Pharmacokinetic Bridging with Oral Lenacapavir for Missed Subcutaneous Q6M Dosing

TUPEB07

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Key Findings

- Lenacapavir (LEN) is approved for the treatment of multidrug-resistant HIV-1 infection in combination with other antiretrovirals, for heavily treatment-experienced people with HIV (PWH)
- While subcutaneous (SC) LEN provides targeted exposure for 6 months, potential interruptions in SC treatment may lead to subtherapeutic concentrations
- In Phase 2/3 studies (CAPELLA and CALIBRATE), participants received LEN 300 mg once weekly (QW) as an oral bridging regimen when they were unable to receive SC LEN at the scheduled visits during the clinical hold of injectable LEN (December 2021 to May 2022)
- During this oral bridging period, mean LEN plasma concentrations and the lower-bound 90% confidence intervals (CI) were above the efficacy target of 15.5 ng/mL indicating that the 300 mg QW dose was adequate for maintaining therapeutic concentrations in case of interruption in SC dosing

Conclusions

- In the CAPELLA and CALIBRATE studies, the mean LEN concentrations and the lower-bound 90% CIs were maintained above IQ4 (15.5 ng/mL) from the first oral LEN bridging visit until SC LEN was resumed approximately 10–30 weeks later
- These results indicate that oral LEN 300 mg QW provides adequate plasma concentrations to bridge SC LEN dosing in PWH who may miss their LEN Q6M SC injection

Background

- LEN, a potent first-in-class capsid inhibitor, is approved in heavily treatment-experienced people with HIV (PWH) for the treatment of multidrug-resistant HIV-1 infection in combination with other antiretrovirals[1,2]
- LEN has a long terminal/apparent half-life of 10–12 days and 8–12 weeks following oral and SC administration, respectively[1,2]
- Current data indicate maximal antiviral activity was achieved at a mean trough concentration of 15.5 ng/mL,[3] i.e., the inhibitory quotient-4 (IQ4; ≥4-fold higher than the *in vitro* protein-adjusted 95% effective concentration in MT-4 cells)[4]
- In the ongoing Phase 2/3 (CAPELLA, NCT04150068[5] **Figure 1**) and Phase 2 (CALIBRATE, NCT04143594[6] **Figure 2**) studies, participants received oral LEN loading doses (600 mg on Days 1 and 2; 300 mg on Day 8), followed by a 927 mg SC maintenance dose given every 6 months (Q6M) starting from Day 15
- PWH receiving long-acting injectable regimens may experience treatment interruptions that could pose challenges due to gaps in treatment. An oral bridging regimen that maintains IQ4 levels would avoid treatment interruptions when SC LEN is not feasible
- Oral bridging with 300 mg QW LEN was used in these clinical studies in participants who were unable to receive subsequent SC LEN at the scheduled visits due to temporary clinical hold

