Pharmacokinetic Bridging with Oral Lenacapavir for Missed Subcutaneous Q6M Dosing

Vamshi Jogiraju, Mark Shelton, Naveed Shaik, Dipti Bhakta, John Ling, Hui Wang, Hadas Dvory-Sobol, Martin Rhee, Ramesh Palaparthy, Renu Singh

Gilead Sciences, Inc., Foster City, CA, USA

Poster #

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Key Findings

- Lenacapavir (LEN) is approved for treating multidrug-resistant HIV-1 in combination with other antiretrovirals for heavily treatment-experienced people with HIV (PWH)
- While subcutaneous (SC) LEN provides and every 6 months (Q6M) treatment option for HIV-1, potential SC treatment interruptions may lead to management challenges due to SC treatment gaps
- In Phase 2/3 studies (CALIBRATE and CAPELLA) participants received LEN 300 mg weekly (QW) as an oral bridging dose when they were unable to receive SC LEN at the scheduled visits
- During this oral bridging period, mean LEN plasma concentrations and the lower-bound 90% confidence interval above the efficacy target of 15.5 ng/mL (for maximal antiviral activity) throughout this period
- Oral 300 mg QW LEN provides adequate concentrations to bridge LEN dosing in participants who may miss their Q6M SC injection

Conclusions

- In the CALIBRATE and CAPELLA 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 at 300 mg QW provides adequate plasma concentrations to bridge LEN dosing in PWH who may miss their LEN Q6M SC injection

Background

- Lenacapavir (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 half-life of 10–12 days and 8–12 weeks following oral and subcutaneous (SC) administration, respectively[1,2]
- LEN trough plasma concentrations >15.5 ng/mL, which is the inhibitory quotient-4 (IQ4; i.e., 4-fold *in-vitro* protein binding-adjusted 95% effective concentration in MT-4 cells[3]), are associated with high rates of virologic suppression[4]
- In the ongoing Phase 2 (CALIBRATE, NCT04143594[5] **Figure 1**) and Phase 2/3 (CAPELLA, NCT04150068[6] **Figure 2**) studies, PWH 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
- While SC LEN provides a Q6M treatment option for HIV-1, potential SC treatment interruptions may lead to management challenges, due to SC treatment gaps
- Oral bridging with 300 mg once weekly (QW) LEN was used in these clinical studies in PWH who were unable to receive SC LEN at the scheduled visits due to temporary clinical hold

