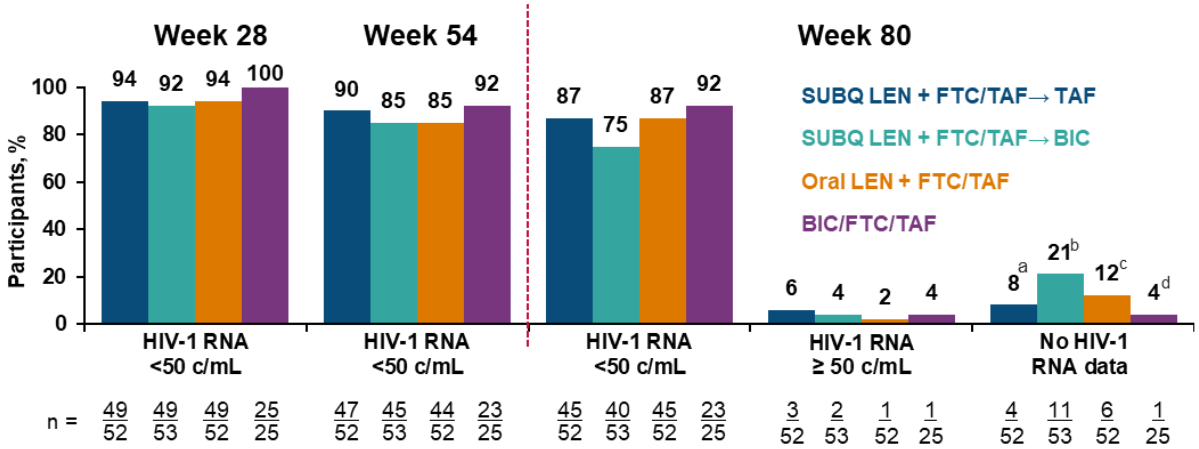

Abbreviation: PI-R=protease inhibitor resistance.
Note: There were no reports of integrase strand transfer inhibitor resistance at baseline.

## Results

### *Efficacy*

There were high rates of virologic suppression (HIV-1 RNA <50 c/mL) by FDA Snapshot analysis across all treatment groups at Week 28, Week 54, and Week 80 (Figure 3).[2,4] At Week 80, the mean (range) change from baseline in CD4 count for the three treatment groups that received LEN was 256 (-384 to 843) cells/µL.[3]

**Figure 3. CALIBRATE Study: Virologic Outcomes Through Week 80 by FDA Snapshot Analysis[2,3,4]**




[a]Participants discontinued the study drug due to AE/death (n=1), investigator's discretion (n=1), or loss to follow-up (n=1); 1 participant had missing data during the analysis window but continued to receive the study drug.
[b]Participants discontinued the study drug due to participant's decision (n=4), AEs (n=3), investigator's discretion (n=2), or loss to follow-up (n=2).
[c]Participants discontinued the study drug due to participant's decision (n=5) or loss to follow-up (n=1).
[d]One participant decided to discontinue the study drug.

### *Post-baseline resistance analyses*

Resistance analyses were performed if participants had suboptimal virologic response (ie, two consecutive visits with HIV-1 RNA ≥50 c/mL and a <1-$log_{10}$ decrease in HIV-1 RNA at Week 10), virologic rebound (ie, two consecutive visits with HIV-1 RNA ≥50 c/mL among those who had previously achieved HIV-1 RNA <50 c/mL, or two consecutive visits with a >1-$log_{10}$ increase in HIV-1 RNA from the nadir), or HIV-1 RNA ≥50 c/mL at study discontinuation. Analyses included an assessment of the genotype and phenotype of HIV-1 capsid, protease, RT, and integrase (Monogram), and, for select samples, deep sequencing analyses (2% cutoff; Seq-IT).[2]

Through Week 80, 10 participants met the criteria for resistance testing (Table 2). Four participants who met the failure criteria resuppressed without a change in regimen and no treatment emergent resistance occurred. In the participants who did not resuppress (n=6) four developed emergent LEN resistance.[4]

One participant in TG2 developed FTC RAM M184I/V before CAI RAMs (Q67H + K70R) and RT RAMs (M184M/I) were detected at Week 10. This pattern of mutation emergence suggested incomplete adherence to FTC/TAF preceding emergent LEN resistance.[2] A participant in TG3 with emergent LEN resistance had a CAI RAM (Q67H) detected at Week 54 and subsequent detection of K70R at Week 80.[3,4] Pill count and drug level assessments suggested inconsistent adherence to oral LEN. There were two participants in TG1 with emergent LEN resistance; one participant had CAI RAMs (Q67H + K70R) at Week 80, and the second had CAI RAM (Q67H) detected at Week 116. There was no evidence of adherence issues by drug concentration for either participant in TG1. [2,3,4]

