Lenacapavir Oral Bridging (300 mg QW) Maintains Efficacy with a Similar Safety Profile When SC LEN Cannot Be Administered

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Disclosures

- **O Ogbuagu:** Gilead Sciences (advisor/consultant, honoraria), ViiV (advisor/consultant), Janssen (advisor/consultant)
- **A Avihingsanon:** Gilead Sciences (grant support, honoraria), ViiV/GSK (grant support, honoraria), MSD (grant support)
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- **H Wang, MS Rhee, H Dvory-Sobol, P Sklar:** Gilead Sciences (employment, stocks/bonds)
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Summary

What was our main question?	Is oral bridging with weekly LEN suitable for PWH when SC LEN is missed?
What did we find?	Throughout oral bridging with weekly LEN, virological suppression was maintained, CD4 remained stable, and the safety profile was consistent with SC LEN in the primary analysis (excluding ISRs)
Why is this important?	Oral bridging with weekly LEN in PWH, including those with MDR HIV-1, is feasible and effective when SC LEN treatment is interrupted

ISR, injection-site reaction; LEN, lenacapavir; MDR, multidrug resistant; PWH, people with HIV; SC, subcutaneous

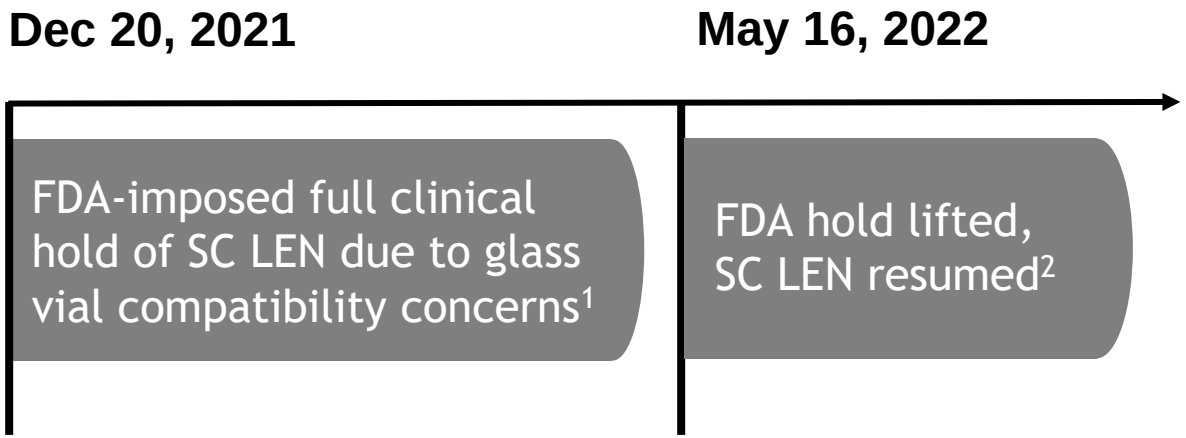
Introduction: Lenacapavir (LEN)

- LEN is a first-in class, long-acting HIV-1 capsid inhibitor which interferes with the capsid-mediated nuclear uptake of pre-integration complexes, inhibiting virion production[1]
- LEN is approved in the US, Europe, and additional countries, to be used in combination with other antiretrovirals for the treatment of MDR HIV-1 in HTE adults[2,3]
- SC LEN provides a Q6M treatment option for PWH[2,3]
- PWH receiving long-acting injectable regimens may experience treatment interruptions that could pose challenges due to gaps in treatment
- LEN has a half-life of 10–12 days following oral administration, making it suitable for QW oral dosing[4]

HTE, heavily-treatment experienced; LEN, lenacapavir; MDR, multidrug resistant; PWH, people with HIV; QW, once weekly; Q6M, once every 6 months; SC, subcutaneous.

1. Link JO, et al. Nature 2020;584:614–618; 2. Sunlenca® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (Accessed July 2023);
3. Sunlenca® Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (Accessed July 2023);
4. Jogiraju V, et al. Poster TUPEB14 presented at IAS 2023.

