



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

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Introduction

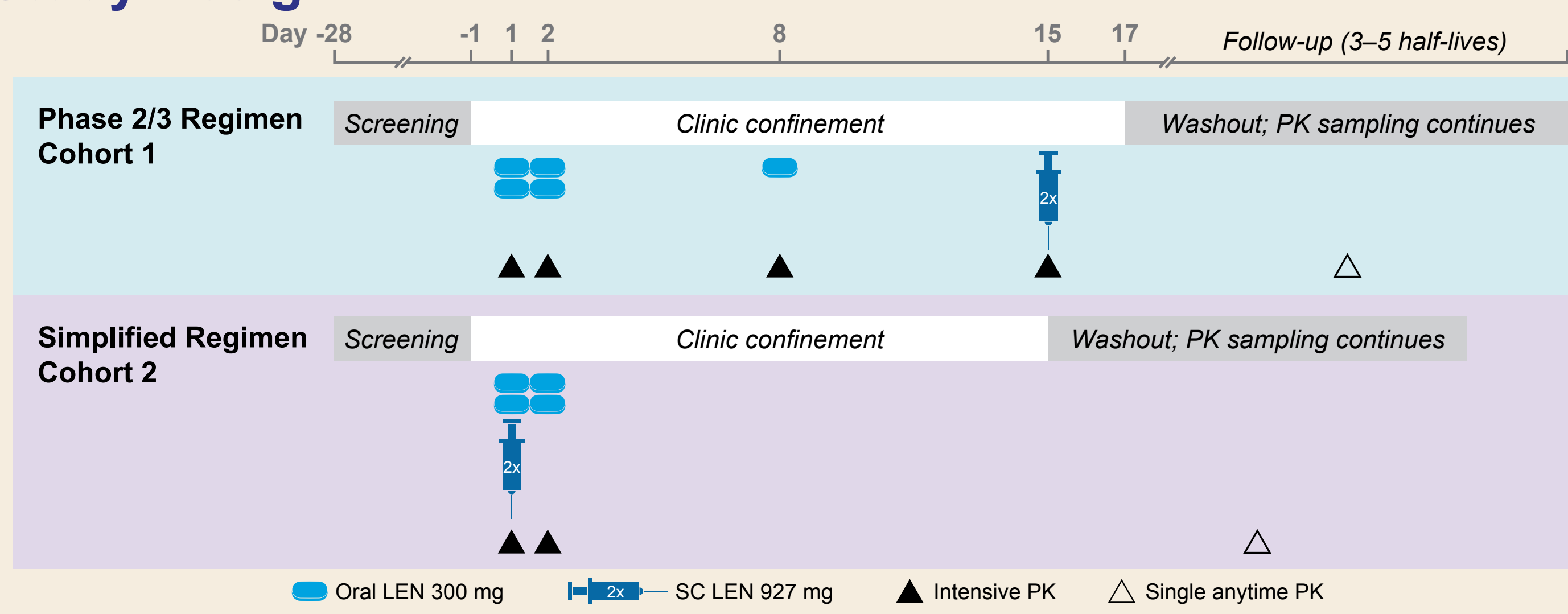
- ◆ Lenacapavir (LEN; GS-6207), a novel, first-in-class, multistage, selective inhibitor of human immunodeficiency virus-1 (HIV-1) capsid function, is being developed for the treatment and prevention of HIV-1 infection
- ◆ Mean trough concentration of 15.5 ng/mL, which is inhibitory quotient 4 (IQ4; ie, 4-fold greater than the in vitro protein-adjusted 95% effective concentration [paEC₉₅] 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 PWH²; 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