**Table 2. CALIBRATE Study: Resistance Population at Week 80[3,4]**

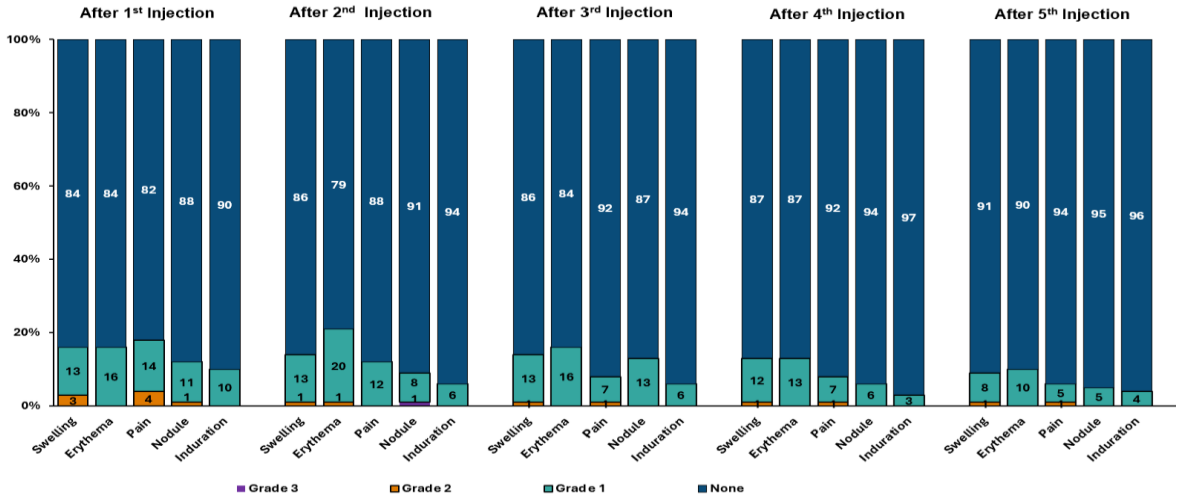
| | SUBQ LEN + FTC/TAF→TAF (n=52) | SUBQ LEN + FTC/TAF→BIC (n=53) | Oral LEN + FTC/TAF (n=52) | BIC/FTC/TAF (n=25) |
|---|---|---|---|---|
| Met criteria for resistance testing, n | 3 | 2 | 4 | 1 |
| Emergent LEN resistance, n | 2 | 1 | 1 | 0 |
| Q67H | 2 | 1 | 1 | 0 |
| K70R | 1 | 1 | 1 | 0 |

### *Safety[3,4]*

Through Week 80, no treatment-related SAEs were reported. The most common AEs in participants receiving LEN (excluding ISRs) included: COVID-19 (n = 30, 19%), influenza (n =29, 18%), and headache (n = 27, 17%). One participant in the TG1 group died due to non–small-cell lung cancer, and 1 participant in TG3 group died of unknown causes; both deaths were considered non–study drug-related. Five participants discontinued treatment with LEN, four participants discontinued due to Grade 1 ISRs: induration (n=3), and erythema and swelling (n=1) and one participant discontinued after Grade 2 increased viral load.

ISRs were the most commonly reported AEs, and most were Grade 1 or 2 in severity. Rates of ISRs for the SUBQ population (TG1 and TG2; n=105) are shown in Figure 4.

**Figure 4. CALIBRATE Study: Frequency of ISR's in the LEN SUBQ population*[4]**




*includes two participants who did not receive SUBQ LEN injection
Injection 1 occurred at Day 15, injection 2 occurred at Week 28, injection 3 occurred at Week 54, injection 4 occurred at Week 80, and injection 5 occurred at Week 106.

After treatment initiation, weight and BMI increased in all treatment groups, and study authors proposed this may be attributable to the "return to health" phenomenon, with a substantial portion of the weight gain occurring by Week 28 and slower increases in weight thereafter to Week 80.[5]

# 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. 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.
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. Hagins D, Berhe M, Crofoot GE, et al. Final efficacy and safety of twice-yearly subcutaneous lenacapavir in treatment-naive people with HIV: randomized study. *AIDS.* 2025.
5. Kumar PN, Goldstein DA, Hengel RL, et al. Weight and metabolic changes with long-acting lenacapavir in a combination regimen in treatment naïve people with HIV 1 at week 80 [Poster 1581]. Paper presented at: ID Week 2023; October 11-15, 2023; Boston, MA.
6. 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

AE=adverse event
ARV=antiretroviral
BIC=bictegravir
c/mL=copies/mL
CAI=capsid protein inhibitor
FTC=emtricitabine
ISR=injection site reaction
LEN=lenacapavir
NNRTI-R=non-nucleoside reverse transcriptase inhibitor resistance
NRTI-R=nucleoside reverse transcriptase inhibitor resistance
PWH=people with HIV
RAM=resistance-associated mutation
RT=reverse transcriptase
SAE=serious adverse event
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TN=treatment naïve

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

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