Injection Site Reactions More Common and Bothersome With Single Doses of Lenacapavir vs Cabotegravir

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Key Takeaways

- **CLARITY is a crossover study that assessed injection-site reactions (ISRs) up to 6 months after a single dose each of long-acting cabotegravir (CAB LA) and long-acting lenacapavir (LEN LA)**
- **ISRs were more frequent, more visible, longer-lasting, and more bothersome after a single dose of LEN LA compared with CAB LA**
- **Differences in ISR profiles across long-acting injectables highlight the role of the patient's experience in regimen choice**

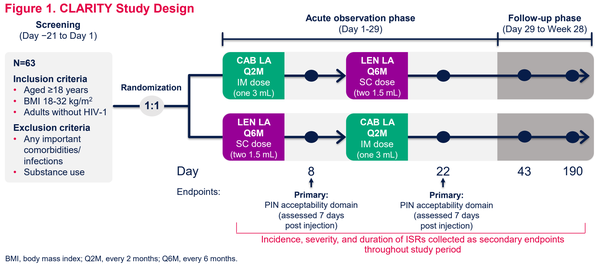
Introduction

- Long-acting injectable (LAI) regimens provide improved adherence, confidentiality, and convenience over daily oral regimens[1]
- Injection-site reactions (ISRs) are common with LAI regimens and may cause long-lasting inflammatory effects, inadvertent disclosure, or lead to discontinuation of therapy and treatment[2-5]
- ISR profiles are important for individuals when selecting an LAI regimen for pre-exposure prophylaxis (PrEP), and the initial injection experience may determine an individual's willingness to continue therapy
- Despite the importance of ISRs, data on the characteristics associated with different LAI regimens are currently lacking
- The CLARITY study (NCT06970223) is a randomized crossover study that evaluates ISRs after a single dose each of long-acting cabotegravir intramuscular (CAB LA) and long-acting lenacapavir subcutaneous (LEN LA) injections[6]
- We have previously shown that a single dose of CAB LA had higher ISR acceptability* and was preferred by participants compared with LEN LA after receiving a single dose each of CAB LA and LEN LA[6,†]
- Here we report detailed visible and palpable ISR events up to 190 days after administration of each study drug

Methods

- CLARITY is an open-label, randomized crossover study comparing a single dose each of CAB LA and LEN LA in 63 people without HIV-1 (Figure 1)
  - A single dose of CAB LA consists of 1 intramuscular gluteal injection, and a single dose of LEN LA consists of 2 subcutaneous abdominal injections

Figure 1. CLARITY Study Design



BMI, body mass index; Q2M, every 2 months; Q6M, every 6 months.

- Healthcare providers assessed ISRs at every study visit after dosing using Division of AIDS criteria
  - Assessed ISRs included pain, erythema, swelling, induration, pigmentation changes, pruritis, warmth, cellulitis, rash, and nodules
- The primary endpoint was defined as the proportion of participants reporting "very acceptable or totally acceptable" local reactions and pain at Day 8 and Day 22 (ie, 7 days after each injection) using the Perception of Injection (PIN) questionnaire, adapted from the validated Vaccinees' Perception of Injection questionnaire[7,8]
- Secondary endpoints included ISR incidence, severity, and duration through 6 months of follow-up
  - As part of the secondary endpoint, the PIN participant-reported outcomes are presented in terms of domain scores (bother, movement, sleep, acceptability) and individual item scores (anxiety before injection, pain during injection, satisfaction, anxiety after injection, willingness to continue) through Day 190
- Exploratory ISR assessments included a combination of 2-D photography and ultrasound scanning
- Semi-structured qualitative interviews were conducted with participants at D8 and D22. Rapid analysis and applied thematic analysis explored perceptions of injection implementation, acceptability, appropriateness, and feasibility. These themes were supported by illustrative quotes and by frequencies of themes identified.

*At Day 22, a higher proportion of participants reported that local reactions and pain were "very acceptable or totally acceptable" after CAB LA vs LEN LA injections (69% vs 48%; $P=0.019$ in a post-hoc analysis). The mean (standard deviation [SD]) acceptability domain score in the Perception of Injection questionnaire was 1.9 (1.1) for CAB LA and 2.4 (1.2) for LEN LA, with lower scores indicating higher acceptability. †After receiving both regimens, 90% ($P<0.001$ in a post-hoc analysis) of participants reported that they preferred CAB LA over LEN LA.

