Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Phase 2/3 in Heavily Treatment-Experienced People with HIV: Week 26 results (CAPELLA study)

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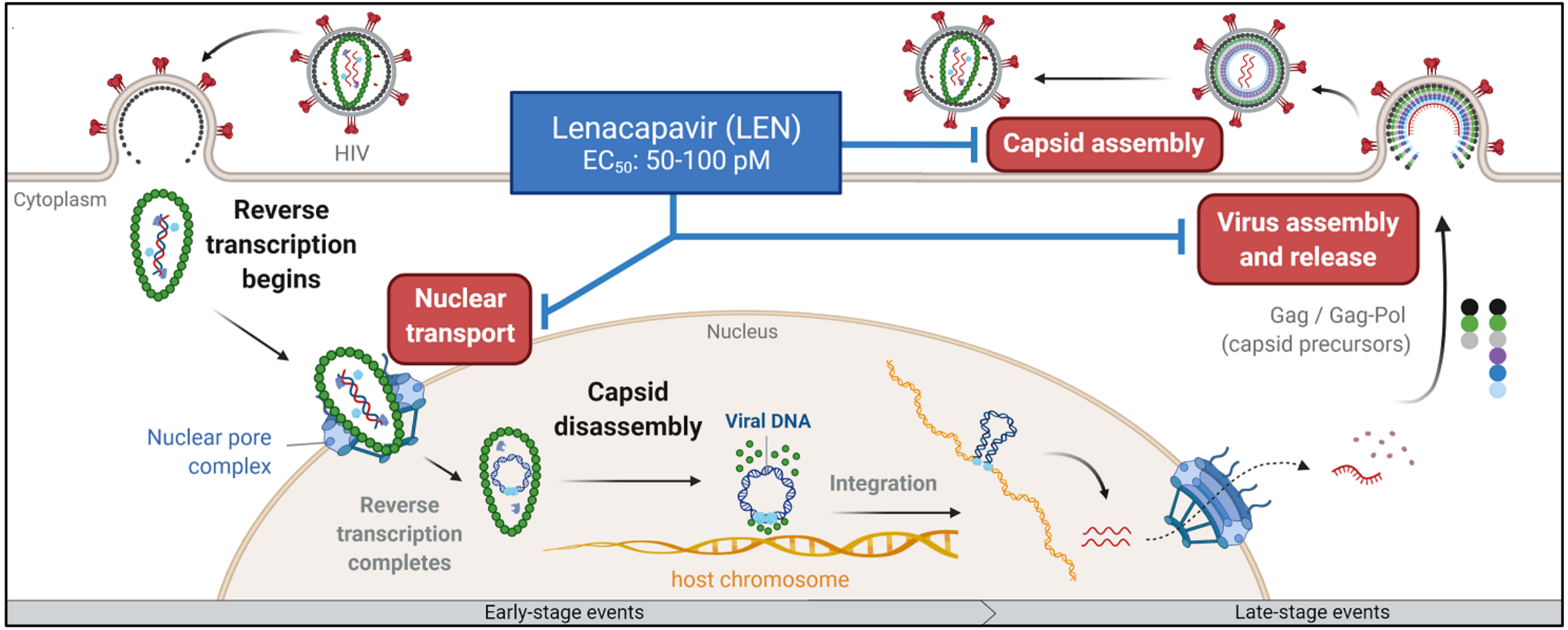
LEN Targets Multiple Stages of HIV Replication Cycle



Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

Introduction

- LEN can meet significant unmet medical needs:
  - A new mechanism of action for HTE people with MDR HIV
  - Reduction of daily pill burden through less frequent dosing for treatment and prevention
- Highly desirable in vitro profile for HTE PWH
  - Retains full activity against NRTI-, NNRTI-, INSTI-, and PI-resistance[1-3]
  - No observed pre-existing resistance[2]
- Previously in CAPELLA, LEN achieved its primary endpoint at 14 days in HTE PWH when added to a failing regimen as a functional monotherapy[4]:
  - Participants achieving ≥0.5 log decline in HIV-1 RNA: LEN 88% vs placebo 17% ($p < 0.0001$)
  - Decline in HIV-1 RNA: LEN 1.9 vs 0.3 $\log_{10}$ copies/mL ($p < 0.0001$)

HTE, heavily treatment-experienced; INSTI, integrase strand transfer inhibitor; MDR, multidrug-resistant; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; PWH, people with HIV.

