PESUB22

Pharmacokinetics of a Simplified Subcutaneous Lenacapavir Regimen Versus Phase 2/3 Regimen

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Introduction

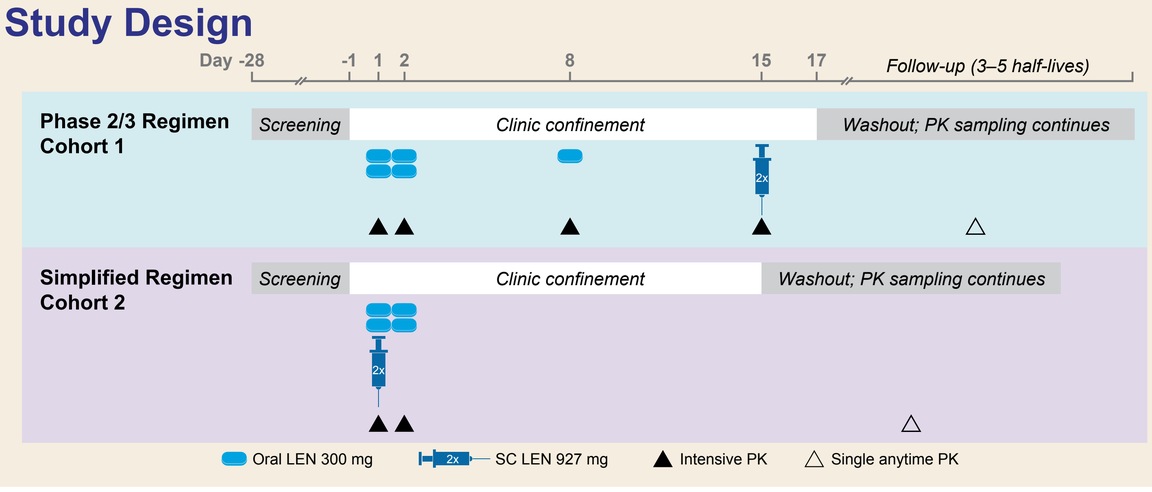
- Lenacapavir (LEN; GS-6207), a novel, first-in-class, multistage, selective inhibitor of human immunodeficiency virus-1 (HIV-1) capsid function, is being developed for the treatment and prevention of HIV-1 infection
- Mean trough concentration of 15.5 ng/mL, which is inhibitory quotient 4 (IQ4; ie, 4-fold greater than the in vitro protein-adjusted 95% effective concentration [paEC$_{95}$] derived from MT-4 cells),[1] has been associated with high rates of virologic suppression in Phase 2/3 clinical studies
- In ongoing Phase 2/3 studies, people with HIV-1 (PWH) received 2 weeks of oral LEN loading (600 mg on Days 1 and 2, and 300 mg on Day 8) prior to starting subcutaneous (SC) injection dose every 6 months (Q6M)
- LEN regimen used in Phase 2/3 regimen has been shown to be safe and effective in PWH[2]; however, a simplified regimen with concurrent dosing of SC and oral LEN (ie, SC LEN 927 mg on Day 1 and Q6M thereafter, with oral 600 mg administered on Days 1 and 2) can be more convenient, ie, reduced number of clinic visits and pill burden, as well as no risk of missing SC injection on Day 15

Objectives

- To characterize and compare the pharmacokinetics (PK) of LEN following Phase 2/3 regimen (Cohort 1) and simplified regimen (Cohort 2)
- To evaluate the safety and tolerability of LEN following Phase 2/3 and simplified regimens

Methods

Study Design



- Phase 1, single-center, open-label, multiple-cohort study in healthy participants following multiple oral LEN doses with single SC LEN injection
- Treatment:
  - **Phase 2/3 regimen (Cohort 1):** oral LEN 600 mg (2 x 300-mg tablets) on Days 1 and 2, oral LEN 300 mg (1 x 300-mg tablet) on Day 8, and SC LEN 927 mg on Day 15 (2 x 1.5 mL of LEN injection, sodium salt 309 mg/mL)
  - **Simplified regimen (Cohort 2):** oral LEN 600 mg (2 x 300-mg tablets) and SC LEN 927 mg on Day 1, followed by oral LEN 600 mg (2 x 300-mg tablets) on Day 2
- For both cohorts, serial PK sample collection was planned from predose through Day 197 and longer to cover 3–5 half-lives
- Safety was monitored throughout the study by assessment of vital signs, physical examinations, electrocardiograms, clinical laboratory tests, and adverse events (AEs)
- Plasma concentrations of LEN were quantified using a validated high-performance liquid chromatography–tandem mass spectrometry method