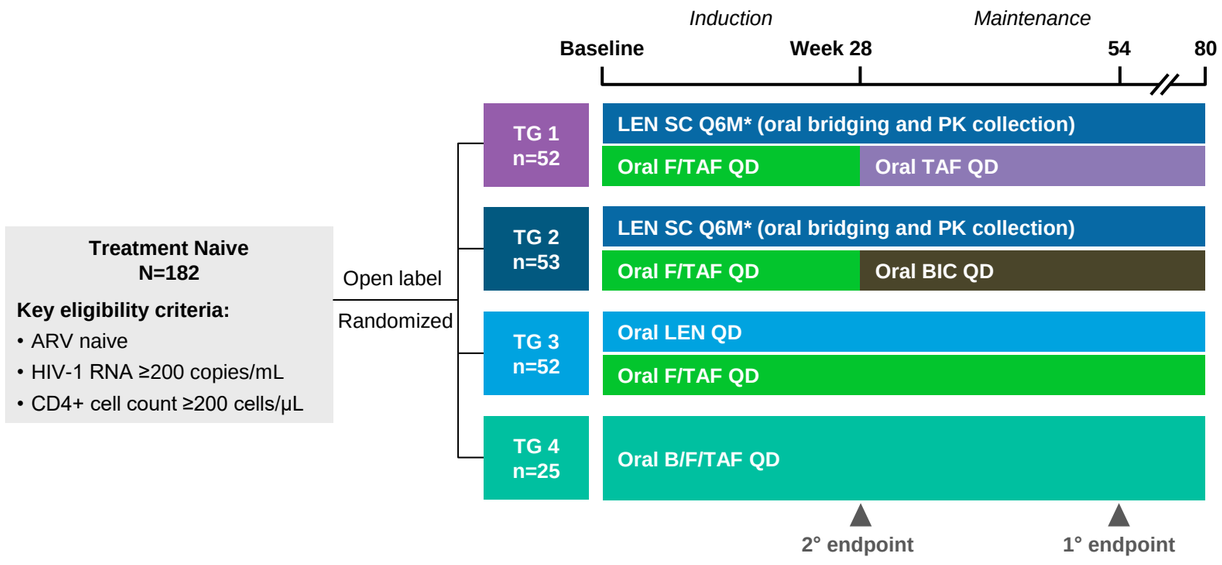
Objective

- 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 SC LEN doses

Methods

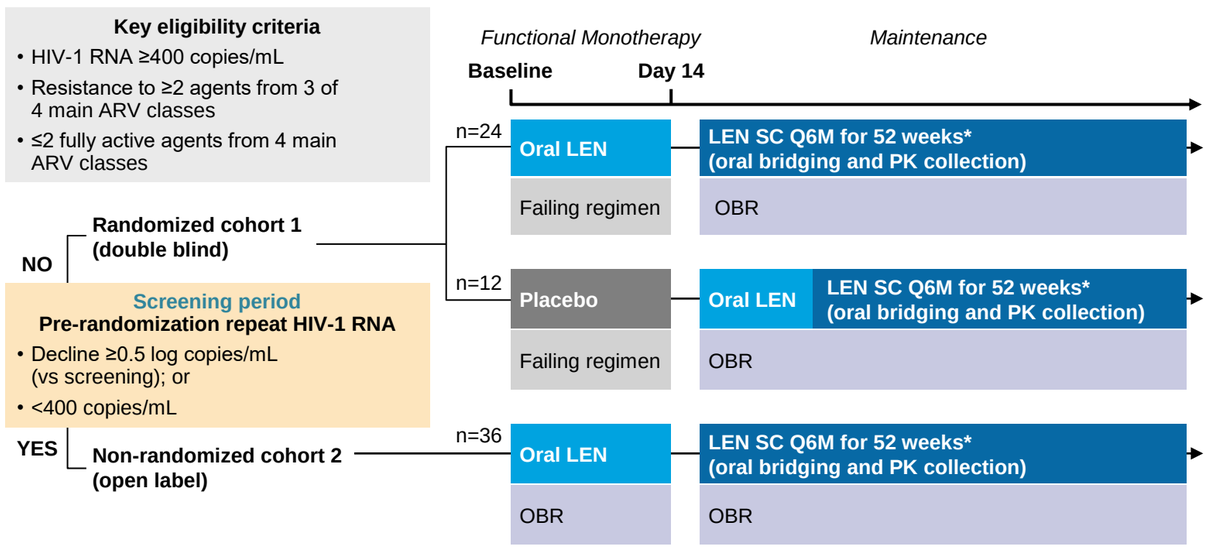
- From December 20th 2021, SC LEN was on full clinical hold imposed by the US Food and Drug Administration, thus, participants in the CALIBRATE (**Figure 1**) and CAPELLA (**Figure 2**) studies were temporarily unable to receive SC LEN
- Modelling and simulation were used to propose a 300 mg QW regimen to bridge the gap when participants were unable to receive SC LEN. This dose was predicted to immediately maintain the lower bound of the 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 descriptively for the oral bridging period in the CALIBRATE (N=82) and CAPELLA (N=57) studies