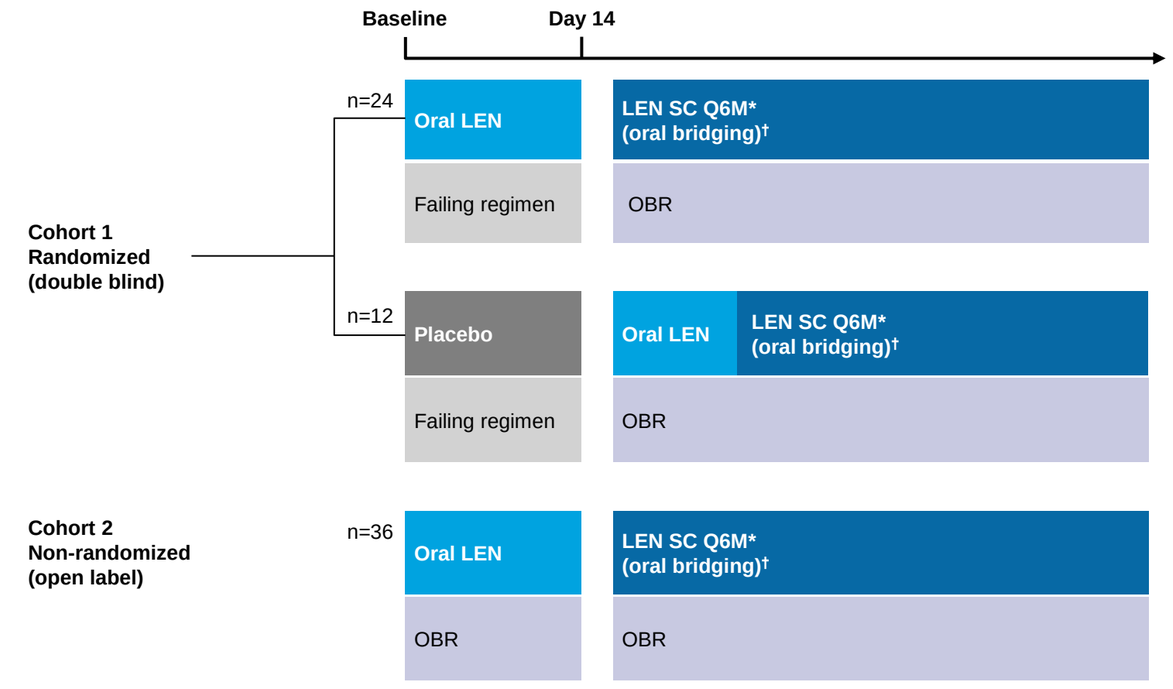
Objective

- To evaluate the pharmacokinetics (PK) of LEN during the oral bridging period to assess the adequacy of 300 mg oral QW LEN for maintaining therapeutic concentrations between missed and resumed SC LEN doses

Methods

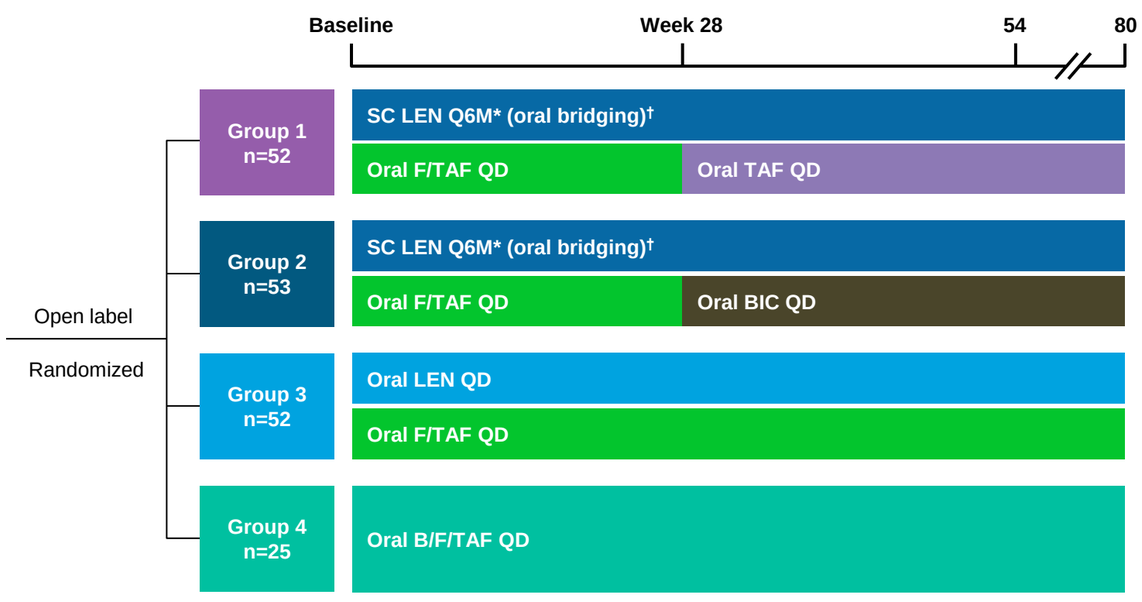
- From December 20 2021, SC LEN was on full clinical hold imposed by the US Food and Drug Administration, therefore, participants in the CAPELLA (**Figure 1**) and CALIBRATE (**Figure 2**) studies were temporarily unable to receive SC LEN
- Modeling and simulation were used to propose a 300 mg oral QW regimen to bridge LEN concentrations when participants were unable to receive SC LEN. This dosing regimen was predicted to immediately maintain the lower bound 90% CI of the arithmetic mean for LEN C_{trough} above IQ4 (i.e., even before reaching steady state) (**Figure 3**)
- During the oral bridging periods in both studies, sparse PK samples were collected at the start, then every ~10–12 weeks (without regard to a prespecified time since dose) until SC LEN was resumed
- In both studies, LEN plasma concentrations were quantified using a validated high-performance liquid chromatography-tandem mass spectrometry method, with a calibrated range of 0.5–500 ng/mL or 0.1–100 ng/mL
- LEN plasma concentrations were summarized using descriptive analysis for the oral bridging period in the CAPELLA and CALIBRATE studies