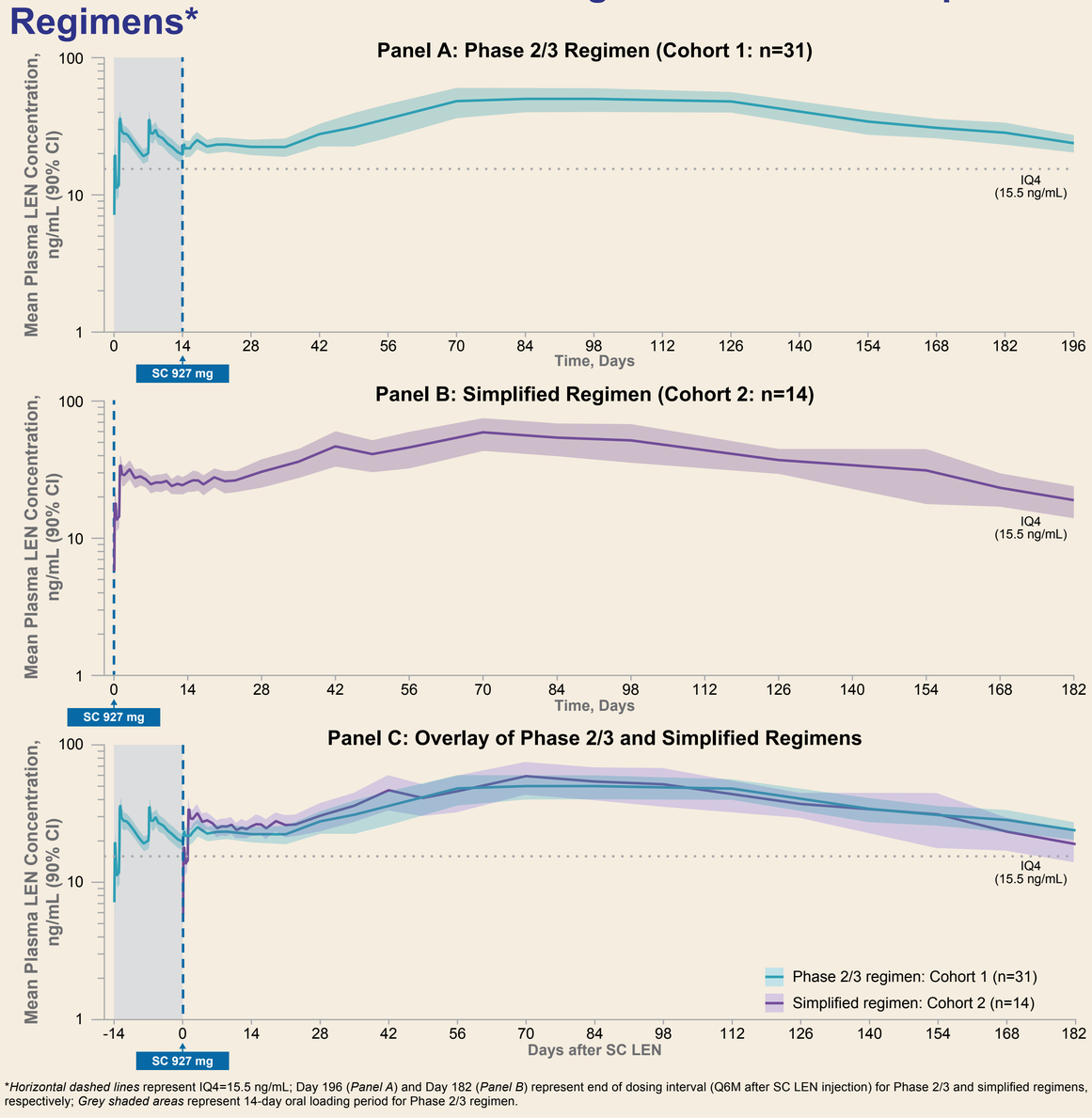
Results

Demographics and Baseline Characteristics

	Phase 2/3 Regimen: Cohort 1 n=31	Simplified Regimen: Cohort 2 n=14
Median age, years (range)	32 (22–43)	33 (20–45)
Sex at birth, n (%)		
Male	19 (61)	11 (79)
Female	12 (39)	3 (21)
Race, n (%)		
White	20 (65)	11 (79)
Black	11 (35)	3 (21)
Median BMI, kg/m^2 (range)	26.8 (21.9–30.3)	25.5 (21.8–29.7)
Median body weight, kg (range)	78.6 (54.3–95.6)	72.2 (58.3–98.3)

BMI, body mass index.

LEN Plasma PK Profiles Following Phase 2/3 and Simplified Regimens*



Horizontal dashed lines represent IQ4=15.5 ng/mL; Day 196 (*Panel A*) and Day 182 (*Panel B*) represent end of dosing interval (Q6M after SC LEN injection) for Phase 2/3 and simplified regimens, respectively; *Grey shaded areas* represent 14-day oral loading period for Phase 2/3 regimen.