1. Yant SR, et al. CROI 2019, poster 480; 2. Margot N, et al. CROI 2020, poster 529; 3. VanderVeen L, et al. CROI 2021, oral 01781
4. Segal-Maurer S, et al. CROI 2021, oral 2228.

Study Design

Key eligibility criteria:

- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents from 4 main ARV classes

NO

Randomized cohort (Double blind)

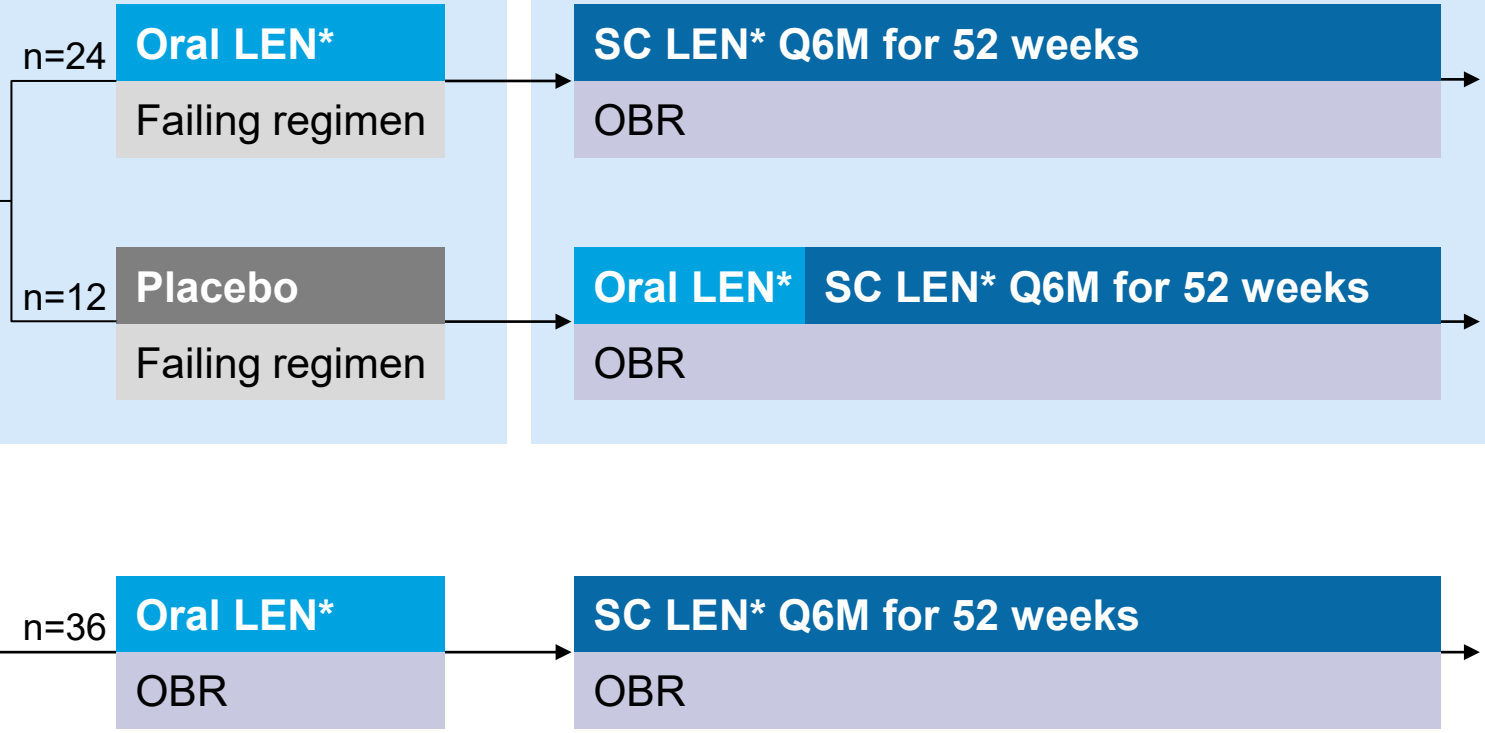
Screening Period

Pre-randomization repeat HIV-1 RNA

- Decline of ≥0.5 $\log_{10}$ copies/mL (vs screening) or
- <400 copies/mL

YES

Nonrandomized cohort (Open label)