Figure 1. CAPELLA Study Design



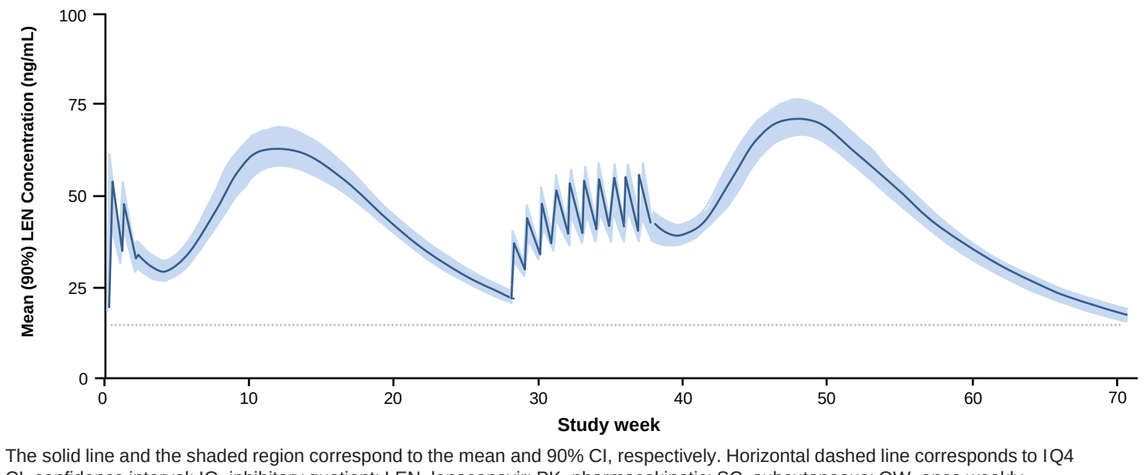
*Administered as 927 mg (2 x 1.5 mL) SC in abdomen on Day 15, then Q6M. †Oral bridging: LEN 300 mg QW
LEN, lenacapavir; OBR, optimized background regimen; Q6M, every 6 months; QW, once weekly;
SC, subcutaneous

Figure 2. CALIBRATE Study Design



*Administered as 927 mg (2x 1.5 mL) SC in abdomen on Day 15, then Q6M. †Oral bridging: LEN 300 mg QW
B/BIC, bictegravir; F, emtricitabine; LEN, lenacapavir; QD, once daily; Q6M, every 6 months;
QW, once weekly; SC, subcutaneous; TAF, tenofovir alafenamide

Figure 3. Simulated PK profile showing oral bridging with LEN 300 mg QW dose between SC injections (without pharmacoenhancers)



The solid line and the shaded region correspond to the mean and 90% CI, respectively. Horizontal dashed line corresponds to IQ4
CI, confidence interval; IQ, inhibitory quotient; LEN, lenacapavir; PK, pharmacokinetic; SC, subcutaneous; QW, once weekly.

Results

CAPELLA study

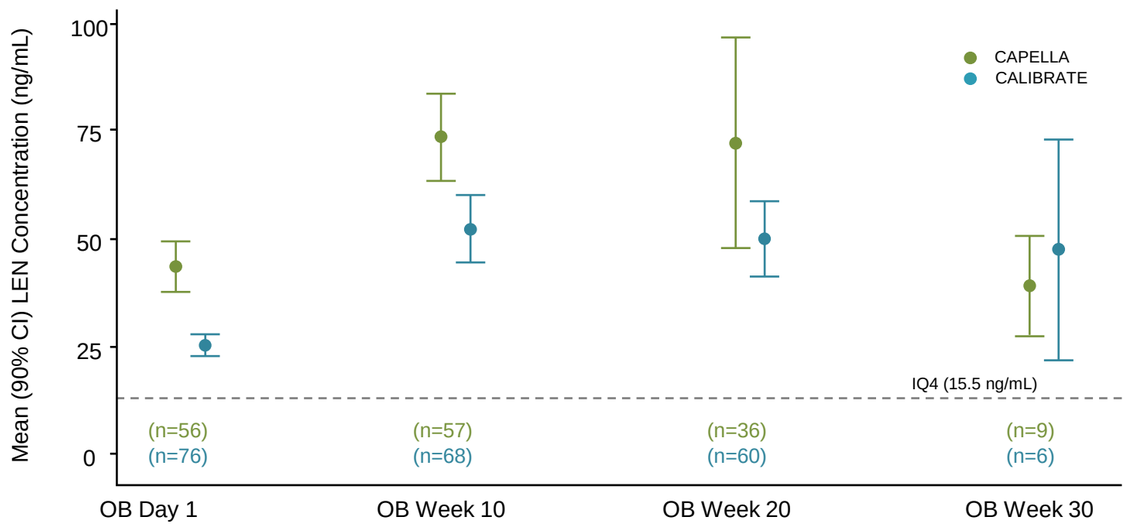
- During the oral bridging period, the mean LEN plasma concentrations and lower bounds of 90% CI on Day 1 and at Weeks 10, 20, and 30 exceeded IQ4 (**Table 1; Figure 4**)
- At the SC LEN resumption visit, the mean (% coefficient of variation [CV]) pre-dose concentration (74.4 ng/mL [105.1%]) and its lower bound 90% CI (56.2 ng/mL) were above IQ4

