Follow-Up of Injection Site Reactions in Clinical Studies of People Using Lenacapavir Every 6 Months for HIV Treatment

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Key Findings

- Subcutaneous (SC) lenacapavir (LEN)-related injection site reactions (ISRs) were largely Grade 1/2, and few participants discontinued study treatment due to ISRs
- Resolution of swelling, erythema, and pain mostly occurred within days, and resolution of nodules and indurations occurred over weeks to months
  - Nodules/indurations were foreign body reactions upon biopsy, manifesting as chronic granulomatous inflammation

Conclusions

- In people with HIV-1 (PWH) receiving SC LEN in the CAPELLA and CALIBRATE studies, ISRs were predominantly mild to moderate, and no Grade 4 ISRs occurred
- ISRs rarely led to study drug discontinuation, with only one discontinuation occurring after the first year of follow-up
- Swelling, erythema, and pain typically resolved within days. Nodules and indurations resolved over weeks to months, likely due to the slow dissolution of the LEN depot into systemic circulation

Background

- LEN is a first-in-class, long-acting HIV-1 capsid inhibitor administered every 6 months (Q6M) by SC injection following initiation dosing[1–6]
- LEN was approved for the treatment of multidrug-resistant HIV-1 in heavily treatment-experienced PWH, in combination with other antiretrovirals (ARVs), in the EU, US, and other countries, based on the results of the ongoing Phase 2/3 CAPELLA study (NCT04150068)[2–8]
- The efficacy and safety of LEN, in combination with other ARVs, is also being investigated in treatment-naïve PWH in the ongoing Phase 2 CALIBRATE study (NCT04143594)[9]
- ISRs may occur following LEN SC administration due to depot formation[10]

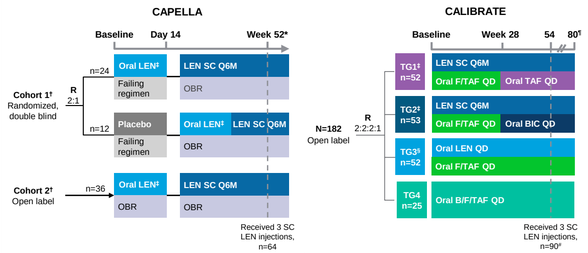
Study Objective

- To characterize SC LEN-related ISRs in CAPELLA and CALIBRATE

Methods

- CAPELLA and CALIBRATE study designs are shown in **Figure 1**
- In both studies, SC LEN 927 mg was administered Q6M as two 1.5 mL injections into the abdomen
- Analysis of ISRs included all participants in CAPELLA and CALIBRATE who received ≥1 dose of SC LEN
- We summarized ISRs occurring after each of the first three SC LEN injections to ensure sufficient duration of post-injection follow-up

Figure 1: CAPELLA and CALIBRATE study designs

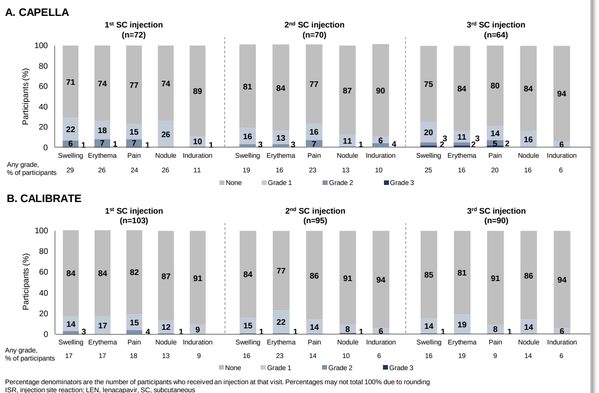


*Participants were treated for at least 54 weeks. A protocol amendment allowed participants successfully completing the Week 52 visit to continue receiving LEN SC Q6M plus OBR; †Participants were assigned to Cohort 1 or 2 according to pre-randomization repeat HIV-1 RNA screening: participants with a decline of ≥0.5 log copies/mL (vs screening) or with <400 copies/mL entered Cohort 1. ‡Participants received LEN oral loading prior to initiating LEN SC (Days 1 and 2: 600 mg; Day 8, 300 mg). §Participants received oral LEN 600 mg on Days 1 and 2, then QD LEN 50 mg from Day 3. ¶At Week 80, participants in TG4 complete the study, and participants in TGs 1–3 may continue beyond Week 80. ††TG1 and TG2 only.
BIC/B, bictegravir; F, emtricitabine; LEN, lenacapavir; PWH, people with HIV; Q6M, every six months; QD, daily; R, randomized; SC, subcutaneous; TAF, tenofovir alafenamide; TG, treatment group; W, week