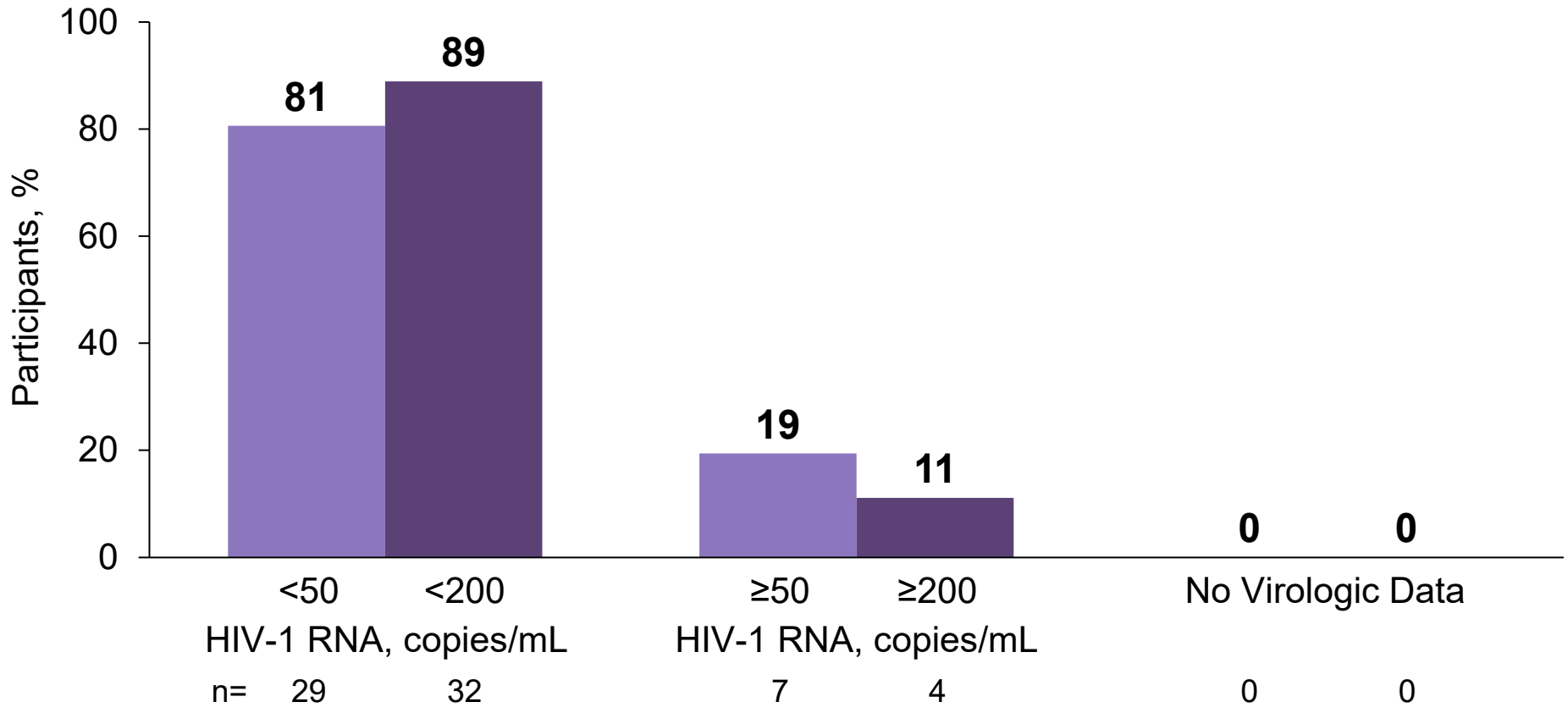
- Efficacy summarized only for randomized cohort (n=36), as most in nonrandomized cohort have not reached Wk 26 yet
- Safety summarized for both the randomized and nonrandomized cohort (n=72)

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15. OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, nevirapine, tipranavir were not allowed).

