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Injection-Site Reaction Experience in Clinical Studies of People Using Lenacapavir For HIV Treatment

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Introduction

Lenacapavir Targets Multiple Stages of HIV Replication Cycle[1,2]

EC_{50}, half-maximal effective concentration; Gag, group-specific antigen; LEN, lenacapavir (GS-6207); Pol, polymerase.

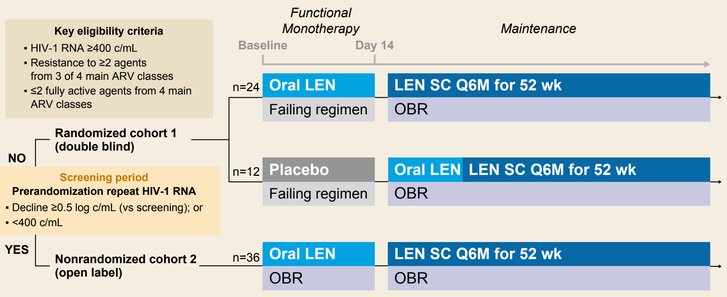
- LEN is a long-acting, first-in-class inhibitor of HIV-1 capsid protein
  - Can be administered subcutaneously (SC; 2 x 1.5 mL [927 mg] in abdomen every 6 months [Q6M])[3-5] or orally (daily or weekly)
- In heavily treatment-experienced and treatment-naïve people with HIV, SC LEN in combination with other antiretroviral (ARV) agents was well tolerated, and led to high rates of virologic suppression through 1 year[6,7]
- For any SC injectable agents, injection-site reactions (ISRs) are often expected

Objectives

- To characterize and describe in detail the observed ISR profile of LEN in HIV clinical studies, and correlate the clinical findings with preclinical findings

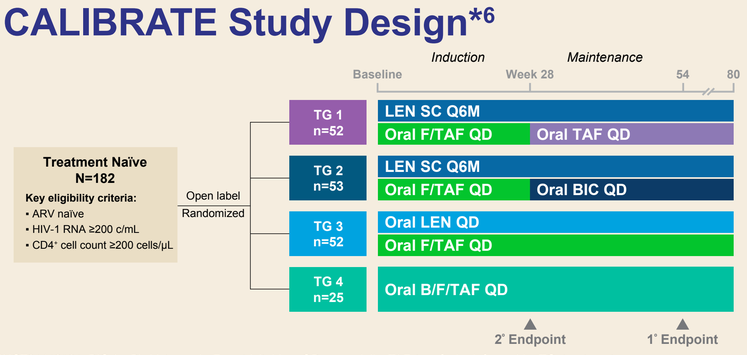
Methods

CAPELLA Study Design*[7]



*ClinicalTrials.gov NCT04150068. OBR, optimized background regimen.

CALIBRATE Study Design*[6]



*NCT04143594. BIC (or B), bictegravir; F, emtricitabine; QD, once daily; TAF, tenofovir alafenamide; TG, treatment group.

Results

Baseline Characteristics*

	CAPELLA N=72	CALIBRATE SC N=105
Age, median (range), years	52 (23–78)	30 (19–61)
Sex, % female at birth	25	6
Race, % Black	38	46
Ethnicity, % Hispanic/Latinx	21	44
Weight, median (range), kg	70.5 (41.4–126)	77.1 (47.6–163.8)
Body mass index, median (range), kg/m^2	25.0 (14.9–42.6)	25.2 (17.5–51.1)
HIV-1 RNA, median (range), $\log_{10}$ c/mL	4.5 (1.3–5.7)	4.3 (2.3–5.8)
>100,000 c/mL, %	19	13
CD4 count, median (range), cells/µL	150 (3–1296)	434 (187–1846)
<200 cells/µL, %	64	1