Figure 1. CALIBRATE Study Design



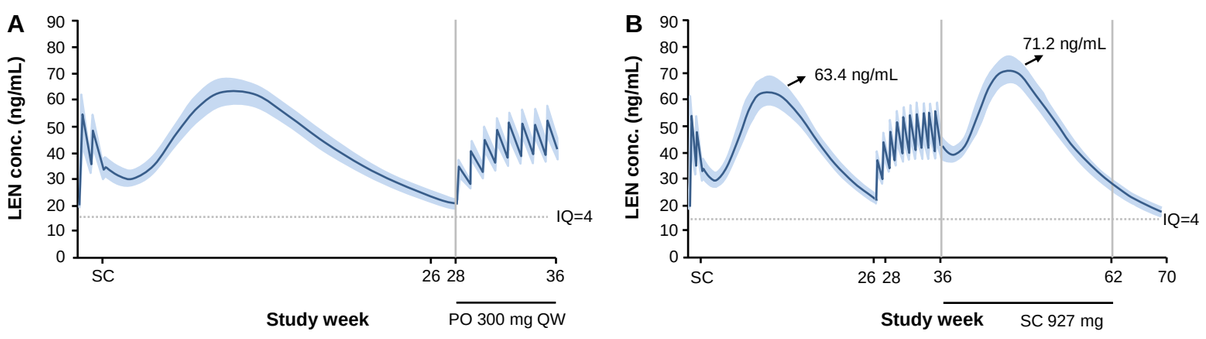
ARV, antiretroviral; B/BIC, bictegravir; F, emtricitabine; LEN, lenacapavir; PK, pharmacokinetics; QD, once daily; Q6M, every 6 months; SC, subcutaneous; TAF, tenofovir alafenamide; TG, treatment group

Figure 2. CAPELLA Study Design



*Administered as 927 mg (2 x 1.5 mL) SC in abdomen on Day 15, then Q6M
ARV, antiretroviral; LEN, lenacapavir; OBR, optimized background regimen; PK, pharmacokinetics; Q6M, every 6 months; SC, subcutaneous

Figure 3. Simulated PK profile showing oral bridging with LEN 300 mg QW dose A) prior to and B) after resuming SC injections



The solid line and the shaded region correspond to the geometric mean and 90% CI, respectively. Horizontal dashed lines correspond to target IQ values of 4 based on phenotypic analyses and PK/PD modeling.
IQ is calculated as trough concentration/in vitro protein-adjusted EC_{95} ($paEC_{95}$) against wild-type vims.
CI, confidence interval; IQ, inhibitory quotient; LEN, lenacapavir; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; QW, once weekly.