- **Phase 2/3 regimen (Cohort 1):**
  - Following oral LEN administration, mean plasma LEN concentration and its lower bound 90% CI were consistently maintained above the target IQ4 of 15.5 ng/mL (4-fold of IQ1; paEC$_{95}$ from MT-4 cells: 3.87 ng/mL) from 2 hours postdose on Day 2 through Day 197
  - Following SC administration on Day 15, median time to maximal concentration (T_{max}) occurred ~85 days postdose
- **Simplified regimen (Cohort 2):**
  - Following LEN administration, mean plasma LEN concentration and its lower bound 90% CI exceeded the target IQ4 (15.5 ng/mL) from 2 hours postdose on Day 2
  - Following SC administration on Day 1, median T_{max} occurred ~70 days postdose
  - Mean LEN concentrations were consistently maintained above the efficacious target of IQ4 for the dosing interval

Summary Statistics of LEN Plasma PK Parameters

PK Parameter*	Phase 2/3 Regimen: Cohort 1			
	Day 1: n=31 Oral LEN 600 mg	Day 2: n=31 Oral LEN 600 mg	Day 8: n=31 Oral LEN 300 mg	Days 15–197: n=30 SC LEN 927 mg
C_{max}, ng/mL	22.0 (45.5)	40.4 (43.4)	39.3 (44.7)	58.7 (58.1)
T_{max}, hours [days]	4.00 (4.00, 6.00) [0.17]	6.00 (4.00, 8.00) [0.25]	6.00 (4.00, 8.00) [0.25]	2028.0 (1682.5, 2688.2) [84.5]
C_{last}, ng/mL	11.8 (57.2)	19.1 (40.0)	19.9 (40.4)	29.8 (67.6)
T_{last}, hours [days]	24.0 (24.0, 24.0) [1.0]	144.0 (144.0, 144.0) [6.0]	168.0 (168.0, 168.0) [7.0]	4319.5 (2689.0, 4365.8) [180.0]
$AUC_{0–196\ days}$, h·ng/mL	134,000.5 (55.9)			

PK Parameter*	Simplified Regimen: Cohort 2	
	Day 1: n=14 Oral LEN 600 mg + SC LEN 927 mg	Days 2–197: n=14 Oral LEN 600 mg
C_{max}, ng/mL	20.1 (34.5)	67.1 (47.2)
T_{max}, hours [days]	6.00 (4.00, 8.00) [0.25]	1653.9 (985.0, 1991.2) [68.9]
C_{last}, ng/mL	14.4 (36.9)	21.4 (93.1)
T_{last}, hours [days]	24.0 (24.0, 24.0) [1.0]	4679.4 (4678.9, 4679.9) [195.0]
$AUC_{0–182\ days}$, h·ng/mL	148,284.1 (56.6)	

*Presented as mean (% coefficient of variation) except T_{max} and time of last observed concentration (T_{last}), which are presented as median (quartiles 1, 3). AUC, area under curve; C_{last}, concentration at last observed time point; C_{max}, maximal concentration.

Comparison of LEN PK Between Phase 2/3 and Simplified Regimens

- LEN concentrations were generally comparable between Phase 2/3 regimen (Cohort 1) and simplified regimen (Cohort 2); slight difference in concentrations between Cohorts 1 and 2 is likely due to lower number of participants in Cohort 2 (14 in Cohort 2 vs 31 in Cohort 1)
- For both regimens, mean LEN concentrations reached the efficacious target rapidly and were maintained throughout the dosing interval
- LEN C_{max} and AUC for the dosing interval were within ±8% and ±11%, respectively, between the Phase 2/3 and simplified regimens

Safety Summary

- For both regimens, LEN was well tolerated, with no Grade 3 or 4 AEs, serious AEs, or deaths reported
- Most common AEs were injection-site reactions

Conclusions

- LEN concentrations of the simplified regimen were generally comparable to those following the Phase 2/3 regimen
- With both regimens, LEN concentrations reached the efficacious target rapidly and were maintained throughout the dosing interval
- These results suggest that the simplified regimen provides similar LEN exposures to the Phase 2/3 regimen and hence is being currently evaluated in clinical studies for prevention of HIV-1 infection (ClinicalTrials.gov NCT04925752 and NCT04994509)

References: **1.** Daar E, et al. CROI 2020, poster 3691; **2.** Dvory-Sobol H, et al. Curr Opin HIV AIDS 2022;17:15-21. **Acknowledgments:** We extend our sincere thanks to the participants for their participation in this study. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, NY, USA, funded by Gilead.

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