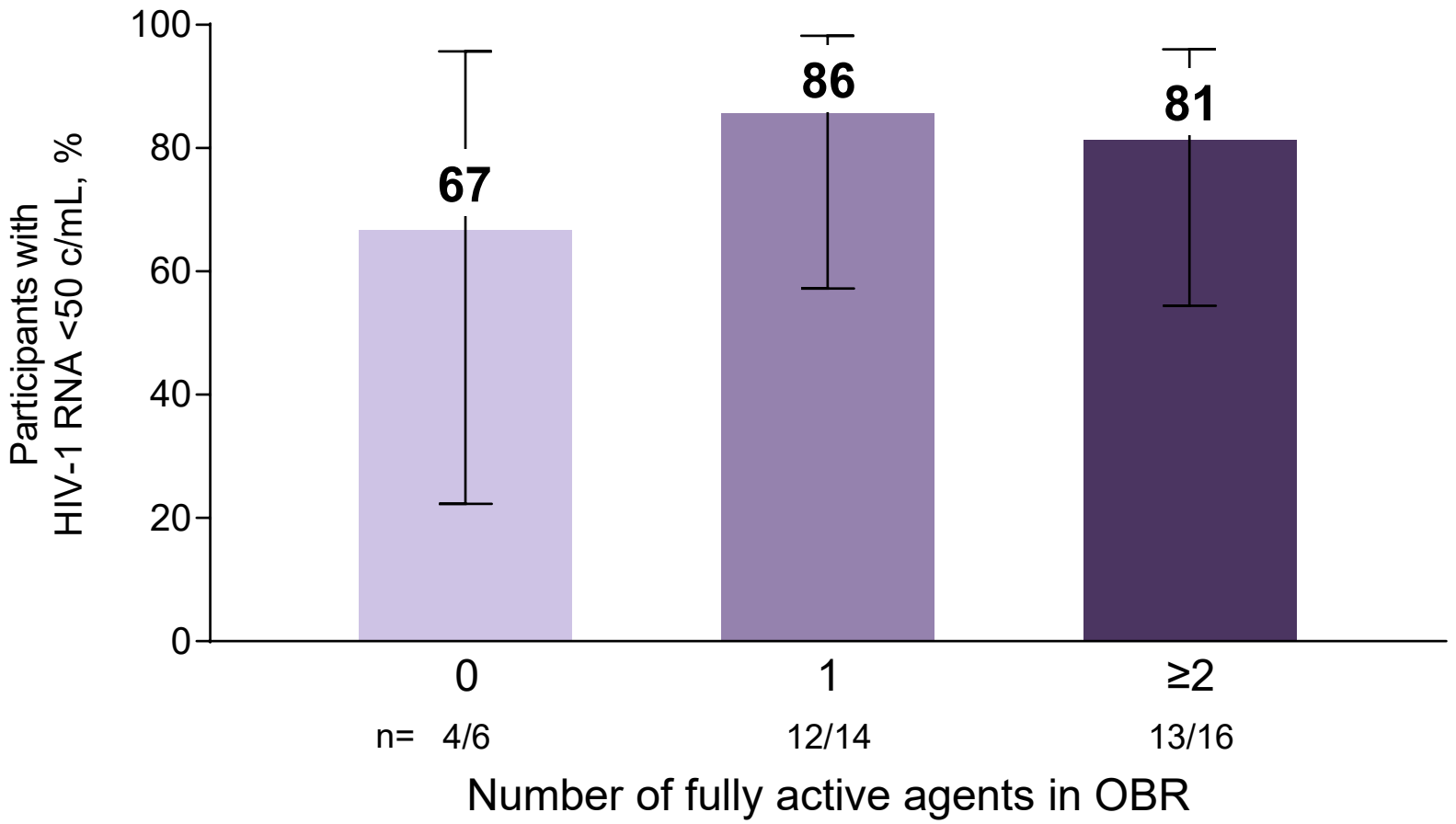
Baseline Characteristics

	Randomized		Nonrandomized	
	LEN n=24	Placebo n=12	LEN n=36	Total N=72
Age, median (range), years	55 (24 – 71)	54 (27 – 59)	49 (23 – 78)	52 (23 – 78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), log_{10} copies/mL	4.2 (2.3 – 5.4)	4.9 (4.3 – 5.3)	4.5 (1.3 – 5.7)	4.5 (1.3 – 5.7)
>75,000 copies/mL, %	17	50	28	28
CD4 count, median (range), cells/μL	172 (16 – 827)	85 (6 – 237)	195 (3 – 1296)	150 (3 – 1296)
≤200 cells/μL, %	67	92	53	64
Years since HIV diagnosis, median (range)	27 (13 – 39)	26 (14 – 35)	23 (9 – 44)	24 (9 – 44)
Number of prior ARV agents, median (range)	9 (2 – 24)	9 (3 – 22)	13 (3 – 25)	11 (2 – 25)
Number of ARV agents in failing regimen, median (range)	3 (1 – 7)	3 (2 – 6)	4 (2 – 7)	3 (1 – 7)
Known resistance to ≥2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

