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Impact of Pharmacoenhancers on the Pharmacokinetics and Safety of Lenacapavir in People with HIV

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Conclusions

- Co-administration of pharmacoenhancers in the CAPELLA study led to a modest increase in lenacapavir (LEN) exposure in people with HIV-1 (PWH); however, this was not considered clinically relevant
- The safety profile of LEN with or without co-administration of pharmacoenhancers was similar in the CAPELLA study
- LEN can be co-administered with background regimens containing pharmacoenhancers, without the need for dose adjustments

Plain Language Summary

- Lenacapavir is a medicine approved to treat HIV infection, and is given together with other HIV medicines
- One type of medicine that may be given with lenacapavir is called a 'pharmacoenhancer'
  - Pharmacoenhancers are drugs, such as cobicistat or ritonavir, that help to raise the level of other HIV medicines in the blood
- We looked at a study of lenacapavir called CAPELLA to find out if pharmacoenhancers change the level of lenacapavir found in people's blood, and if pharmacoenhancers affect safety
- We found that levels of lenacapavir in the blood were a little higher in people taking lenacapavir with pharmacoenhancers compared with those who were not taking pharmacoenhancers
- The safety of lenacapavir was similar in people who were taking pharmacoenhancers and those who were not, and the types of side effects that happened were the same
- These results show that lenacapavir can be given safely with pharmacoenhancers without needing to change the dose of lenacapavir

Background

- LEN is a potent, first-in-class, long-acting, HIV-1 capsid inhibitor that interferes with capsid-mediated nuclear uptake of pre-integration complexes and impairs virion production[1,2]
- LEN is approved for the treatment of heavily treatment-experienced PWH in combination with other antiretrovirals, based on the results from the Phase 2/3 CAPELLA study (NCT04150068)[2–4]
  - CAPELLA participants received oral LEN loading doses (Days 1 and 2: 600 mg; Day 8: 300 mg) followed by subcutaneous (SC) LEN maintenance (927 mg every 6 months) starting from Day 15, in combination with an optimized background regimen[4]
- Current data indicate that the maximal antiviral activity of LEN is achieved when the lower bound of the 90% confidence interval (CI) of mean trough concentration (C_{trough}) is ≥15.5 ng/mL, which is the inhibitory quotient-4 (IQ4)[5]
- Pharmacoenhancers, such as ritonavir and cobicistat, are commonly used with protease inhibitors to increase protease inhibitor plasma concentrations when treating HIV-1 infection[6]
- LEN is a substrate of P-glycoprotein, CYP3A, and UGT1A1; pharmacoenhancers that inhibit P-glycoprotein and CYP3A are likely to affect LEN pharmacokinetics (PK)[1,2]

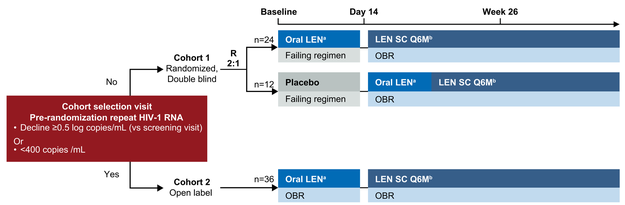
Objective

- To evaluate the impact of pharmacoenhancers on LEN PK and safety in PWH enrolled in the CAPELLA study after the oral loading period at Day 15 and after the first SC injection at Week 26

Methods

- CAPELLA is an ongoing, global, Phase 2/3 study with a randomized, double-blind cohort (Cohort 1) and a single-arm, open-label cohort (Cohort 2) **(Figure 1)**[4]
- In CAPELLA, PK samples were collected throughout the oral loading period (Days 1, 2, 5, 8, and 15) and sparse PK sampling was conducted during the maintenance period (Weeks 4, 10, 16, 22, and 26)
- Plasma concentrations of LEN were quantified using a validated high-performance liquid chromatography–tandem mass spectrometry method
- Observed LEN plasma concentrations were summarized in CAPELLA participants receiving optimized background regimens with or without pharmacoenhancers at the end of the oral loading period on Day 15 and at the end of first SC-dosing interval at Week 26
- Treatment-emergent adverse event (AE) data were assessed among CAPELLA participants receiving background regimens with or without pharmacoenhancers

Figure 1. CAPELLA Study Design[4]



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

Results

- Of the 72 enrolled CAPELLA participants, 42 participants were receiving pharmacoenhancers at baseline (cobicistat, n=19; ritonavir, n=23)