Examination of Oral LEN Efficacy and Safety Following Oral Bridging in CAPELLA and CALIBRATE Participants



The clinical hold provided the opportunity to examine the efficacy and safety of oral bridging using QW LEN

- Due to the clinical hold, participants in CAPELLA and CALIBRATE were temporarily unable to receive SC LEN
- Oral bridging of LEN was used for participants who had an injection due during the hold period, until SC dosing could be resumed

Objective: Post-hoc analysis to assess efficacy and safety of oral LEN (300 mg PO QW) in MDR and treatment-naïve PWH in CAPELLA and CALIBRATE when SC LEN dosing was interrupted

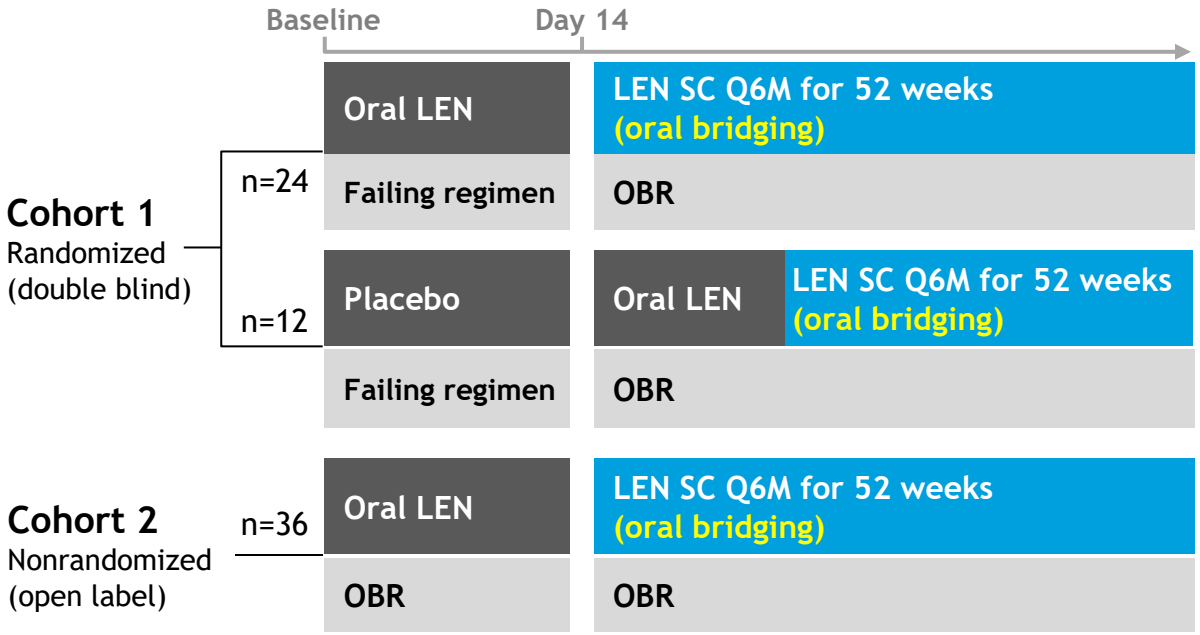
FDA, Food and Drug Administration; LEN, lenacapavir; MDR, multidrug resistant; PWH, people with HIV; PO, orally; QW, once weekly; SC, subcutaneous.

1. https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/gilead-announces-clinical-hold-on-studies-evaluating-injectable-lenacapavir-for-hiv-treatment-and-prevention-due-to-vial-quality-concerns (Accessed July 2023); 2. https://www.gilead.com/news-and-press/press-room/press-releases/2022/5/fda-lifts-clinical-hold-on-investigational-lenacapavir-for-the-treatment-and-prevention-of-hiv (Accessed July 2023)

CAPELLA and CALIBRATE Study Designs

Capella

Population (N=72): HTE with MDR HIV-1; HIV-1 RNA ≥400 c/mL[1]



