Comparison of Long-Acting Lenacapavir Phase 2/3 Regimen vs Simplified Regimen Using Population-PK Analysis and Simulation

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Key Findings

- Lenacapavir (LEN) is approved for the treatment of multidrug-resistant HIV-1 in combination with other antiretrovirals for heavily treatment-experienced people with HIV (HTE PWH)
- Two LEN dosing regimens are approved in the USA:
  - Phase 2/3 regimen: Days 1 and 2: 600 mg orally; Day 8: 300 mg orally then subcutaneous (SC) LEN dosing (927 mg every 6 months [Q6M]) starting on Day 15
  - Simplified regimen: Day 1: 600 mg orally and 927 mg SC injection; Day 2: 600 mg orally; then SC LEN dosing with 927 mg SC Q6M
- Pharmacokinetic (PK) data in HTE PWH are currently not available for the simplified regimen
- Simulation using a LEN PopPK model indicated that the simplified regimen was comparable with the Phase 2/3 regimen in HTE PWH: at steady state the accumulation ratio was 1.2-fold for both regimens
- Thus, no differences in the efficacy and safety of LEN in HTE PWH are expected between the two regimens

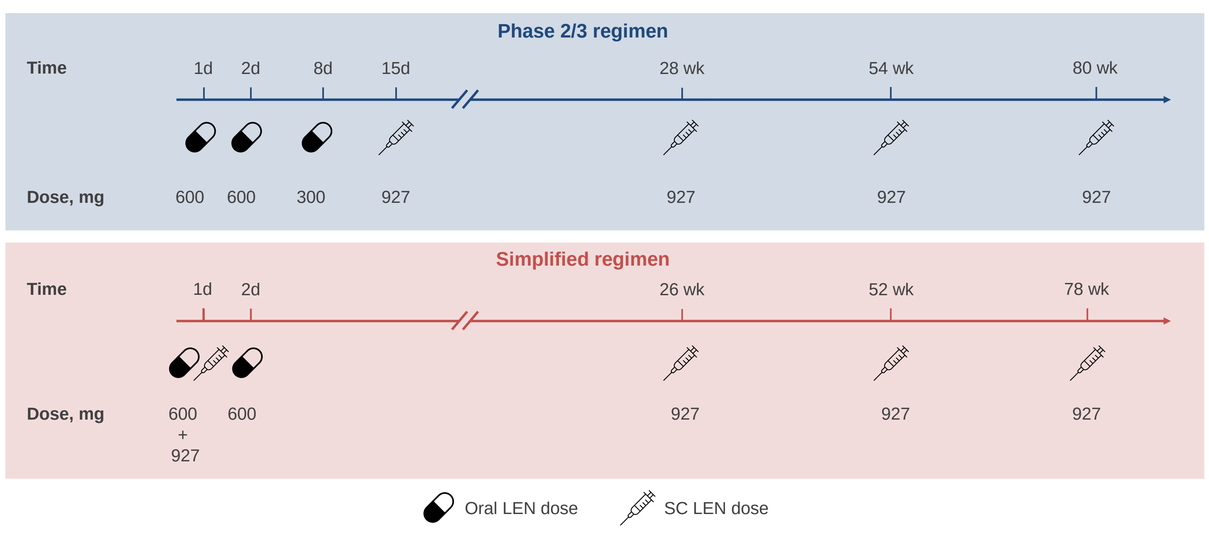
Conclusions

- Simulated LEN PK for the first SC dose and at steady state for the Phase 2/3 and simplified regimens were comparable across all exposure metrics with steady-state LEN concentrations being identical in HTE PWH
- No differences in the safety and efficacy of LEN are expected based on the PK similarity of the Phase 2/3 and simplified regimens
- These data support the use of the simplified regimen for ongoing LEN treatment and prevention studies

Background

- LEN, a potent first-in-class capsid inhibitor, is approved for the treatment of multidrug-resistant HIV-1 in combination with other antiretrovirals for HTE PWH[1,2]
- LEN has shown near maximum antiviral activity when the lower bound of the 90% confidence interval (CI) of mean trough concentration (C_{trough}) is maintained above 15.5 ng/mL,[3] which is the inhibitory quotient-4 (IQ4; ≥4-fold greater than the *in vitro* protein-adjusted 95% effective concentration in MT-4 cells)[4]
- In the ongoing pivotal Phase 2/3 study (CAPELLA, NCT04150068[5]), participants received oral LEN loading doses (Days 1 and 2: 600 mg; Day 8: 300 mg) then SC LEN dosing (927 mg Q6M) starting on Day 15 (Phase 2/3 regimen; **Figure 1**)
- This Phase 2/3 regimen and a simplified regimen (Day 1: 600mg orally and 927 mg SC injection; Day 2: 600 mg orally; then SC LEN dosing with 927 mg SC Q6M; **Figure 1**) were recently approved by the FDA[1]
- In a healthy volunteer study, LEN plasma concentrations were comparable between the Phase 2/3 regimen and the simplified regimen for 6 months after the first SC dose[6]
- PK data in HTE PWH are currently not available for the simplified regimen

Figure 1. Phase 2/3 and simplified LEN dosing regimens



d, day; LEN, lenacapavir; SC, subcutaneous, wk, week.