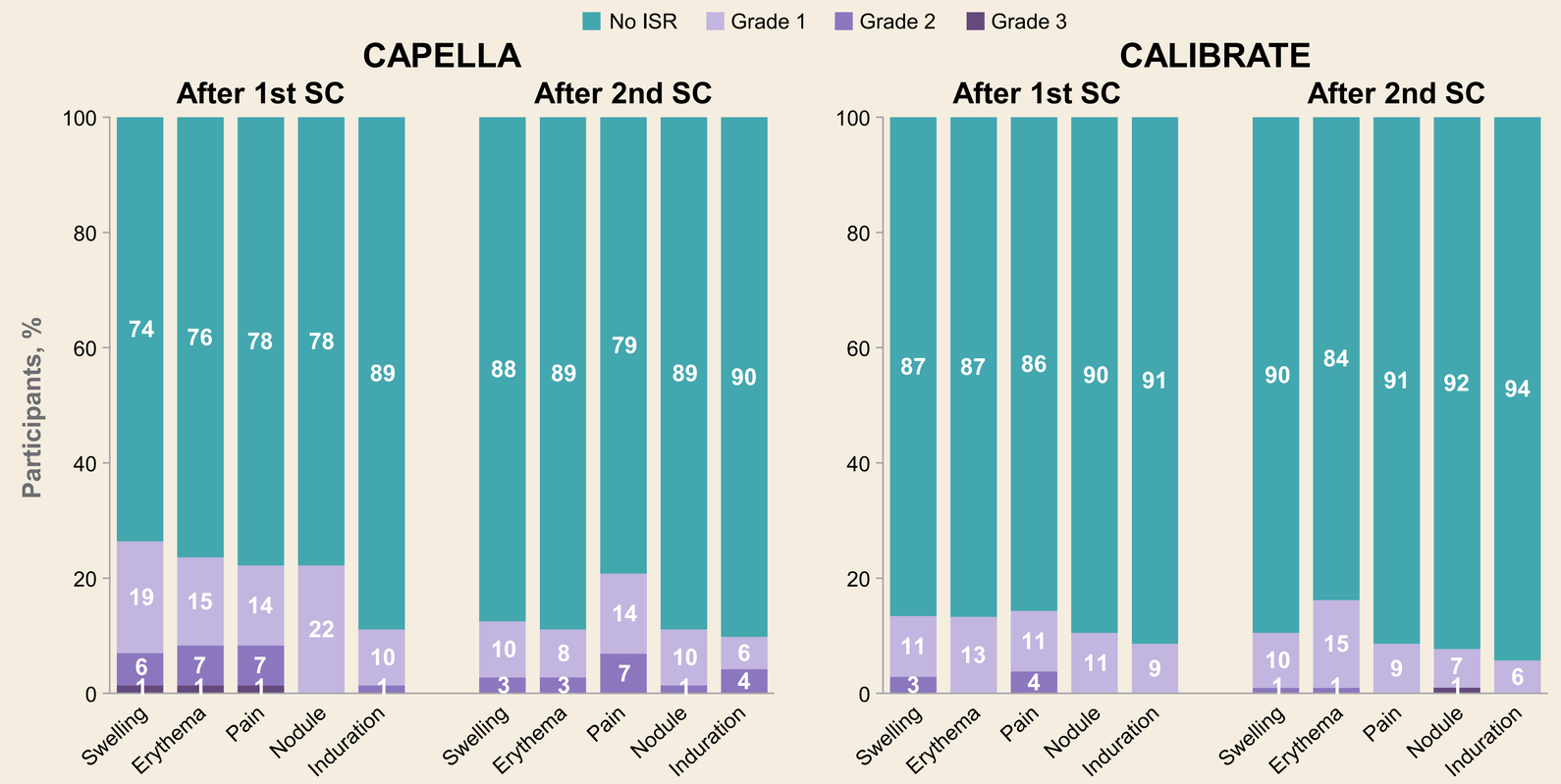
*Including Cohorts 1 and 2 in CAPELLA, and TG 1 and 2 in CALIBRATE.

Exposure to LEN SC*

	CAPELLA N=72	CALIBRATE SC N=105
Received LEN SC dose, n (%)†		
1st dose at baseline	72 (100)	103 (98)
2nd dose at 6 months postbaseline	70 (97)	95 (90)
Exposure, median, wk‡	54	64
Q1, Q3	44, 72	57, 81
Min, Max	13, 92	8, 93

*Including Cohorts 1 and 2 in CAPELLA, and TG 1 and 2 in CALIBRATE; †3rd and 4th LEN doses were not summarized as many participants were not yet due for them (eg, CAPELLA) or did not yet have sufficient follow-up after receiving them (eg, CALIBRATE); ‡Exposure during studies was calculated as last study day minus 1st dose date of oral LEN plus 1; for ongoing participants, last study day was imputed by data cut date. Max, maximum; Min, minimum; Q, quartile.

Incidence and Severity of ISRs Related to LEN SC*



*Only includes adverse events (AEs) related to LEN as determined by the investigator and excludes those not related to it; includes ISRs >10% in both studies.

- After the 1st and 2nd doses of LEN SC, most participants (70–90%) had no ISRs of swelling, erythema, pain, nodule, and induration
- Most ISRs were Grade 1 (42% [30/72] in CAPELLA and 48% [49/103] in CALIBRATE) or Grade 2 (18% [13/72] and 7% [7/103], respectively)
- No serious or Grade 4 ISRs were reported; 3 participants (2%) had Grade 3 ISRs: 1 participant with swelling and erythema, which resolved on Days 4 and 8, respectively; 1 participant with pain, which resolved on Day 1; and 1 participant with a nodule

Discontinuations Due to ISRs*

Study	ISR	Severity	Onset/Resolution	Discontinuation
CAPELLA (n/N = 1/72)	Nodule	Grade 1	Days 18 and 380†/ ongoing at discontinuation	Day 379 (Week 52)
CALIBRATE (n/N = 3/103)	Induration	Grade 1	Day 15/ongoing at discontinuation	Day 211 (Week 28)
	Induration	Grade 1	Day 15/ongoing at discontinuation	Day 156 (Week 22)
	Erythema and swelling	Grade 1	Day 196/Day 206	Day 399 (Week 57)

*Only includes AEs related to LEN and excludes those not related to it; †2 reported AEs of nodule.