Results

Participant Baseline Demographics

- A diverse group of 63 participants (33% female, 38% Hispanic or Latine, and 29% Black or African American) were enrolled
- A total of 26 participants (31% female, 23% Black or African American) completed interviews at D8 and/or D22

Frequency of ISR Events Among Participants

- Participants experienced fewer ISR events after CAB LA compared with LEN LA injections (Table 1)
  - The median (range) number of ISRs per participant was 2 (0-8) after CAB LA and 10 (3-20) after LEN LA

Table 1. Participant-Level Summary of ISR Frequency Through Day 190[a]

Variable, n (%)	CAB LA (n=61)[b]	LEN LA (n=62)[b]
Participants who experienced any ISR event	55 (90)	62 (100)
Number of ISR events[c]		
0	6 (10)	0
1	18 (30)	0
2	14 (23)	0
3 to 5	18 (30)	7 (11)
≥6	5 (8)	55 (89)

[a]In participants who received ≥1 injection. [b]One participant received CAB LA on Day 1 but did not receive LEN LA on Day 15. [c]Participants could experience more than 1 type of ISR event in response to injection.

Summary of Overall ISR Events

- The total number of ISRs (CAB LA, n=150; LEN LA, n=642) was lower with CAB LA compared with LEN LA injections (Table 2)
- ISRs experienced after CAB LA injections resolved faster than those experienced after LEN LA injections (3% vs 22% not recovered/not resolved at Day 190)

Table 2. Summary of Overall ISRs Through Day 190[a]

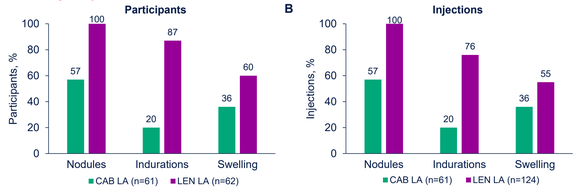
Variable, n[b]	CAB LA (n=61)[c]	LEN LA (n=62)[c]
Total injections[d]	61	124
ISR events	150	642
Visible ISR events, n (% of all events)[e]	43 (29)	331 (52)
Maximum grade, n (% of all injections)		
Grade 1	37 (61)	59 (48)
Grade 2	13 (21)	59 (48)
Grade 3	5 (8)	6 (5)
Outcome, n (% of all events)[f]		
Recovered/Resolved	146 (97)	504 (79)
Not recovered/not resolved	4 (3)	138 (22)

[a]In participants who received ≥1 injection. [b]Unless otherwise noted. [c]One participant received CAB LA on Day 1 but did not receive LEN LA on Day 15. [d]A single dose of CAB LA requires 1 injection; a single dose of LEN LA requires 2 injections. [e]Defined as having any erythema, hyperpigmentation, and/or visible nodules, indurations, or swelling. [f]Percentages may total >100% due to rounding.

Summary of Nodule, Induration, and Swelling Events

- Fewer participants experienced nodules (CAB LA, 57%; LEN LA, 100%), indurations (CAB LA, 20%; LEN LA, 87%), and swelling (CAB LA, 36%; LEN LA, 60%) after CAB LA vs LEN LA injections (Figure 2)
- The proportions of nodules (14% vs 63%), indurations (83% vs 89%), and swelling events (77% vs 87%) that were visible were lower after CAB LA than LEN LA injections (Table 3)

Figure 2. (A) Proportions of Participants With ISRs and (B) Proportions of Injections Resulting in ISRs[a] Through Day 190



[a]A single dose of CAB LA consists of 1 injection; a single dose of LEN LA consists of 2 injections.

- The duration of nodules was shorter after CAB LA vs LEN LA injection, with 2 (6%) nodules with CAB LA persisting >180 days vs 101 (82%) nodules with LEN LA (Table 3)

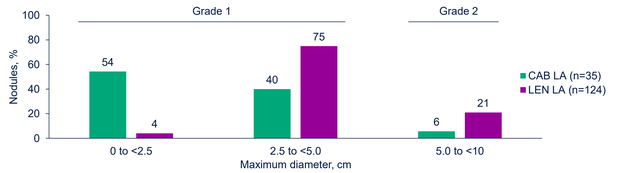
Table 3. Summary of Nodules, Indurations, and Swelling[a]

Characteristic	CAB LA (n=61)[b]	LEN LA (n=62)[b]
Nodules, n	35	124
Nodules unresolved by Day 190, n (%)	4 (11)	120 (97)
Duration of nodules, median (range), days[c]	64.0 (7-182)	196.5 (2-224)
Nodules visible at any time, n (%)	5 (14)	78 (63)
Indurations, n	12	94
Indurations unresolved by Day 190, n (%)	0 (0)	0 (0)
Duration of indurations, median (range), days[c]	12.0 (2-42)	14.0 (2-59)
Indurations visible at any time, n (%)	10 (83)	84 (89)
Swelling, n	22	68
Swelling unresolved by Day 190, n (%)	0 (0)	0 (0)
Duration of swelling, median (range), days[c]	5.0 (2-36)	7.0 (2-202)
Swelling visible at any time, n (%)	17 (77)	59 (87)

[a]In participants who received ≥1 injection. [b]One participant received CAB LA on Day 1 but did not receive LEN LA on Day 15. [c]Includes both resolved and unresolved ISRs (up to data cut-off date of Dec 29, 2025).

