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Sunlenca® (lenacapavir) Oral Initiation Dosing

This document is in response to your request for information regarding the use of Sunlenca® (lenacapavir [LEN]) and oral initiation dosing.

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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 can be initiated using one of the two recommended dosage regimens. Maintenance dosing is administered by SUBQ injection every 6 months regardless of the initiation regimen. Healthcare providers should determine the appropriate initiation regimen for the patient. LEN oral tablets may be taken with or without food.

- Initiation Option 1: Day 1, 927 mg SUBQ (2 × 1.5 mL injections) and 600 mg orally (2 × 300 mg tablets); Day 2, 600 mg orally (2 × 300 mg tablets).
- Initiation Option 2: Day 1, 600 mg orally (2 × 300 mg tablets); Day 2, 600 mg orally (2 × 300 mg tablets); Day 8, 300 mg orally (1 × 300 mg tablet); Day 15, 927 mg SUBQ (2 × 1.5 mL injections).
- Maintenance: 927 mg SUBQ (2 × 1.5 mL injections) every 6 months (26 weeks) from the date of the last injection ±2 weeks.

Clinical Data on Oral Initiation Dosing of LEN

Due to the slow initial release of SUBQ LEN, an oral initiation regimen is necessary to achieve the target LEN concentration more quickly. PK simulations were conducted to support the use of LEN with an oral initiation regimen followed by SUBQ maintenance once every 6 months.[2]

- The combination of oral LEN initiation doses followed by a single SUBQ injection was predicted to achieve the LEN target concentration of 24 ng/mL within a few days after administration; the target concentration was expected to be maintained through 26 weeks (6 months).

A phase 1 study in healthy volunteers evaluated the PK, safety, and tolerability of a LEN regimen used in a phase 2/3 study, including individual doses of oral LEN and SUBQ LEN, as well as a simplified regimen of concurrent dosing of oral LEN and SUBQ LEN.[3]

- For both regimens, mean LEN concentrations reached the efficacious target (IQ4 of 15.5 ng/mL) rapidly and were maintained throughout the dosing interval of 6 months.

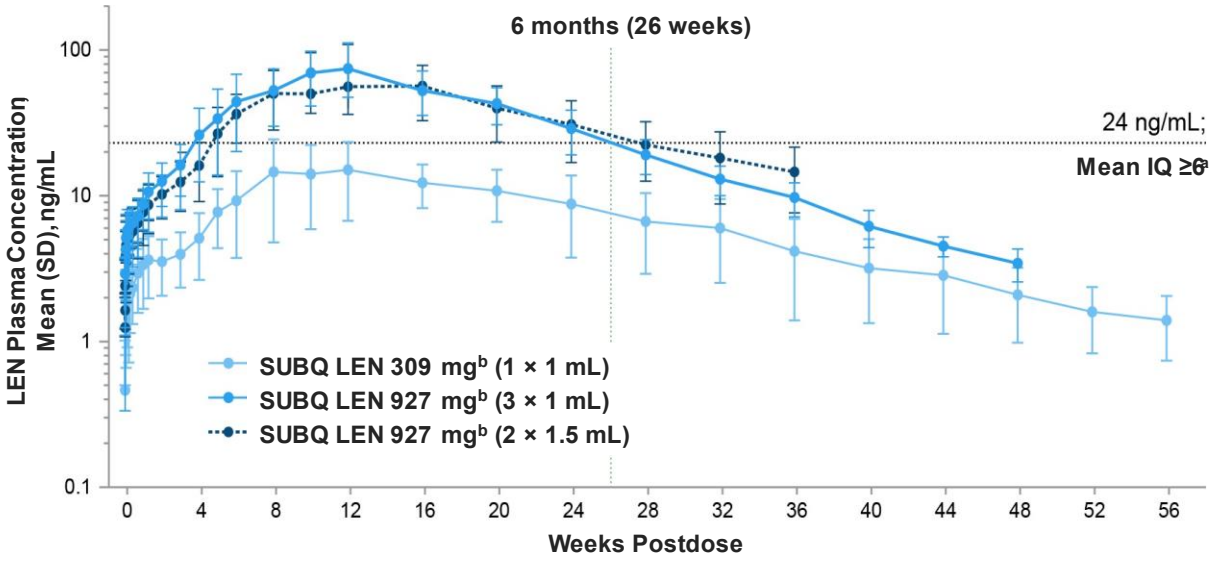
- LEN concentrations in the simplified regimen were generally comparable to those in the phase 2/3 regimen.
- Both regimens were well tolerated, and there were no Grade 3, Grade 4, or serious AEs. No deaths were reported.