PK Analyses

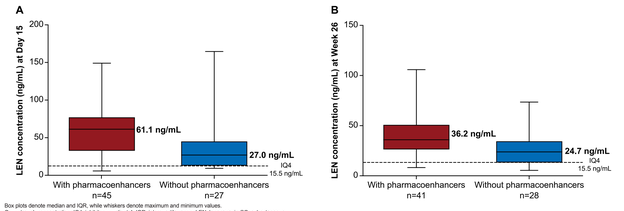
- LEN concentrations from 72 CAPELLA participants were analyzed:
  - Day 15: with pharmacoenhancers, n=45; without pharmacoenhancers, n=27
  - Week 26: with pharmacoenhancers, n=41; without pharmacoenhancers, n=28
- In participants with and without pharmacoenhancers, respectively, median (range) body weight was 70 (46–124) kg and 80 (42–118) kg at Day 15, and 69 (42–123) kg and 79 (43–118) kg at Week 26
- Lower bound of the 90% CI of mean C_{trough} were above the therapeutic target of IQ4 at Day 15 and Week 26 for both groups (with or without pharmacoenhancers) **(Table 1)**
- Following administration of oral loading doses of LEN in CAPELLA, Day 15 median C_{trough} were 61.1 and 27.0 ng/mL with and without pharmacoenhancers, respectively **(Figure 2A)**
- Following administration of oral loading doses and first SC dose of LEN in CAPELLA, Week 26 median C_{trough} were 36.2 ng/mL and 24.7 ng/mL with and without pharmacoenhancers, respectively **(Figure 2B)**

Table 1. Mean (90% CI) LEN C_{trough} at Day 15 and Week 26, With and Without Pharmacoenhancers, in CAPELLA

Mean (90% CI)	With Pharmacoenhancers	Without Pharmacoenhancers
Day 15 C_{trough}, ng/mL	59.3 (51.6; 67.0); n=45	35.9 (25.7; 46.0); n=27
Week 26 C_{trough}, ng/mL	40.9 (35.7; 46.1); n=41	28.5 (22.7; 34.4); n=28

CI, confidence interval; C_{trough}, trough concentration; LEN, Lenacapavir.

Figure 2. LEN C_{trough} at A. Day 15, and B. Week 26, With and Without Pharmacoenhancers, in CAPELLA



Box plots denote median and IQR, while whiskers denote maximum and minimum values.
C_{trough}, trough concentration; IQ4, inhibitory quotient-4; IQR, interquartile range; LEN, lenacapavir; SC, subcutaneous.

- In a separate Phase 1 study in people without HIV-1,[1] LEN when co-administered with cobicistat resulted in 2.1-fold and 2.3-fold increase in maximum concentration and area under the curve, respectively, consistent with the LEN exposure change observed in the presence of pharmacoenhancers in the CAPELLA study following the oral loading period
  - After the end of first SC dosing interval at Week 26, the increase in LEN exposure with versus without pharmacoenhancers is minimal
- The modest increases in C_{trough} with pharmacoenhancers in CAPELLA are not considered to be clinically relevant; as such there is no LEN dose adjustment required

Safety

- For CAPELLA participants, the safety profile of LEN was generally similar for participants with (n=42) or without (n=30) pharmacoenhancers in their optimized background regimen (OBR) at baseline, respectively **(Table 2)**:
  - Grade ≥3 AEs: 21.4% vs 13.3%
  - LEN-related AEs: 61.9% vs 63.3%
  - Serious AEs: 2.4% vs 10.0%
- In participants with and without pharmacoenhancers, the most common treatment-emergent AEs (reported in >3% of participants [excluding injection site reactions]) were cough, diarrhea, nausea, abdominal distention, arthralgia, and headache **(Table 3)**

Table 2. Safety Overview of Participants With or Without Pharmacoenhancers in OBR at baseline in CAPELLA

Participants, n (%)	With Pharmacoenhancers n=42	Without Pharmacoenhancers n=30
AEs Grade ≥3	40 (95.2) 9 (21.4)	26 (86.7) 4 (13.3)
TRAEs Grade ≥3	26 (61.9) 3 (7.1)	19 (63.3) 1 (3.3)
SAEs[a]	1 (2.4)[b]	3 (10.0)[c]
AEs leading to discontinuation of treatment or study	0	1 (3.3)
Death	0	1 (3.3)[d]

[a]No treatment-related SAEs were reported in either group. [b]Abdominal pain, clostridium difficile infection, and pancreatic mass in the same participant. [c]Dizziness, femoral neck fracture, malignant neoplasm, and prostatigia, n=1 each. [d]Due to malignant neoplasm, not related to study drug.
AE, adverse event; OBR, optimized background regimen; SAE, serious adverse event; TRAE, treatment-related adverse event.

Table 3. Most Common TEAEs (excluding injection site reactions) in Participants With Pharmacoenhancers, and Corresponding Events in Participants Without Pharmacoenhancers, in OBR at Baseline in CAPELLA

Participants, n (%)	With Pharmacoenhancers n=42	Without Pharmacoenhancers n=30
Constipation	4 (9.5)	0
Cough	4 (9.5)	1 (3.3)
Diarrhea	4 (9.5)	2 (6.7)
Nausea	4 (9.5)	2 (6.7)
Abdominal distension	3 (7.1)	1 (3.3)
Arthralgia	3 (7.1)	1 (3.3)
Dyspnea	3 (7.1)	0
Headache	3 (7.1)	2 (6.7)
Myalgia	3 (7.1)	0

OBR, optimized background regimen; TEAE, treatment-emergent adverse event.

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