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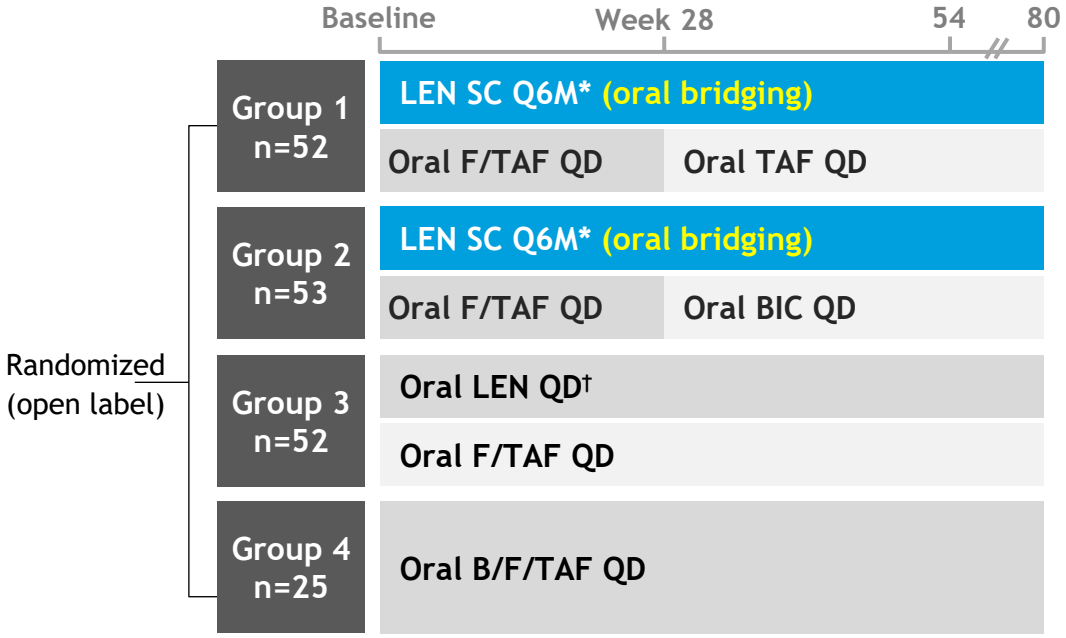
Population (N=183): ARV-naïve[2]



Oral bridging: 300 mg QW, initiated within two weeks of the next scheduled injection
During the period of oral bridging, participants were given 1-2 bottles containing 5 pills and were seen every 10-12 weeks

Here, we report data for Cohorts 1 and 2 (combined) in CAPELLA and Groups 1 and 2 in CALIBRATE

*Participants received LEN oral loading prior to initiating LEN SC. †Participants in CALIBRATE Group 3 received oral LEN 600 mg on Days 1 and 2, followed by 50 mg QD from Day 3 onwards.
ARV, antiretroviral; BIC, bictegravir; B/F/TAF, bictegravir/emtricitabine/tenofovir; BL, baseline; c/mL, copies/mL; F/TAF, emtricitabine/tenofovir; HTE, heavily treatment-experienced; LEN, lenacapavir; MDR, multidrug resistant; OBR, optimized background regimen; Q6M, every 6 months; QD, once daily; QW, once weekly; SC, subcutaneous, TAF, tenofovir.
1. NCT04150068. Available at: https://clinicaltrials.gov/ct2/show/NCT04150068 (Accessed July 2023). 2. NCT04143594. Available at: https://clinicaltrials.gov/ct2/show/NCT04143594 (Accessed July 2023).

Baseline Characteristics

Groups receiving oral LEN (oral bridging analysis set)

	CAPELLA (n=57)	CALIBRATE	
		Group 1 (n=44)	Group 2 (n=38)
Age, years Mean (SD)	50 (13.2)	35 (9.9)	33 (8.9)
Sex at Birth Male, n (%)	45 (78.9)	39 (88.6)	37 (97.4)
Race, n (%) Asian Black White Other	15 (26.8) 16 (28.6) 25 (44.6) 1 (1.8)	0 21 (47.7) 20 (45.5) 3 (6.9)	0 16 (42.1) 21 (55.3) 1 (2.6)
BMI (kg/m^2) Mean (SD)	26.7 (5.82)	29.3 (8.59)	27.8 (6.36)
Virologically suppressed (HIV-1 RNA <50 c/mL) at oral bridging baseline, n (%)	46 (80.7)	44 (100)	38 (100)

	CAPELLA	CALIBRATE
Continued study drug at the start of clinical hold	n=64	n=85
Received oral bridging	n=57	n=82
Not received oral bridging	n=7*	n=3†