Clinical Data on Oral Initiation Dosing of LEN

LEN Dosing Regimen Simulations in Phase 2/3 Studies[2,4]

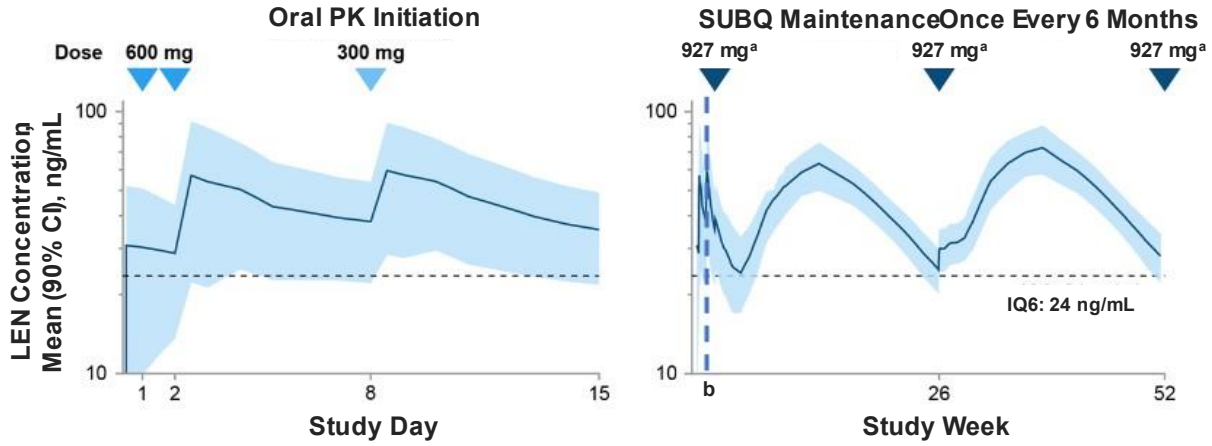
The formulation of LEN 309 mg/mL SUBQ injection has a slow initial drug release that requires an oral initiation dose prior to administration of the first injection. In a phase 1 study, LEN plasma concentrations were ≥24 ng/mL (mean IQ ≥6 ng/mL) for 26 weeks after administration of a single LEN 927 mg SUBQ injection (Figure 1). The T_{max} of LEN ranged from 11 to 14 weeks after dose administration, and the half-life ranged from 7 to 11 weeks. PK simulations were conducted using PK results for the SUBQ injection from this phase 1 study and PK results for the oral LEN tablet from a separate study. The combination of oral LEN initiation doses followed by a single SUBQ injection was predicted to achieve the LEN target concentration of 24 ng/mL within a few days after administration; the target concentration was expected to be maintained through 26 weeks (6 months; Figure 2).

Figure 1. LEN Plasma Concentration-Time Profiles (Begley et al)[2,4]



[a]The IQ is the ratio of LEN plasma concentration to the effective concentration to cause inhibition by 95%.
[b]Dose originally presented as 300 mg and 900 mg, equivalent to current formulation.
Note: The LEN target concentration of 24 ng/mL was calculated using observed antiviral activity and corresponds to a mean IQ ≥6 (range, 6.2–20.3) ng/mL.

Figure 2. Predicted PK of LEN Dosing in Phase 2/3 Studies (Begley et al)[2,4]



[a]Dose originally presented as 900 mg, equivalent to current formulation.
[b]End of oral PK initiation period.

PK Study of Simplified LEN Regimen Compared With Phase 2/3 LEN Regimen in Healthy Volunteers[3]

Study design and demographics

A phase 1, open-label, multicohort study evaluated the PK, safety, and tolerability of a LEN regimen used in a phase 2/3 study (Cohort 1), including individual doses of oral LEN and SUBQ LEN, as well as a simplified regimen of concurrent dosing of oral LEN and SUBQ LEN (Cohort 2) in healthy volunteers (Figure 3; Table 1). PK samples were collected before dosing began through at least Day 197 to cover three to five half-lives. Safety parameters, including AEs, were monitored throughout the study in both treatment groups.

