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Population-PK Analysis to Guide Dosing Window Following Lenacapavir SC Administration

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Introduction

- Lenacapavir (LEN) is a potent first-in-class capsid inhibitor recently approved for heavily treatment-experienced people with multidrug-resistant HIV-1 infection in combination with other antiretrovirals and is in development for the prevention of HIV-1 infection[1]
- Current data indicate that LEN exhibits near maximal antiviral activity when the lower bound of the 90% confidence interval (CI) of mean trough concentration (C_{trough}) is maintained above inhibitory quotient-4 (IQ4; ≥ 4-fold greater than the in vitro protein-adjusted 95% effective concentration)
- In the ongoing pivotal Phase 2/3 study, participants received oral LEN loading (600 mg on Days 1 and 2; 300 mg on Day 8) followed by every 6 months (Q6M) 927 mg subcutaneous (SC) injection starting from Day 15 (ie, Phase 2/3 regimen); this Phase 2/3 regimen and a more convenient simplified regimen (927 mg SC Q6M, and oral 600 mg on Days 1 and 2) were recently approved by the FDA[2]
- The LEN SC formulation requires administration by a healthcare professional; therefore, a specified dosing window around Q6M (ie, 26 weeks) in which the SC injection can be scheduled in line with regular healthcare professional visits without compromising efficacy and safety would help in maintaining adherence and increasing patient convenience

Objective

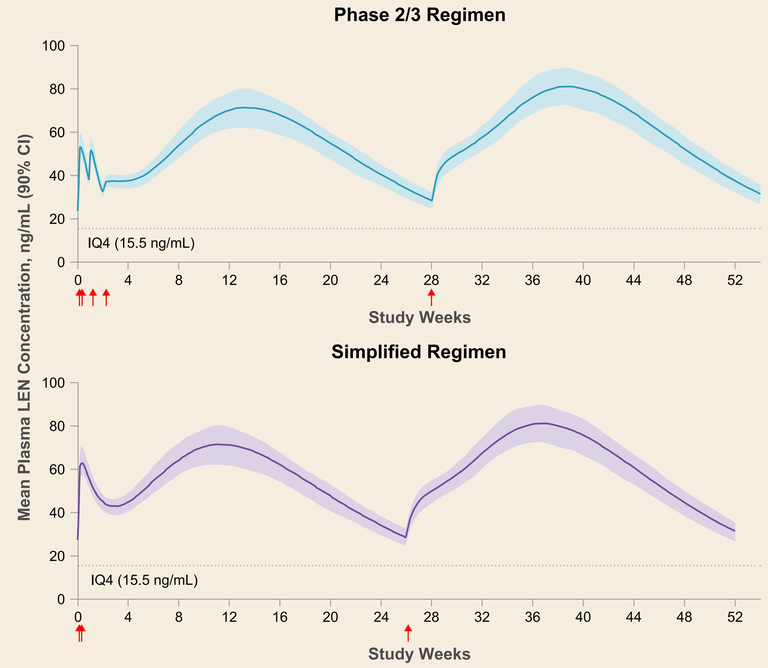
- To determine the flexibility in the dosing window following LEN SC injection (Phase 2/3 or simplified regimen) by simulating various scenarios to assess the impact of potential shifts (advancement or delay) in Q6M dosing on LEN concentration

Methods

- A previously developed 2-compartment LEN population-pharmacokinetics (PopPK) model with 1st-order absorption and linear elimination was used to simulate LEN concentrations[3]
- PopPK analysis of data from 7 Phase 1-3 studies was performed using nonlinear mixed-effects modeling software (NONMEM® [ICON plc, Dublin, Ireland])
  - Several intrinsic and extrinsic factors/covariates including pharmacoenhancers (cobicistat and ritonavir), body weight, age, sex, race, ethnicity, dose, disease status (treatment naïve and heavily treatment experienced), food, formulation, and estimated glomerular filtration rate were evaluated
  - 1st-order conditional estimation with interaction was the primary method used for PopPK model parameter estimation
- Using the PopPK model, plasma concentrations were simulated for various scenarios for the 2nd LEN SC dose to evaluate the dosing window following the Phase 2/3 or simplified regimen (Figure 1)

Results

Figure 1. Simulated LEN Concentration-Time Profiles for Phase 2/3 and Simplified Regimens in Adults With HIV



Red arrows indicate LEN dosing, occurring on Days 1, 2, 8, and 15, and Week 28 for Phase 2/3 regimen, and on Days 1 and 2, and Week 26 for simplified regimen.