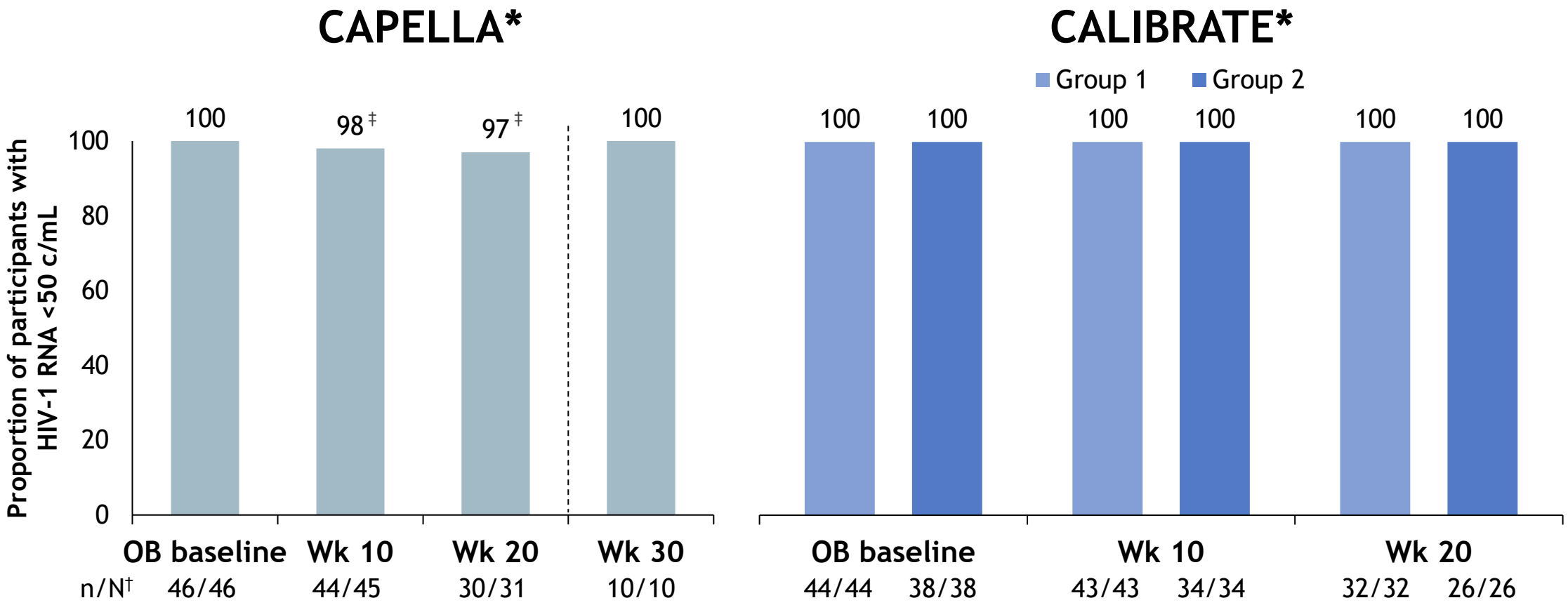
Those who did not receive oral bridging either discontinued prior to receiving it or did not need it

The oral bridging analysis set comprised all participants with ≥1 dose of oral bridging of LEN

Median duration of LEN oral bridging across CAPELLA and CALIBRATE: 18 weeks

*Prematurely discontinued study drug without receiving oral bridging, n=3; continued study drug without receiving oral bridging, n=4. †Prematurely discontinued study drug without receiving oral bridging, n=1; continued study drug without receiving oral bridging, n=2.
BMI, body mass index; c/mL, copies per milliliter; LEN, lenacapavir; SD, standard deviation.