Objective

- To compare the simulated steady-state LEN exposure metrics between the Phase 2/3 and simplified regimens in HTE PWH

Methods

- LEN plasma concentrations were simulated using a previously developed 2-compartment population-PK (PopPK) model with 1st-order process for oral absorption, and parallel 1st-order and transit compartments for SC absorption and linear elimination[7]
- Using the PopPK model, plasma concentrations were simulated with both the Phase 2/3 and the simplified regimens (**Figure 2**), and LEN exposure metrics were compared (**Figure 3**)
- Key exposure metrics were the area under the concentration-time curve over the dosing interval (AUC_{tau}), maximum concentration of LEN (C_{max}), and C_{trough}
- External validation was conducted using observed data for the simplified regimen in healthy participants (Phase I study, GS-US-200-5709, Cohort 2)

Results

PK Simulations

- Simulated LEN exposure in HTE PWH for the Phase 2/3 and simplified regimens are shown in **Table 1** for the first dose and at steady-state
- The simplified regimen was comparable with the Phase 2/3 regimen up to 6 months after the first SC dose (**Table 1**)
- Exposure metrics (AUC_{tau}, C_{max}, C_{trough}) were identical at steady-state for both regimens (**Table 1**)
- Steady-state was achieved by the second SC dose with 1.2-fold accumulation for both regimens (**Figure 2**)
- As shown in **Figure 3C**, the lower bounds of the 90% CIs of simulated mean LEN C_{trough} were found to be consistently above the IQ4 threshold of 15.5 ng/mL for both regimens over the treatment duration

External validation

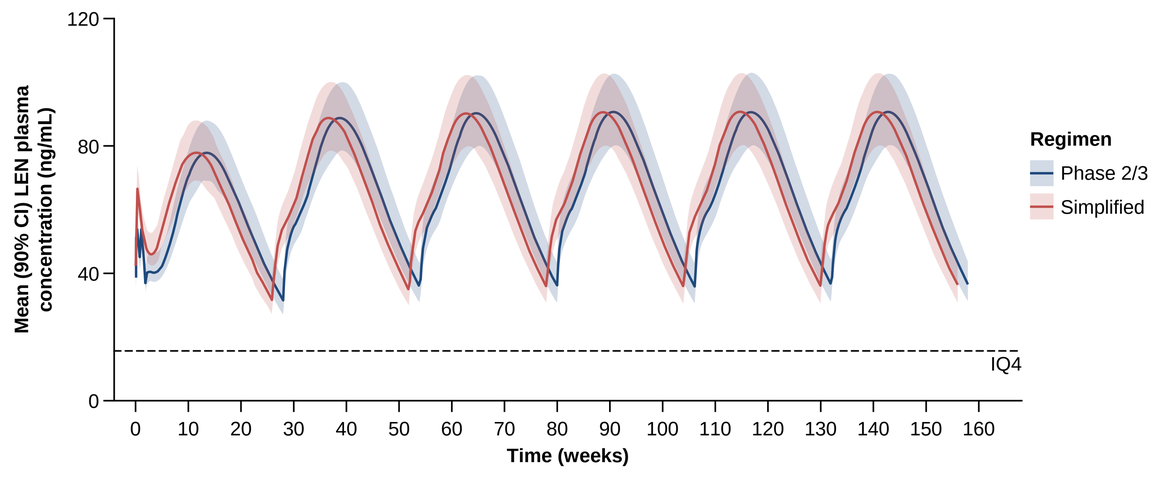
- External validation indicated that the PopPK model captured the simplified regimen data adequately (**Figure 4**)
- As C_{max} is driven by SC administration, both regimens resulted in similar C_{max} over the duration of treatment (**Figure 4**), thus there are no safety concerns

Table 1. Simulated LEN exposure metrics for Phase 2/3 and simplified regimens of LEN in HTE PWH

	Phase 2/3 regimen			Simplified regimen		
Parameter, Mean (%CV)	**Days 1–15**	**Day 15 – End of month 6**	**Steady state**	**Days 1–15**	**Day 15 – End of month 6**	**Steady state**
AUC_{tau}, h•ng/mL	15,600 (52.9)	250,000 (66.6)	300,000 (68.5)	18,800 (53.6)	238,000 (67.5)	300,000 (68.5)
C_{max}, ng/mL	69.6 (56.0)	87 (71.8)	97.2 (70.3)	80.1 (55.7)	87.1 (71.9)	97.2 (70.3)
C_{trough}, ng/mL	35.9 (56.8)	32.7 (88)	36.2 (90.6)	49 (57.9)	32.7 (88)	36.2 (90.6)

