Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People with Multi-Drug Resistant HIV: Week 104 Results

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Key Findings

- Lenacapavir (LEN) is approved for the treatment of multidrug-resistant (MDR) HIV-1 infection, in combination with other antiretrovirals (ARVs), for heavily treatment-experienced (HTE) people with HIV (PWH) based on the results of the ongoing Phase 2/3 CAPELLA trial
- With an additional year of follow-up from the previous analyses, CAPELLA participants continued to experience high and sustained rates of virologic suppression (82% by missing=excluded analysis at Week 104)
- Consistent with previous analyses, clinically meaningful increases in CD4 cell count were observed through Week 104, with a mean increase of 122 cells/μL from baseline
- The safety profile of LEN was consistent with previous analyses; no participants discontinued LEN due to treatment-emergent adverse events (TEAEs) after Week 52, and no participants experienced a treatment-related serious adverse event (SAE)

Conclusions

- With longer follow-up, LEN combined with an optimized background regimen (OBR) continued to result in high and sustained rates of virologic suppression through Week 104 in HTE PWH, with a clinically relevant increase in CD4 count from baseline to Week 104
- Consistent with previous analyses, LEN was well tolerated
  - No participants experienced a treatment-related SAE
  - Only one participant discontinued study drug due to TEAEs (Grade 1 injection site reaction [ISR], prior to Week 52)
- These data further support the use of LEN for the treatment of HTE PWH with MDR HIV-1 infection

References: 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 October 2023). 3. Segal-Maurer S, et al. *N Engl J Med.* 2022;386:1793–1803. 4. Ogbuagu O, et al. *Lancet HIV.* 2023;10:e497–e505. 5. Ogbuagu O, et al. Oral presentation 1585 presented at IDWeek 2022.

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Background

- LEN is a first-in-class, long-acting HIV-1 capsid inhibitor which targets viral nuclear import, virion assembly, and capsid core assembly, thereby inhibiting virion production[1]
- LEN is indicated for the treatment of MDR HIV-1 in HTE PWH, in combination with other ARVs[2]
  - LEN is administered every six months (Q6M) by subcutaneous (SC) injection following initiation dosing[2]
- The approval of LEN was based on the results of the ongoing Phase 2/3 CAPELLA trial (NCT04150068), in which LEN combined with an OBR resulted in a high rate of virologic suppression in HTE participants with MDR HIV-1[3]
  - At Week 52, 78% of participants achieved virologic suppression, with a mean increase in CD4 cells of 97 cells/μL[4,5]
- After reporting the efficacy and safety data in CAPELLA through Week 52, the protocol was amended to allow longer follow-up; here we report Week 104 results

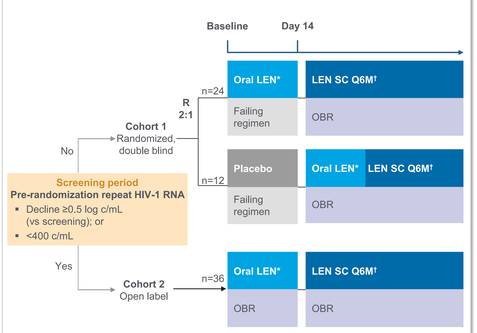
Objectives

- To assess the efficacy (by virologic outcomes at Week 104 per FDA Snapshot algorithm and missing=excluded analysis, and change from baseline in CD4 cell count), resistance emergence, and safety of LEN in HTE PWH with MDR HIV-1 through Week 104

Methods

- CAPELLA is an ongoing, Phase 2/3 study in HTE PWH with MDR HIV-1. Participants received LEN oral initiation followed by SC LEN Q6M combined with an investigator-selected OBR (**Figure 1**)[3,4]
- Following the protocol amendment, participants could continue to receive study drug until SC LEN became accessible through an access program or commercially available

Figure 1: CAPELLA study design



*Days 1 and 2: 600 mg; Day 8, 300 mg. †927 mg as two 1.5-mL injections in the abdomen on Day 15, then Q6M. c/mL, copies/mL; LEN, lenacapavir; OBR, optimized background regimen; Q6M, every 6 months; R, randomized; SC, subcutaneous