Figure 3. Study Design (Jogiraju et al)[3]

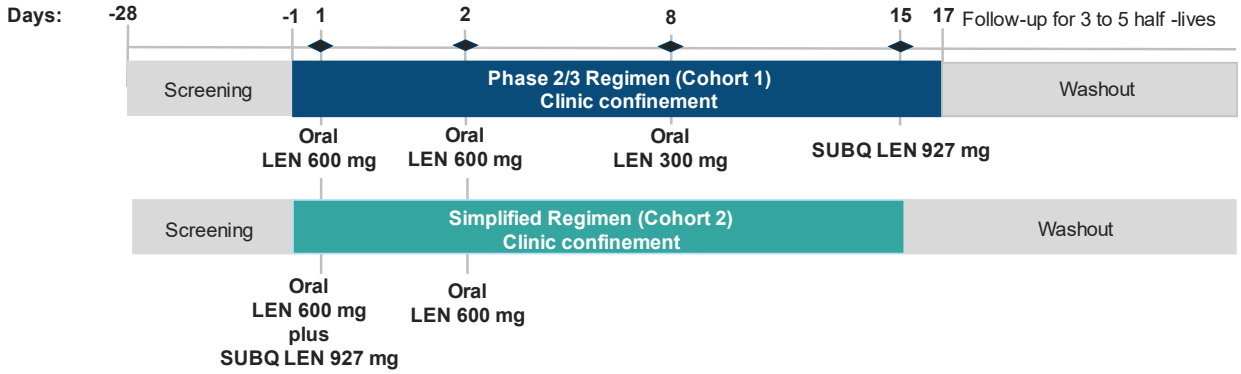


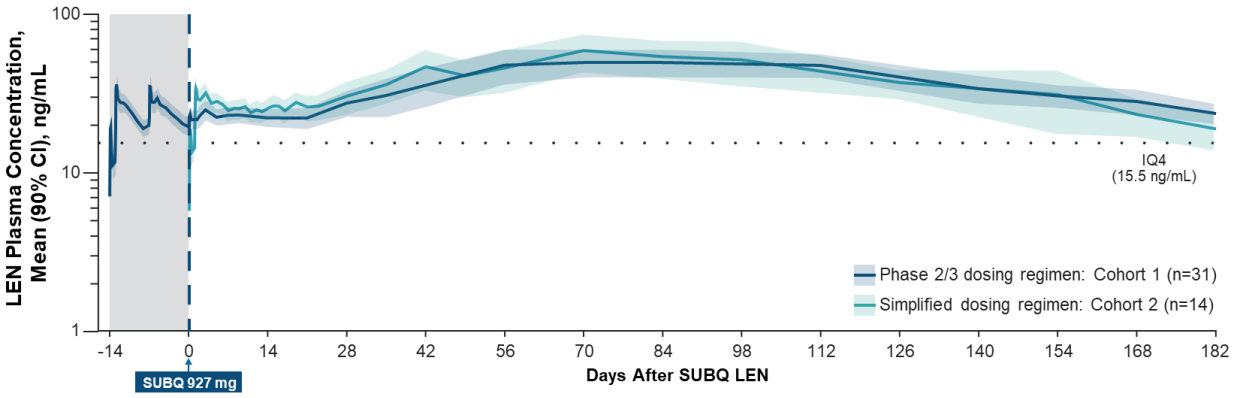
Table 1. Key Baseline Demographics and Characteristics (Jogiraju et al)[3]

Key Demographics and Characteristics	Phase 2/3 Regimen: Cohort 1 (n=31)	Simplified Regimen: Cohort 2 (n=14)
Age, median (range), years	32 (22–43)	33 (20–45)
Male, n (%)	19 (61)	11 (79)
Race, White/Black, n (%)	20 (65)/11 (35)	11 (79)/3 (21)
Body weight, median (range), kg	78.6 (54.3–95.6)	72.2 (58.3–98.3)
BMI, median (range), kg/m^2	26.8 (21.9–30.3)	25.5 (21.8–29.7)