Efficacy (M=E analysis) During Oral Bridging Amongst Participants Suppressed at the Switch to Oral LEN

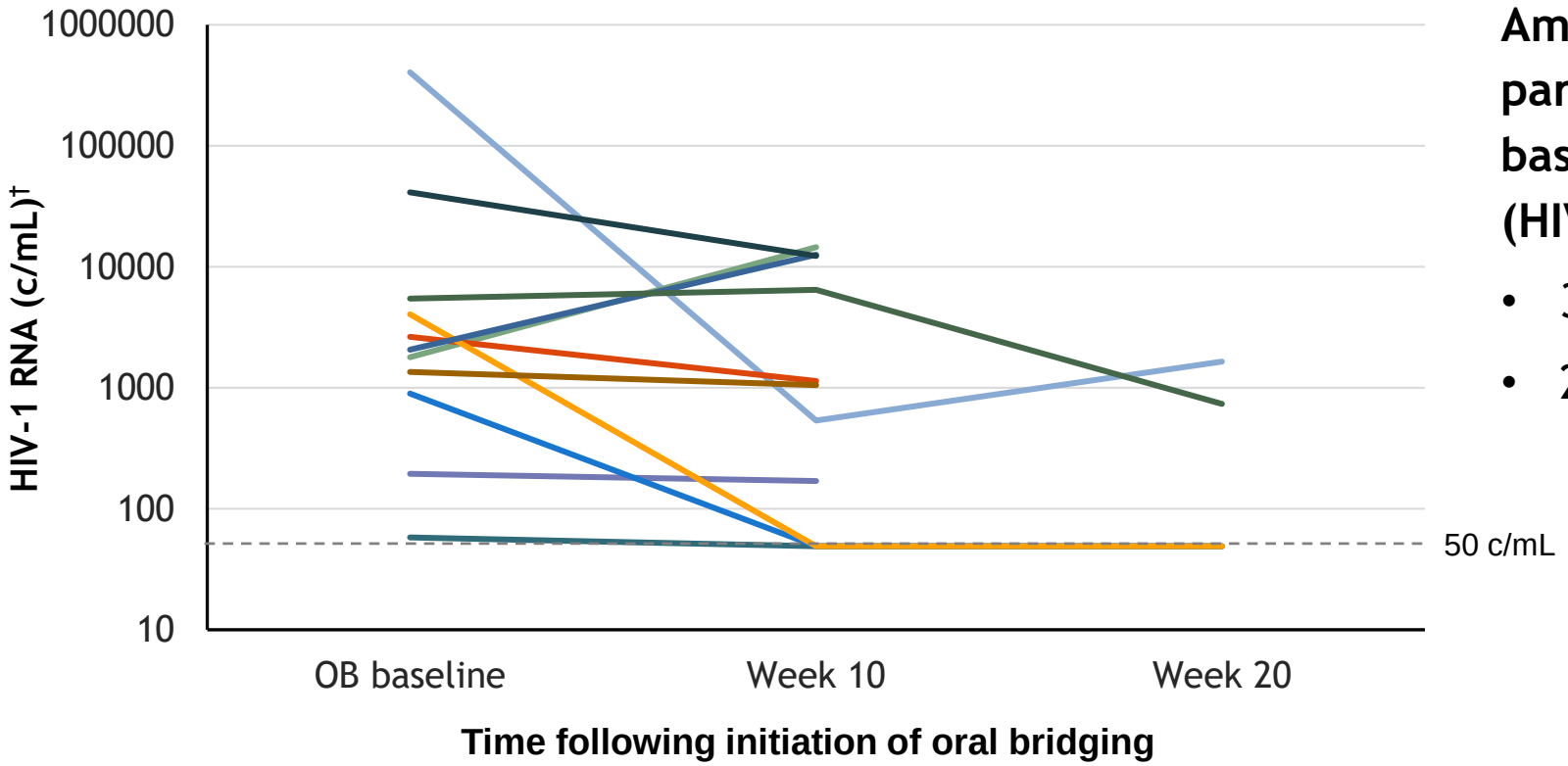


CD4 counts remained stable throughout oral bridging amongst participants suppressed at oral bridging baseline

*Participants had virologic suppression at oral bridging baseline; missing = excluded; †Denominators reflect participants who reached the specified duration of oral bridging; ‡Of participants with baseline HIV-1 RNA <50 c/mL, one did not maintain HIV-1 RNA <50 c/mL during the oral bridging period at Week 10 and 20 (Week 10 values: 920 c/mL; Week 20 values: 57 c/mL). The participant developed a LEN resistance-associated mutation (N74D), and had missed two, non-consecutive doses of oral LEN prior to the elevated HIV-1 RNA results. The participant resuppressed after the oral bridging period with no optimized background regimen change.

c/mL, copies per milliliter; LEN, lenacapavir; M=E, missing = excluded; OB, oral bridging; wk, week.