Table 1. LEN plasma concentrations during the oral bridging period in CAPELLA

PK Parameter Mean (%CV)	Day 1* (n=56)	Week 10 (n=57)	Week 20 (n=36)	Week 30 (n=9)
Concentration (ng/mL)	46.1 (56.3)	76.2 (59.6)	74.8 (116.1)	41.7 (45.7)
Lower 90% CI of concentration (ng/mL)	40.3	66.1	50.4	29.9

*Start of oral bridging, 26–28 weeks from last SC dose. IQ4 of LEN = 15.5 ng/mL
CI, confidence interval; CV, coefficient of variation; IQ, inhibitory quotient; LEN, lenacapavir; PK, pharmacokinetics

Figure 4. LEN plasma concentrations during the oral bridging period in CAPELLA and CALIBRATE (with or without pharmacoenhancers)



CI, confidence interval; IQ, inhibitory quotient; LEN, lenacapavir; OB, oral bridging

CALIBRATE study

- For each treatment group (TG) receiving SC LEN (TG 1 with TAF; TG 2 with BIC), the mean LEN plasma concentrations and lower bounds of 90% CI on Day 1 and at Weeks 10, 20, and 30 exceeded IQ4 during the oral bridging period (**Table 2**)
- For SC LEN total (TG 1 and 2 combined), the mean LEN plasma concentrations and lower bounds of 90% CI on Day 1 and at Weeks 10, 20, and 30 exceeded IQ4 during the oral bridging period (**Table 2; Figure 4**)
- At the SC LEN resumption visit, pre-dose concentration exceeded IQ4 with mean (%CV) and lower bounds 90% CI values, respectively, TG 1: 49.4 mg/mL (84.6%), 38.6 ng/mL; TG 2: 52.2 ng/mL (66.6%), 42.7 ng/mL; TG 1 and 2 combined: 50.7 ng/mL (75.7%), 43.6 ng/mL

Table 2. LEN plasma concentrations during the oral bridging period in CALIBRATE

SC LEN + (F/TAF → TAF) Treatment Group 1				
PK Parameter Mean (%CV)	**Day 1* (n=41)**	**Week 10 (n=35)**	**Week 20 (n=32)**	**Week 30 (n=3)**
Concentration (ng/mL)	28.8 (47.7)	50.9 (67.0)	53.1 (84.5)	43.7 (74.7)
Lower 90% CI of concentration (ng/mL)	25.2	41.1	39.6	NR
SC LEN (F/TAF → BIC) Treatment Group 2				
	Day 1* (n=35)	**Week 10 (n=33)**	**Week 20 (n=28)**	**Week 30 (n=3)**
Concentration (ng/mL)	26.7 (47.3)	59.3 (73.6)	51.9 (70.2)	56.5 (62.5)
Lower 90% CI of concentration (ng/mL)	23.0	46.4	40.2	NR
SC LEN TOTAL: SC LEN + (F/TAF → TAF) AND SC LEN + (F/TAF → BIC)				
	Day 1* (n=76)	**Week 10 (n=68)**	**Week 20 (n=60)**	**Week 30 (n=6)**
Concentration (ng/mL)	27.8 (47.4)	54.9 (70.8)	52.5 (77.7)	50.1 (62.3)
Lower 90% CI of concentration (ng/mL)	25.3	47.1	43.7	24.4

*Start of oral bridging, 26–28 weeks from last SC dose. IQ4 of LEN = 15.5 ng/mL
BIC, bictegravir; CI, confidence interval; CV, coefficient of variation; F, emtricitabine; IQ, inhibitory quotient; LEN, lenacapavir; NR, not reported due to small sample size; PK, pharmacokinetics; SC, subcutaneous; TAF, tenofovir alafenamide

References: 1. Sunlenca US PI 2022, available on https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf last accessed 12 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 12 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. Gupta SK, et al. *Lancet HIV* 2023;10:e15–e23.

Acknowledgments: Medical writing support was provided by Jackie Phillipson of Ashfield MedComms (Macclesfield, UK), an Inizio company, and funded by Gilead Sciences, Inc.

Disclosures: **V Jogiraju, N Shaik, D Bhakta, J Ling, H Wang, H Dvory-Sobol, M Rhee, R Palaparthy**, and **R Singh** are all employees and shareholders of Gilead Sciences, Inc.
M Shelton is an employee and shareholder of Certara, Inc.

Presented at the 12th IAS Conference on HIV Science, 23–26 July 2023, Brisbane, Australia