Results

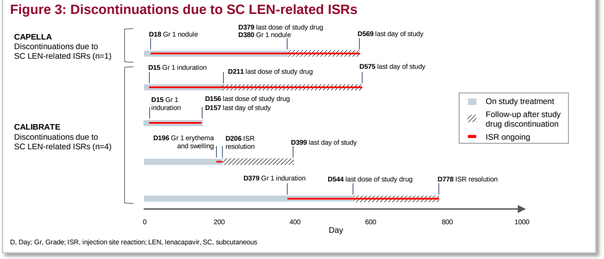
- Overall, 175 participants received ≥1 dose of SC LEN
  - All 72 participants enrolled in CAPELLA received ≥1 dose of SC LEN
  - In CALIBRATE, 103/105 participants randomized to receive SC LEN received ≥1 dose of SC LEN
  - Median (interquartile range [IQR]) SC LEN injections received: CAPELLA, 10 (8–10); CALIBRATE, 6 (6–8)
- Median (IQR) duration of exposure was 125 (111–140) and 88 (83–107) weeks in CAPELLA and CALIBRATE, respectively
- After the 1st, 2nd, and 3rd SC LEN injections, respectively, ISRs occurred in 63%, 46%, and 55% of CAPELLA participants and 42%, 52%, and 43% of CALIBRATE participants
- **Figure 2** shows the frequency and severity of the most common ISRs
  - ISRs were predominantly Grade 1/2; no Grade 4 ISRs occurred
- Five participants discontinued study treatment due to ISRs (**Figure 3**), with only one ISR leading to discontinuation after the first year of follow-up
- Swelling, erythema, and pain typically resolved within days (**Table 1**) (median duration for both studies combined: 10, 5, and 3 days, respectively). Nodules and indurations took longer to resolve (**Table 1**), with a median duration of 252 and 202 days, respectively (245 and 194 days for resolved events) for both studies combined
- Dermatology evaluation and/or skin biopsy were performed for six participants with nodules or indurations lasting ≥6 months (**Table 2**)
  - Chronic granulomatous inflammation consistent with foreign body reaction to drug depot was observed, consistent with pre-clinical findings[10]
  - Nodules and indurations were palpable, but not visible to participants or clinicians (**Figure 4**)

Figure 2: 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

Figure 3: Discontinuations due to SC LEN-related ISRs



D, Day; Gr, Grade; ISR, injection site reaction; LEN, lenacapavir, SC, subcutaneous

Table 1: Duration of most common SC LEN-related ISRs

Median (IQR) duration, days	CAPELLA (N=72)	CALIBRATE (N=103)
Swelling	8 (4–15)	11 (6–15)
Erythema	5 (3–8)	5 (2–11)
Pain	3 (1–4)	2 (1–6)
Nodule	252 (113–524)	250 (100–369)
Induration	183 (63–498)	215 (144–415)

IQR, interquartile range; ISR, injection site reaction; LEN, lenacapavir, SC, subcutaneous

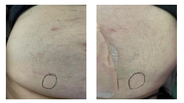
Table 2: Summary of biopsy and dermatology evaluations

ISR	Day	Summary of biopsy/dermatology evaluation report
CAPELLA		
Nodule (Grade 1)	15	• Granulomatous foreign body reaction in adipose panicle and fatty tissue necrosis, compatible with foreign body panniculitis
Nodule (Grade 2)	204	• Area palpable; no erythema or swelling (no biopsy performed)
Nodule (Grade 1)	15, 215	• Abdominal injection scars present; 4 SC indurations found, 2 on each side of abdomen (no biopsy performed)
CALIBRATE		
Swelling (Grade 1)	561	• Focal dermal fibrosis, possibly representing edge of old rupture cyst or folliculitis • Focal areas of granulomatous inflammation surrounding small collections of amorphous material, consistent with a granulomatous reaction to injected medication
Nodule (Grade 1)	380	• SC periumbilical nodules apparent upon deep palpation; no tenderness upon palpation; no overlying skin changes • Biopsy: minimal chronic inflammation; no granulomatous inflammation of foreign body reaction; no evidence of panniculitis
Nodule (Grade 1)	463	• Fibrosis and giant cell reaction, compatible with ISR

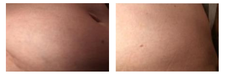
Biopsy/dermatology evaluation findings summarized for 6 participants who met the ISR criteria for dermatological assessment.
ISR, injection site reaction; SC, subcutaneous

Figure 4: Images of nodules and indurations

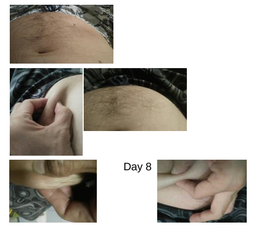
A. Induration occurring after 1st SC LEN dose: Week 62 Visit*



B. Nodule occurring at 1st SC LEN dose at Day 15†



C. Induration occurring after 1st SC LEN dose‡



*The participant had a non-tender indurated area ~2 x 2 cm at both abdominal sites of SC injections, with no erythema or warmth, after the Week 62 visit. The induration decreased in size but did not resolve completely. †In addition to nodules, the participant had an AE of injection site pain resolving after 8 days from the same injection. ‡In addition to induration, the participant had injection site AEs of moderate pain and mild erythema on Day 1; pain and erythema resolved after Day 2, and induration resolved after a week.
AE, adverse event; LEN, lenacapavir; SC, subcutaneous

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