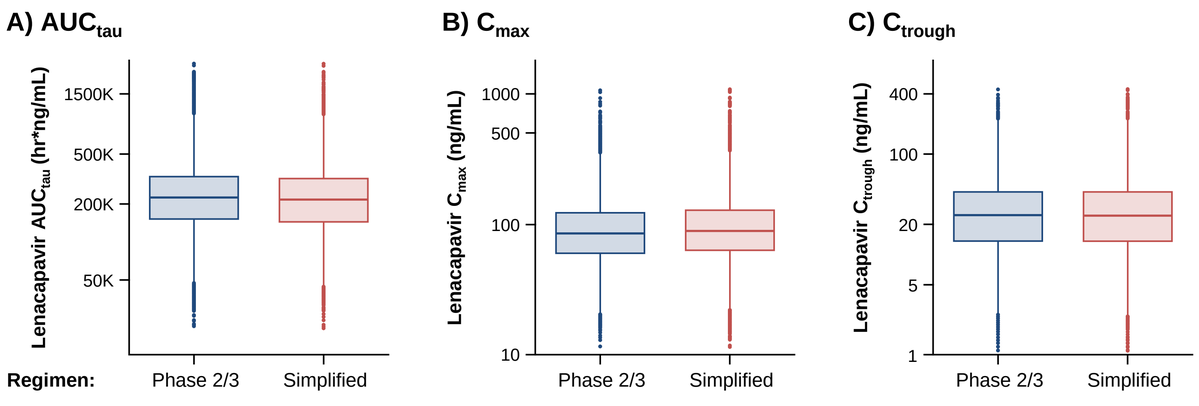
AUC_{tau}, area under curve over dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; HTE, heavily treatment-experienced; LEN, lenacapavir; PWH, people living with HIV; %CV, percentage coefficient of variation, simulations conducted using approximately 40,000 virtual patients

Figure 2. Simulated plasma LEN concentration-time curves with multiple dosing for Phase 2/3 and simplified regimens in HTE PWH



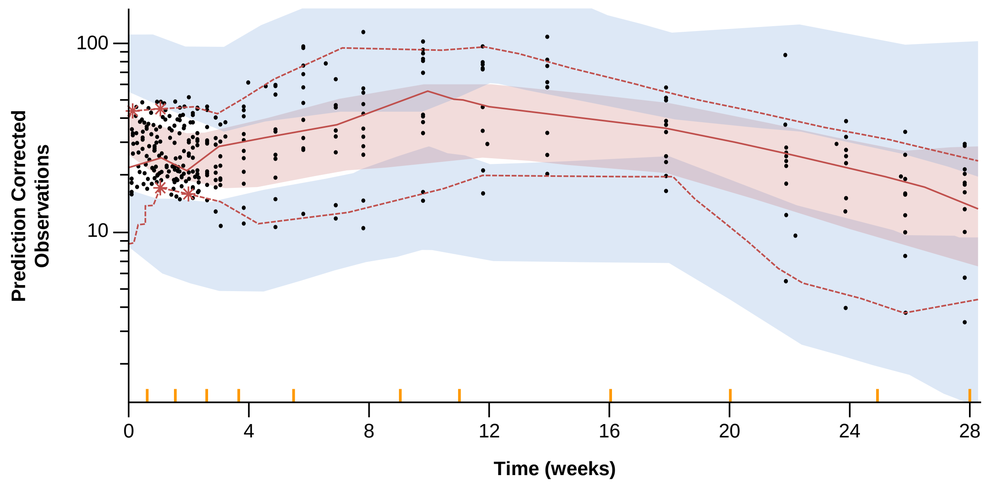
CI, confidence intervals; HTE, heavily treatment-experienced; LEN, lenacapavir; IQ4, inhibitory quotient-4; PWH, people with HIV.

Figure 3. Simulated A) LEN AUC_{tau} B) LEN C_{max}, and C) LEN C_{trough} for the Phase 2/3 and simplified regimens in HTE PWH over the treatment duration for the first dose



AUC_{tau}, area under curve over dosing interval; C_{max}, maximum concentration; C_{trough}, trough concentration; HTE, heavily treatment-experienced; K, thousand; LEN, lenacapavir; PWH, people with HIV.

Figure 4. Prediction-corrected visual predictive check plots – External validation of simplified LEN regimen



Prediction-corrected visual predictive check plots show medians (solid red lines) and spreads (5^{th}-95^{th} percentiles [dashed red lines]) of observed data in all participants; red areas are 95% CIs of simulated medians and blue areas are 95% CIs of simulated 5^{th} and 95^{th} percentiles; black circles are individual observed data corrected by model predictions; orange dashes indicate boundaries of visual predictive check bins.
CI, confidence interval; d, day; LEN, lenacapavir; PK, pharmacokinetic; wk, week.

References: 1. Sunlenca US PI SmPC 2022, available on https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf last accessed 10 July 2023; 2. Sunlenca EU SmPC 2022, available on https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf last accessed 10 July 2023; 3. Shaik N et al. Poster PESUB23 presented at AIDS 2022; 4. Link JO, et al. *Nature* 2020;584:614–618/ 5. Segal-Maurer S, et al. *N Engl J Med* 2022;386:1793–1803; 6. Jogiraju V et al. Poster PESUB22 presented at AIDS 2022; 7. Shaik N et al. Poster EPB174 presented at AIDS 2022.

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