Results

- 72 participants were enrolled in CAPELLA, with baseline disease characteristics consistent with the profile of a HTE population with MDR HIV-1 (**Table 1**)
- Most participants (n=66/72 [92%]) remained on the study beyond Week 52
  - Five participants discontinued study drug prior to Week 52
    - Lost to follow-up, n=3
    - Investigator's discretion, n=1
    - Death, n=1
  - One participant completed the study without entering the post-Week 52 phase
- At Week 104, 62% of participants achieved virologic suppression (HIV-1 RNA <50 copies/mL) per FDA Snapshot algorithm (**Figure 2A**)
- When analyzed as missing=excluded, 82% of participants achieved virologic suppression at Week 104 (**Figure 2B**)
  - Of the 10 participants with HIV-1 RNA ≥50 copies/mL at Week 104, viral load ranged from 67–24,500 copies/mL; of these participants, 6 were suppressed (<50 copies/mL) at ≥1 visit during the study

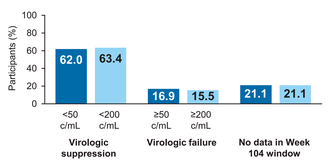
Table 1: Baseline characteristics

	Total N=72
Median (range) age, years	52 (23–78)
Sex at birth, n (%)	
Male	54 (75.0)
Female	18 (25.0)
Race, n (%)*	
Asian	15 (21.1)
Black	27 (38.0)
White	29 (40.8)
HIV-1 RNA	
Median (range), log_{10} c/mL	4.5 (1.3–5.7)
>100,000 c/mL, n (%)	14 (19.4)
CD4 cell count	
Median (range), cells/μL	150 (3–1296)
<200 cells/μL, n (%)	46 (63.9)
Median (range) number of prior ARVs	11 (2–25)
Known resistance to ≥2 drugs in class, n (%)	
NRTI	71 (98.6)
NNRTI	70 (97.2)
PI	58 (80.6)
INSTI	50 (69.4)
All four major classes	33 (45.8)

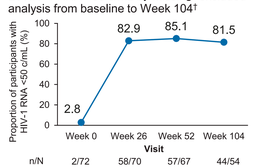
*Collection of race information not permitted by local regulations, n=1 (Cohort 1); participant excluded from percentage calculation.
ARV, antiretroviral; c/mL, copies/mL; INSTI, integrase strand transfer inhibitor; (N)NRTI, (non-) nucleotide reverse transcriptase inhibitor; PI, protease inhibitor

Figure 2: Virologic outcomes

A: FDA snapshot analysis at Week 104*



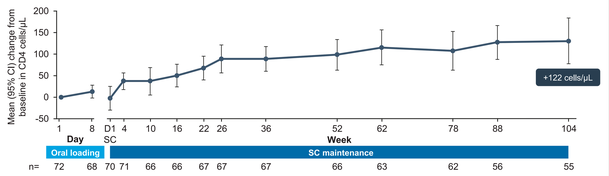
B: HIV-1 RNA <50 c/mL by missing=excluded analysis from baseline to Week 104†



*The Week 104 window is Day 688 to Day 778 inclusive (n=71); participants who had missing HIV-1 RNA at Week 104 and had completed the study before reaching the upper limit of the analysis window for Week 104 were excluded (n=1). †The denominator for percentages is the number of participants with non-missing HIV-1 RNA values at each time point. c/mL, copies/mL; FDA, Food and Drug Administration

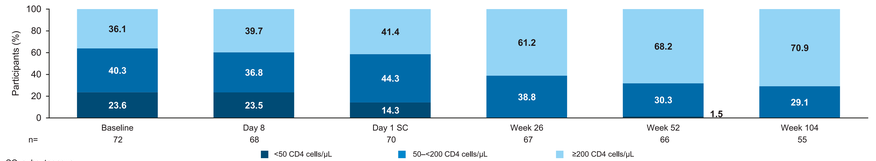
- Mean increase in CD4 count from baseline to Week 104 was 122 cells/μL (95% CI: 80; 165) (**Figure 3**)
- From baseline to Week 104, the proportion of participants with CD4 count <200 and <50 cells/μL decreased from 64% to 29% and 24% to 0%, respectively (**Figure 4**)