- Phase 2/3 and simplified regimens' simulated LEN C_{trough} values at various weeks are shown in Table 1 and Figure 2

Table 1. LEN C_{trough} Following Phase 2/3 or Simplified Regimen Administration

	Phase 2/3 Regimen		Simplified Regimen	
	LEN C_{trough} ng/mL (90% CI)	IQ	LEN C_{trough} ng/mL (90% CI)	IQ
Week 24	34.6 (29.4, 38.5)	8.9 (7.5, 9.9)	36.4 (31.0, 40.9)	9.4 (8.0, 10.5)
Week 26	29.2 (24.6, 32.5)	7.5 (6.3, 8.4)	30.3 (25.9, 33.9)	7.8 (6.7, 8.7)
Week 28	24.5 (20.4, 27.3)	6.3 (5.2, 7.0)	25.9 (21.9, 28.9)	6.7 (5.6, 7.4)

Figure 2. Simulated LEN C_{trough} at Weeks 24-32 in Adults With HIV

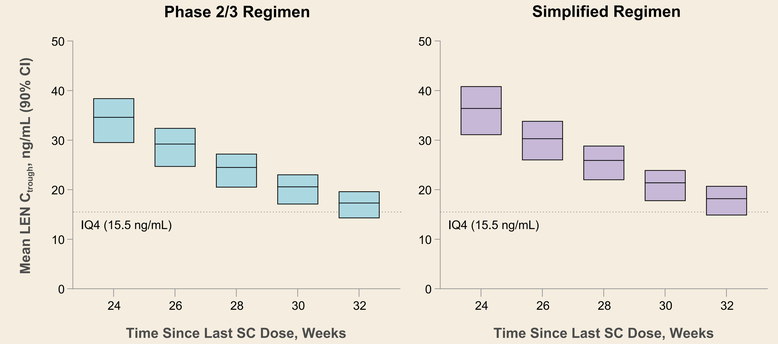


Table 1 reports values for Weeks 24, 26, and 28; Phase 2/3, mean LEN C_{trough} (90% CI) ng/mL at Weeks 30 and 32: 20.6 (17.0, 23.1) and 17.3 (14.2, 19.7), respectively; corresponding simplified, mean LEN C_{trough}: 21.4 (17.7, 24.0) and 18.2 (14.8, 20.8).

- As shown in Figure 2, the lower bounds of the 90% CIs of simulated LEN C_{trough} were found to be consistently above the IQ4 threshold of 15.5 ng/mL for both regimens up to 28 weeks after the last SC dose
- Due to slow release of LEN following SC administration, successive SC injections at Week 24 resulted in similar C_{max} compared with dosing at Week 26; thus there are no safety concerns
- Similarly, SC injection at Week 28 maintained LEN concentrations above the target therapeutic concentration (lower bound 90% CIs were 20.4 ng/mL [IQ 5.2] and 21.9 ng/mL [IQ 5.6] for the Phase 2/3 and simplified regimens, respectively) throughout the dosing interval

Summary

- SC dosing of Q6M LEN using the Phase 2/3 and simplified regimens provided a ± 2-week dosing window
  - *When maintenance SC dose is administered 2 weeks earlier (ie, Week 24):* LEN C_{max} is predicted to be similar to SC dosing occurring at Week 26
  - *When maintenance SC dose is administered 2 weeks later (ie, Week 28):* LEN C_{trough} was maintained above the efficacy target (lower bound 90% CI of C_{trough} above IQ4) for both regimens
- For individuals who cannot receive SC LEN within this window (ie, those whose dosing falls beyond the 28-week window), restart of oral LEN loading (600 mg on Days 1 and 2, and 300 mg on Day 8 for Phase 2/3 regimen, and 600 mg on Days 1 and 2 for simplified regimen) followed by SC LEN is recommended

Conclusion

- In administering SC LEN Q6M, a 4-week dosing window (± 2 weeks around the scheduled injection) is adequate to maintain safe and efficacious exposure

References: **1.** Dvory-Sobol H, et al. Curr Opin HIV AIDS 2022;17:15-21; **2.** Sunlenca [prescribing information]. Foster City, CA; 2022; **3.** Shaik N, et al. AIDS 2022, poster EPB174. **Acknowledgments:** This study was funded by Gilead Sciences, Inc. Certara, Inc. was compensated for the research conduct by Gilead. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead. **Disclosures:** **NA Shaik, M Rhee, S Girish, R Palaparthy, R Singh:** employees and shareholders of Gilead; **F Bellanti, C Comisar:** employees and shareholders of Certara.

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