- 4 of 175 participants (2%) discontinued due to ISRs
- Although all those ISRs were Grade 1 and the investigators felt that study drug discontinuation was not warranted, participants did not wish to continue LEN SC

Duration of ISRs After 1st LEN SC Dose*

Median (Q1, Q3), Days	CAPELLA N=72	CALIBRATE SC N=105
Swelling	10 (4, 21)	10 (5, 30)
Erythema	6 (3, 8)	5 (2, 11)
Pain	3 (1, 6)	4 (1, 9)
Nodule	235 (72, 422)	301 (140, 369)
Induration	99 (22, 224)	213 (143, 445)

*For ongoing ISRs, data cut day was used as last day; duration was reported by the investigator.

Injection-Site Nodules and Indurations: Further Description

- Injection-site nodules and indurations resolved over a longer period (weeks to months) than other ISRs (pain, redness, and swelling; days)
- They were often not visible to a participant or clinician and only palpable on deep palpation; they were generally small, measuring ~1–4 cm
- There were no findings to suggest any of the following:
  - Gross inflammation; if any, resolving within days
  - Tissue damage (eg, necrosis) or sterile abscess
  - Administration in a deeper tissue than the intended SC space (eg, muscle)
- No investigator felt strongly that further dermatologic consultation or skin biopsy was clinically indicated

Dermatologic Evaluations

Following a protocol requirement for ISRs of long duration, 2 participants underwent biopsies of the injection site

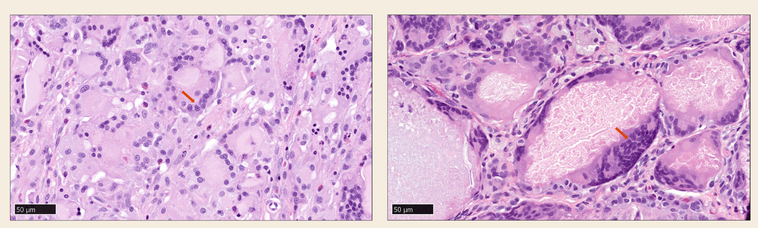
ISR	Status	Dermatologic Evaluation and Biopsy Findings
Participant 1 with induration (Grade 1)	Still on LEN SC	▪ Biopsy performed 54 wk postinjection ▪ Skin biopsy of 3 different injection sites in abdomen ▪ Multinucleated foreign body-type giant cell reactions present within deep dermis and SC space in all 3 sites ▪ No significant polarizable foreign body material (eg, glass) ▪ These findings are consistent with nonclinical findings in animals
Participant 2 with nodule (Grade 1)	Still on LEN SC	▪ Biopsy performed 34 wk postinjection ▪ Histochemical staining with Congo red supported diagnosis of amyloidosis ▪ Participant received T20 twice a day for >3 years; the investigator stated that it could not be ruled out whether biopsy was of LEN or T20 injection site ▪ "Pharmaceutical amyloidosis" associated with use of SC T20 has been described in the literature[8]

T20, enfuvirtide.

ISRs in Animal Studies

Single Dose of LEN 300 mg/mL SC in Female Rabbits

Day 28* **Day 91†**



*Skin site from rabbit sacrificed 28 days (n=3) after LEN 300 mg/mL SC (dose volume: 1.0 mL); SC tissue was expanded by marked granulomatous inflammation; granulomatous inflammation was characterized by infiltration of multinuclear macrophages; †Skin site from rabbit sacrificed 91 days (n=3) after LEN 300 mg/mL SC (dose volume: 1.0 mL); granulomatous inflammation similar to Day 28 was still evident, but with lesser severity (slight or moderate), indicating partial reversal; granulomatous inflammation was characterized predominantly by macrophages and multinuclear giant cells, which surrounded core of eosinophilic acellular material.

Conclusions

- Most participants who received LEN SC had no ISRs
- For participants who had ISRs:
  - Most were mild or moderate in severity (Grade 1 or 2)
  - There were no serious or Grade 4 ISRs
  - From the 1st to 2nd doses of LEN SC, the incidence generally declined
  - Swelling, pain, and erythema resolved within a few days
  - Nodules and indurations took longer to resolve (weeks to months)
  - Discontinuations due to ISRs were infrequent
  - ISRs were described by investigators generally as benign in nature
- Clinical findings of ISRs were consistent with preclinical findings, which were foreign body reactions manifesting as chronic granulomatous inflammation

References: **1.** Link JO, et al. Nature 2020;584:614-8; **2.** Zila V, et al. Cell 2021;184:1032-46; **3.** Begley R, et al. AIDS 2020, abstr PEB0265; **4.** Begley R, et al. CROI 2020, abstr 470; **5.** Daar EM, et al. CROI 2020, poster 3691; **6.** Gupta SK, et al. CROI 2022, abstr 1292; **7.** Ogbuagu O, et al. CROI 2022, poster 491; **8.** Morilla ME, et al. Ann Intern Med. 2009;151:515–6.

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