Results

In the phase 2/3 regimen group, the mean plasma LEN concentration was maintained above the target IQ4 of 15.5 ng/mL from 2 hours after the administration of oral LEN on Day 2 through Day 197. The median T_{max} was approximately 85 days after administration of the SUBQ dose on Day 15. In the simplified regimen group, the mean plasma LEN concentration exceeded the target IQ4 of 15.5 ng/mL at 2 hours after the administration of oral LEN on Day 2 and was consistently maintained above the target IQ4 during the dosing interval. The median T_{max} occurred approximately 70 days after administration of the SUBQ dose on Day 1. An overlay of the LEN concentrations for the two treatment regimens is presented in Figure 4.

Figure 4. LEN Plasma Concentration After Phase 2/3 and Simplified Dosing Regimens (Jogiraju et al)[3]



LEN PK parameters were generally comparable between cohorts (Table 2).

Table 2. PK Parameters of LEN Phase 2/3 Regimen and Simplified Regimen (Jogiraju et al)[3]

PK Parameters	Phase 2/3 Regimen: Cohort 1			
	Day 1: Oral LEN 600 mg (n=31)	Day 2: Oral LEN 600 mg (n=31)	Day 8: Oral LEN 300 mg (n=31)	Days 15–197: SUBQ LEN 927 mg (n=30)
C_{max}, mean (CV), ng/mL	22 (45.5)	40.4 (43.4)	39.3 (44.7)	58.7 (58.1)
T_{max}, median (Q1, Q3), hours [days]	4 (4, 6) [0.17]	6 (4, 8) [0.25]	6 (4, 8) [0.25]	2028 (1682.5, 2688.2) [84.5]
C_{last}, mean (CV), ng/mL	11.8 (57.2)	19.1 (40)	19.9 (40.4)	29.8 (67.6)
T_{last}, median (Q1, Q3), hours [days]	24 (24, 24) [1]	144 (144, 144) [6]	168 (168, 168) [7]	4319.5 (2689, 4365.8) [180]
$AUC_{0–196\ days}$, mean (CV), h·ng/mL	134,000.5 (55.9)			
PK Parameters	**Simplified Regimen: Cohort 2**			
	Day 1: Oral LEN 600 mg + SUBQ LEN 927 mg (n=14)		Days 2–197: Oral LEN 600 mg (n=14)	
C_{max}, mean (CV), ng/mL	20.1 (34.5)		67.1 (47.2)	
T_{max}, median (Q1, Q3), hours [days]	6 (4, 8) [0.25]		1653.9 (985, 1991.2) [68.9]	
C_{last}, mean (CV), ng/mL	14.4 (36.9)		21.4 (93.1)	
T_{last}, median (Q1, Q3), hours [days]	24 (24, 24) [1]		4679.4 (4678.9, 4679.9) [195]	
$AUC_{0–182\ days}$, mean (CV), h·ng/mL	148,284.1 (56.6)			

Abbreviation: Q=quartile.

Safety

Overall, LEN was well tolerated in both regimens, and there were no Grade 3 or 4 AEs or serious AEs. Injection site reactions were the most common AEs. No deaths were reported.

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. Begley R, Lutz J, Rhee M, et al. Lenacapavir Sustained Delivery Formulation Supports 6-Month Dosing Interval [Poster PEB0265]. Paper presented at: AIDS 2020: 23rd International AIDS Conference Virtual; 06-10 July, 2020.
3. Jogiraju V, Graham H, West S, et al. Pharmacokinetics of a Simplified Subcutaneous Lenacapavir Regimen Versus Phase 2/3 Regimen [Poster PESUB22]. Paper presented at: AIDS 2022; 29 July-2 August, 2022; Montreal, Quebec, Canada.
4. Gilead Sciences Inc. Data on File.

Abbreviations

AE=adverse event
AUC=area under the concentration-time curve
C_{last}=concentration at last observed time point
C_{max}=maximum observed drug concentration
CV=coefficient of variation
IQ4/6=inhibitory quotient 4/6
LEN=lenacapavir
PK=pharmacokinetic(s)
SUBQ=subcutaneous(ly)
T_{last}=time of last observed concentration
T_{max}=time to maximum drug concentration

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Sunlenca US Prescribing Information available at: http://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

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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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