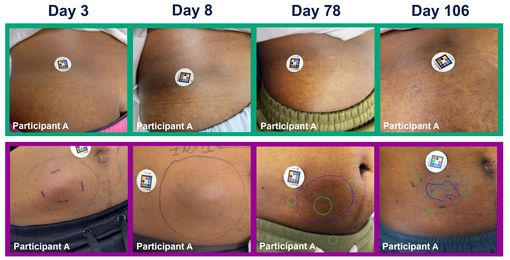
- Nodules were smaller in diameter after CAB LA vs LEN LA injections (Figures 3 and 4)

Figure 3. Maximum Size of Nodules[a-d]



[a]**The median diameter of nodules was 2.0 cm for CAB LA and 4.1 cm for LEN LA. Most (54%) CAB LA nodules were <2.5 cm in diameter, while approximately 95% of LEN LA nodules were >2.5 cm in diameter.** [b]Includes both resolved and unresolved ISRs (up to data cut-off date of Dec 29, 2025). [c]Modified DAIDS grading criteria for indurations/swelling (in which ISRs <2.5 cm in diameter or <6.25 cm^2 in surface area are also categorized as Grade 1) were extrapolated for nodules. By these criteria, 33/35 of CAB LA and 98/124 of LEN LA nodules were Grade 1, and 2/35 of CAB LA and 26/124 of LEN LA nodules were Grade 2. [d]By modified DAIDS grading criteria, indurations were 83% Grade 1 and 17% Grade 2 after CAB LA, and 98% Grade 1 and 2% Grade 2 after LEN LA. After CAB LA, 55% of swelling events were Grade 1 and 46% were Grade 2; after LEN LA, 34% of swelling events were Grade 1, 57% were Grade 2, and 9% were Grade 3.

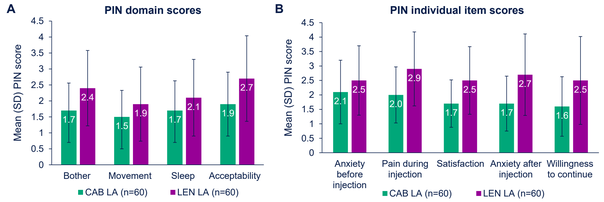
Figure 4. Representative Images of ISRs After CAB LA and LEN LA Injections



Participant-Reported PIN Scores

- Across all PIN domains and individual items of assessment, participants consistently reported better results (indicated by lower scores) for CAB LA compared with LEN LA (Figure 5)
- At Day 190, the proportions of participants reporting "very or totally acceptable" local reactions and pain were 70% for CAB LA and 37% for LEN LA
- Most (85%) participants indicated a preference for CAB LA over LEN LA at Day 190

Figure 5. Mean (A) PIN Domain and (B) Individual Item Scores At Day 190



Lower scores indicate better outcomes.

Participant Experiences With ISRs

- Among participants who completed qualitative interviews at Days 8 and 22 (n=22), 91% expressed that their experiences with ISRs differed between CAB LA and LEN LA injections, primarily due to differences in severity of physical responses such as nodules and swelling

> *"The nodules that I got in my abdomen were slightly larger and have been longer lasting than the one in the buttock" – Participant referencing LEN LA vs CAB LA, respectively**
>
> *"More redness, obviously the swelling, the tenderness, the pain when you put pressure on it and the nodules all were more severe or noticeable with these injections compared to the first" – Participant referencing LEN LA**

*Representative quotes displayed were the only two quotes provided for this topic as part of the third-party thematic analysis of interview data.

Conclusions

- In CLARITY, ISRs after a single dose of LEN LA were more frequent, visible, severe, bothersome, and slower to resolve compared with those after a single dose of CAB LA, resulting in lower acceptability of local reactions and pain with LEN LA
  - In particular, nodules were larger, longer lasting, and more frequently visible after LEN LA vs CAB LA
- ISR profiles differentiate participant experiences with LAIs and can inform patient-provider discussions regarding optimal regimen choice

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