Figure 3: CD4 cell count change from baseline



CI, confidence interval; D, day; SC, subcutaneous

Figure 4: CD4 cell count changes by category



SC, subcutaneous

- Five additional participants had emergent LEN resistance in the 2nd year of CAPELLA, bringing the total number of participants with LEN resistance to 14 after two years (**Table 2**)
- All 14 participants had high risk of emergent LEN resistance (no fully active drugs in OBR or inadequate OBR adherence) (**Table 2**)
  - The main capsid mutations were M66I (n=6), Q67H (n=5), K70N/H (n=2), and N74D (n=1), occurring singly or in more complex patterns
- Seven of 14 participants resuppressed after LEN resistance emergence whilst remaining on LEN (**Table 2**)

Table 2: Emergent LEN resistance

n	Total N=72
Emergent LEN resistance	
RAMs observed: M66I; Q67H/K/N; K70H/N/R/S; N74D/H/K; A105S/T, and T107A/C/N/S	14
No fully active agents in OBR	4
Inadequate adherence to OBR*	10
Resuppressed after LEN resistance emergence whilst remaining on LEN	
Yes†	7
With OBR change	2
Without OBR change	5
No‡	7
Continued study drug§	4
Discontinued study drug for reasons not related to efficacy¶	3

*Based on OBR plasma concentrations. †Pharmacokinetic analysis of 2 participants indicated improved adherence (analysis ongoing, n=5). ‡All 7 participants had CD4 count <200 cells/μL at baseline; whilst these participants had some increase in CD4 count during the study, three participants returned to baseline CD4 count. §Returned to baseline viral load, n=2; >1 log_{10} reduction in HIV-1 RNA, n=2 (1.1 and 1.8 log_{10}). ¶Due to: death (n=1); investigator's discretion due to non-compliance (n=1); lost to follow-up (n=1). LEN, lenacapavir; OBR, optimized background regimen; RAM, resistance-associated mutation

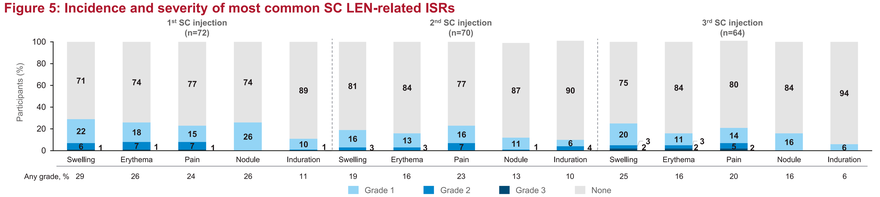
Table 3: Safety

n (%)	Total N=72
Most common TEAEs (occurring ≥15% of participants, excluding ISRs and COVID-19)	
Diarrhea	14 (19.4)
Nausea	14 (19.4)
Urinary tract infection	12 (16.7)
Cough	11 (15.3)
TEAEs	71 (98.6)
Grade ≥3	24 (33.3)
TRAEs	57 (79.2)
Grade 3	6 (8.3)*
Serious TEAEs	15 (20.8)
TEAEs leading to premature study drug discontinuation	1 (1.4)†
All deaths	3 (4.2)‡

*Grade 3 TRAEs: ISR, n=4; immune reconstitution inflammatory syndrome, n=1; abdominal abscess, n=1; rash, n=1. †Due to Grade 1 injection site nodule. ‡Deaths due to: malignant neoplasm, n=1; acute respiratory failure, n=1; unknown cause, n=1. ISR, injection-site reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

- The median duration of follow-up on LEN was 125 (interquartile range 111–140) weeks
- Safety outcomes are reported in **Table 3**
  - There were three deaths during the study
  - No participants experienced a treatment-related SAE or a Grade ≥4 treatment-related adverse event
- ISRs were predominantly mild-to-moderate; four participants (5.6%) had a Grade 3 ISR, with no Grade 4 ISRs reported (**Figure 5**)
  - 22 participants experienced a total of 74 events of nodule; 40/74 (54%) events had resolved, with median (interquartile range) duration of 253 (113–457) days
  - 11 participants experienced a total of 21 events of induration; 16/21 (76%) events had resolved, with median (interquartile range) duration of 120 (29–236) days
  - After the 4th SC injection, eight participants had new nodules and two participants had new indurations; of these participants, one had an ongoing induration from the 3rd injection and one had ongoing indurations from the 1st, 2nd, and 3rd injections
  - Further data on ISRs will be presented at European AIDS Conference 2023

Figure 5: Incidence and severity of most common SC LEN-related ISRs



Percentage denominators are the number of participants who received an injection at that visit. Percentages may not total 100% due to rounding. ISR, injection site reaction; LEN, lenacapavir, SC, subcutaneous