Viral Load During Oral Bridging Amongst CAPELLA Participants* Not Suppressed at the Switch to Oral LEN



Amongst the 11 viremic participants at oral bridging baseline, suppression (HIV RNA <50 c/mL) occurred in:

- 3/11 (27%) at Week 10
- 2/4 (50%) at Week 20

None of the 11 viremic participants at oral bridging baseline experienced more than 1 log increase in viral load during oral bridging

*Data are shown for 11 participants in CAPELLA without virologic suppression (i.e. HIV-1 RNA ≥50 c/mL) at oral bridging baseline; no participants in CALIBRATE had HIV-1 RNA ≥50 c/mL at oral bridging baseline. Resistance testing and pharmacokinetic analyses for these participants are ongoing. †For illustrative purposes, samples with <50 c/mL are shown on figure as 49 c/mL
c/mL copies per milliliter; LEN, lenacapavir

Safety Profile of LEN During Oral Bridging

Groups receiving oral LEN (oral bridging analysis set)

TEAE	CAPELLA (n=57)	CALIBRATE	
		Group 1 (n=44)	Group 2 (n=38)
Any-grade, n (%)	28 (49.1)	28 (63.6)	25 (65.8)
GI disorders	7 (12.3)	4 (9.1)	7 (18.4)
Treatment-related, n (%)	2 (3.5)	1 (2.3)	2 (5.3)
Grade ≥3, n (%)	1 (1.8)	2 (4.5)	1 (2.6)
Serious, n (%)	1 (1.8)	1 (2.3)	1 (2.6)
Selected AEs*, %	Cough: 5.3 Diarrhea: 5.3 URTI: 5.3	**Group 1 and 2 total:** Nasopharyngitis: 4.9 Syphilis: 4.9 Oropharyngeal pain: 4.9	

- Treatment with LEN oral bridging was generally well tolerated in CAPELLA and CALIBRATE, with a safety profile consistent with SC LEN in the primary analysis (excluding ISRs)
- No Grade ≥3 or serious TEAEs were considered related to study drug in either study
- One death occurred during oral bridging (CAPELLA; cause unknown, not deemed related to study treatment by the investigator)
  - Prior to oral bridging, this participant had experienced a TEAE of alcoholic hepatitis
- No TEAE led to early discontinuation in either study

Adverse events were coded according to MedDRA Version 25.0. Severity grades were defined by division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1; July 2017). Data collected during oral bridging period were included. *CAPELLA: COVID-19, 7.0%; CALIBRATE: influenza, 8.5%; COVID-19, 4.9%.
AE, adverse event; ISR, injection-site reaction; GI, gastrointestinal; LEN, lenacapavir; MedDRA, medical dictionary for regulatory activities; SC, subcutaneous; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Conclusions

- High rates of virological suppression were maintained in both studies throughout oral bridging
- In both studies, CD4 cell count remained stable during oral bridging
- Orally administered LEN had a favorable safety profile in CAPELLA and CALIBRATE, and was consistent with SC LEN (excluding ISRs)
- This analysis supports the efficacy and safety of oral bridging in PWH, including those with MDR HIV-1 whose SC LEN treatment was interrupted

ISR, injection-site reaction; LEN, lenacapavir; MDR, multidrug resistant; PWH, people with HIV; SC, subcutaneous.

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Calibrate

Dominican Republic: E Koenig; **United States:** P Benson, DS Berger, M Berhe, C Brinson, P Cook, DR Coulston, GE Crofoot, FA Cruickshank, D Cunningham, E DeJesus, C Dietz, V Drelichman, E Gardner, A Gaur, D Goldstein, SK Gupta, D Hagins, R Hengel, T Hodge, C-B Hsiao, A Khalsa, CA Kinder, P Kumar, C McDonald, A Mills, JO Morales-Ramirez, C Newman, G Oguchi, O Osiyemi, MN Ramgopal, PJ Ruane, W Sanchez, JL Santana-Bagur, L Santiago, A Scribner, J Sims, GI Sinclair, JL Stephens, M Wohlfeiler, AK Wurapa

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Oral bridging PK poster (IAS 2023)