Results

CALIBRATE study

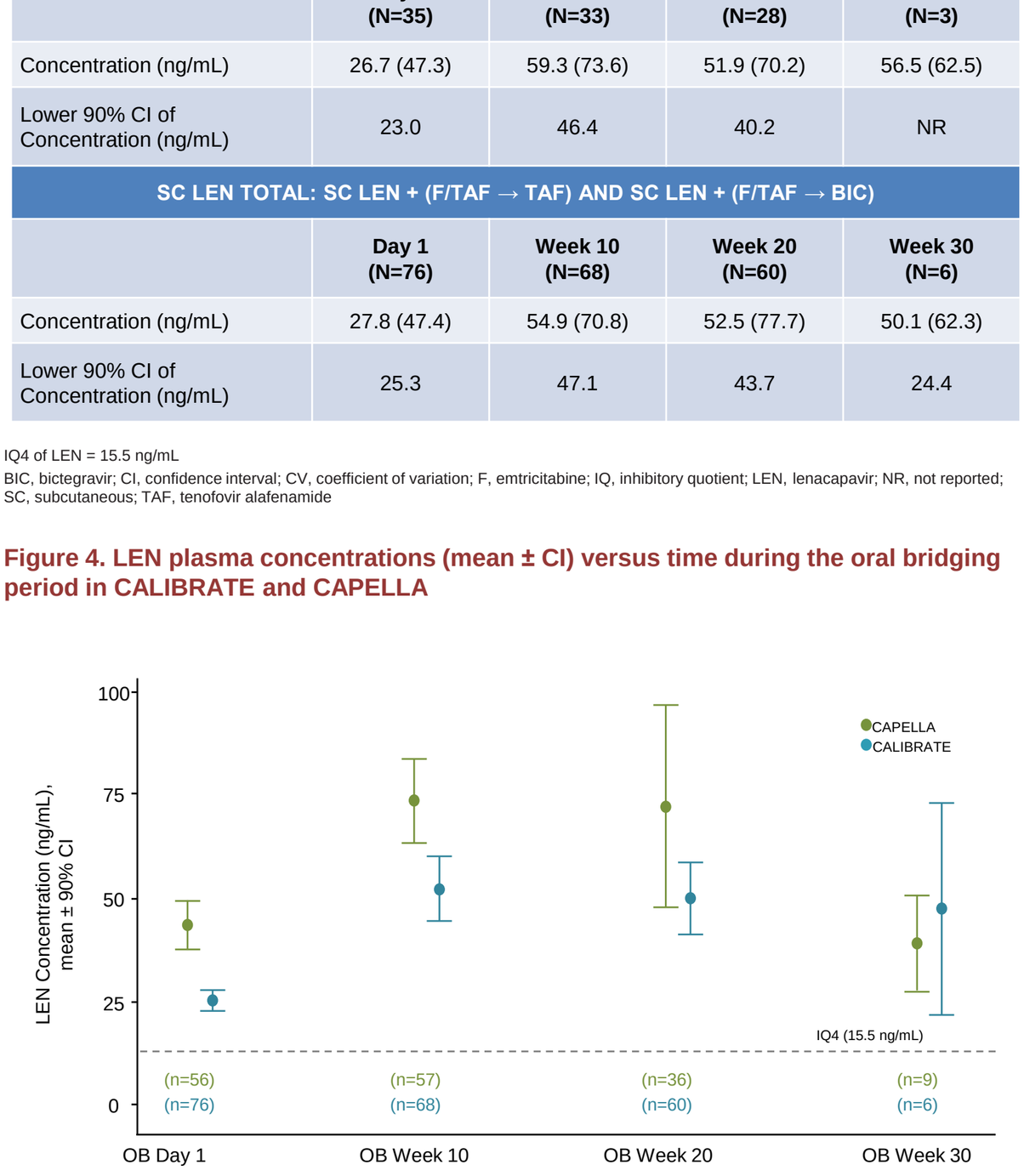
- For each treatment group (TG) receiving SC LEN (TG 1 combined with TAF; TG 2 combined with BIC), the mean LEN plasma concentrations on Day 1 and Weeks 10, 20 and 30 all exceeded the IQ4 during the oral bridging period (**Table 1**)
- For SC LEN total (TG 1 and 2 combined), the mean LEN plasma concentrations on Day 1, and Weeks 10, 20 and 30 all exceeded the IQ4 during the oral bridging period (**Table 1; Figure 4**)
- At the SC resumption visit, LEN pre-dose concentration also exceeded the 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: 52.5 ng/mL (66.6%), 42.7 ng/mL; TG 1 and 2 combined: 50.7 ng/mL (75.7%), 43.6 ng/mL

Table 1. Descriptive analysis of LEN plasma concentrations during the oral bridging period in CALIBRATE

PK Parameter Mean (%CV)	Day 1 (N=41)	Week 10 (N=35)	Week 20 (N=32)	Week 30 (N=3)
SC LEN + (F/TAF → TAF) Treatment Group 1				
Concentration (ng/mL)	28.8 (47.7)	50.9 (67.0)	53.01 (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

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; SC, subcutaneous; TAF, tenofovir alafenamide

Figure 4. LEN plasma concentrations (mean ± CI) versus time during the oral bridging period in CALIBRATE and CAPELLA



CI, confidence interval; LEN, lenacapavir; OB, oral bridging; SC, subcutaneous

CAPELLA study

- During the oral bridging period, the mean LEN pre-dose plasma concentrations and the lower bound 90% CI at Day 1 and Weeks 10, 20 and 30 all exceeded the efficacy target of IQ4 (15.5 ng/mL) (**Table 2; Figure 4**)
- At the SC resumption visit, the mean (%CV) LEN pre-dose concentration was 74.4 ng/mL (105.1%) and the lower bound 90% CI of 56.2 ng/mL also exceeded the IQ4

Table 2. Descriptive analysis of LEN plasma concentrations during the oral bridging period in CAPELLA

PK Parameter Mean (%CV)	Oral Bridging Day 1 (N=56)	Oral Bridging Week 10 (N=35)	Oral Bridging Week 20 (N=32)	Oral Bridging Week 30 (N=3)
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

IQ4 of LEN = 15.5 ng/mL
CI, confidence interval; CV, coefficient of variation; IQ, inhibitory quotient; LEN, lenacapavir

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