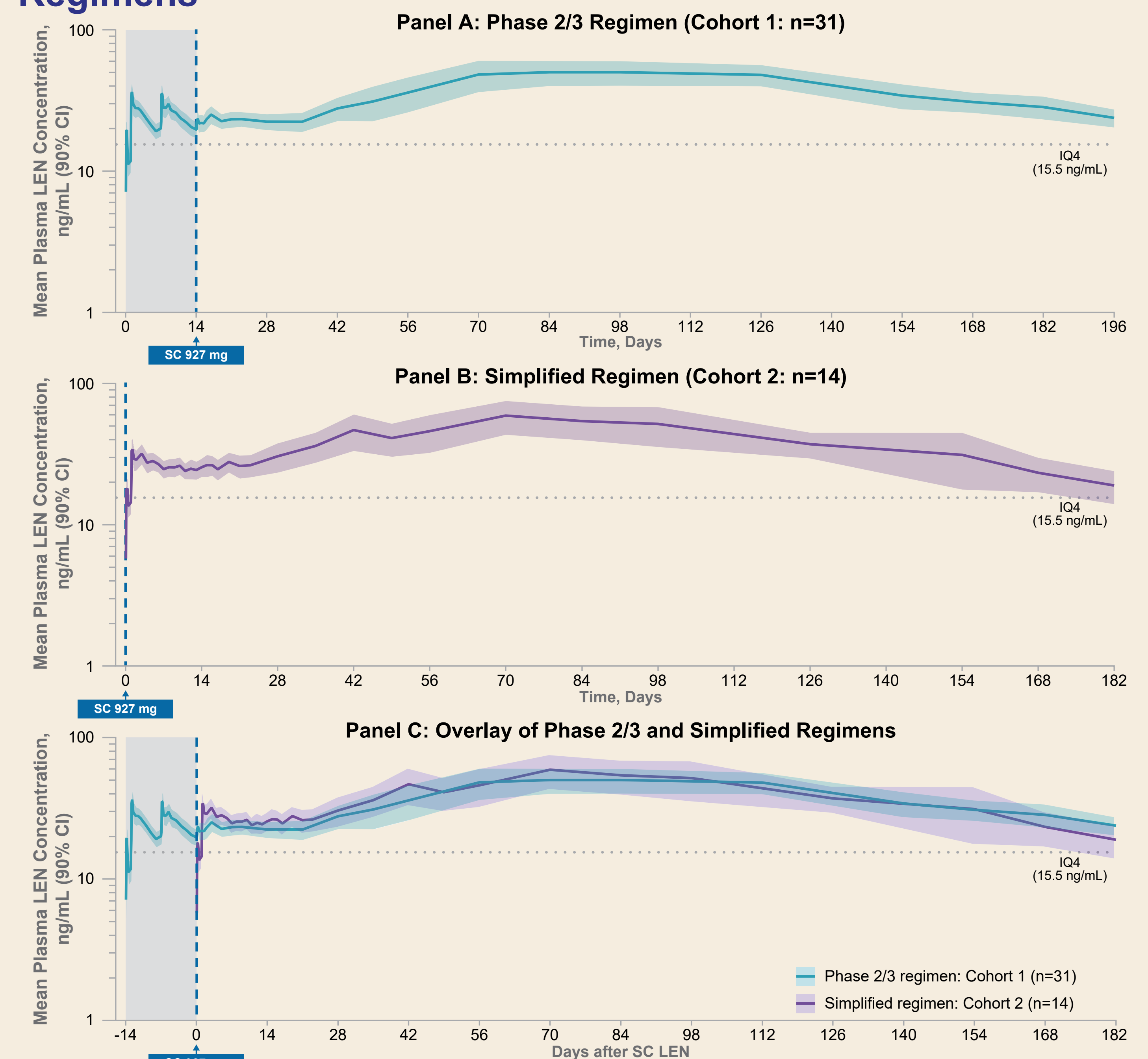
	Phase 2/3 Regimen: Cohort 1 n=31	Simplified Regimen: Cohort 2 n=14
Median age, years (range)	32 (22–43)	33 (20–45)
Sex at birth, n (%)		
Male	19 (61)	11 (79)
Female	12 (39)	3 (21)
Race, n (%)		
White	20 (65)	11 (79)
Black	11 (35)	3 (21)
Median BMI, kg/m ² (range)	26.8 (21.9–30.3)	25.5 (21.8–29.7)
Median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

BMI, body mass index.

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)

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; paEC₉₅ 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