Efficacy at Week 26 in the Randomized Cohort (n=36): FDA-Snapshot Algorithm



Efficacy by Number of Fully Active Agents in OBR



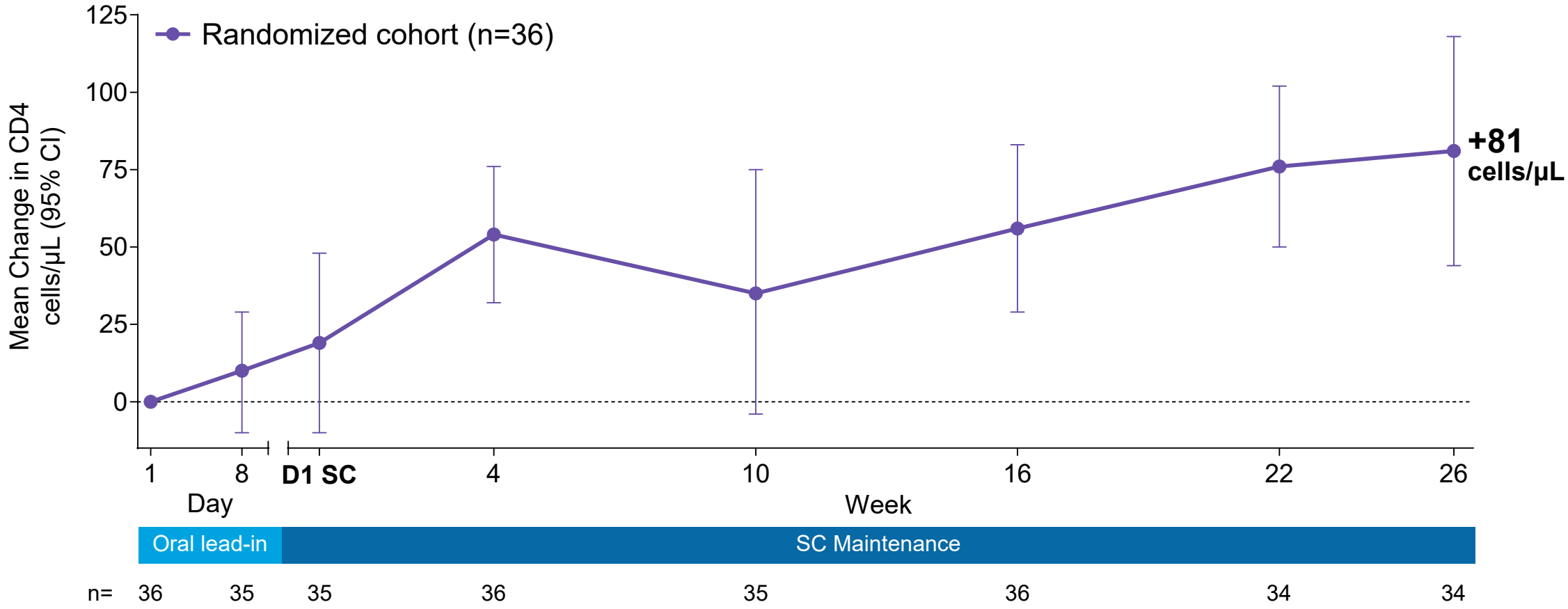
Emergent LEN Resistance*

n (%)	Randomized Cohort n=36
Participants meeting criteria for resistance testing	11 (31)
No emergent LEN resistance	7 (19)
Emergent LEN resistance	4 (11)
M66I	4
Q67H	1
K70N/R/S	1
N74D	1

- All 4 participants with emergent LEN resistance remained on LEN
  - 3 participants re-suppressed at a later visit: 2 without and 1 with OBR change
  - 1 participant with no fully active agent never suppressed (max 1.7 $\log_{10}$ copies/mL decline in HIV-1 RNA)
- No participant developed additional resistance to the agents in the OBR

*Capsid genotypic and phenotypic resistance testing performed any participants with confirmed HIV-1 RNA ≥50 copies/mL and <1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at the Week 4 visit, at any visit after achieving HIV-1 RNA <50 copies/mL and a rebound to ≥50 copies/mL, and at any visit, with >1 $\log_{10}$ increase in from the nadir. HIV-1, protease, reverse-transcriptase and integrase genotypic and phenotypic testing were performed if the rebound or suboptimal virologic response were confirmed.

Changes in CD4



- LEN led to clinically meaningful improvement in CD4 cell count
- Participants with very low CD4 (<50 cells/µL) decreased from 22% (8/36) at baseline to 0 (0/34) at Week 26

D1 SC, the first day SC LEN was administered.

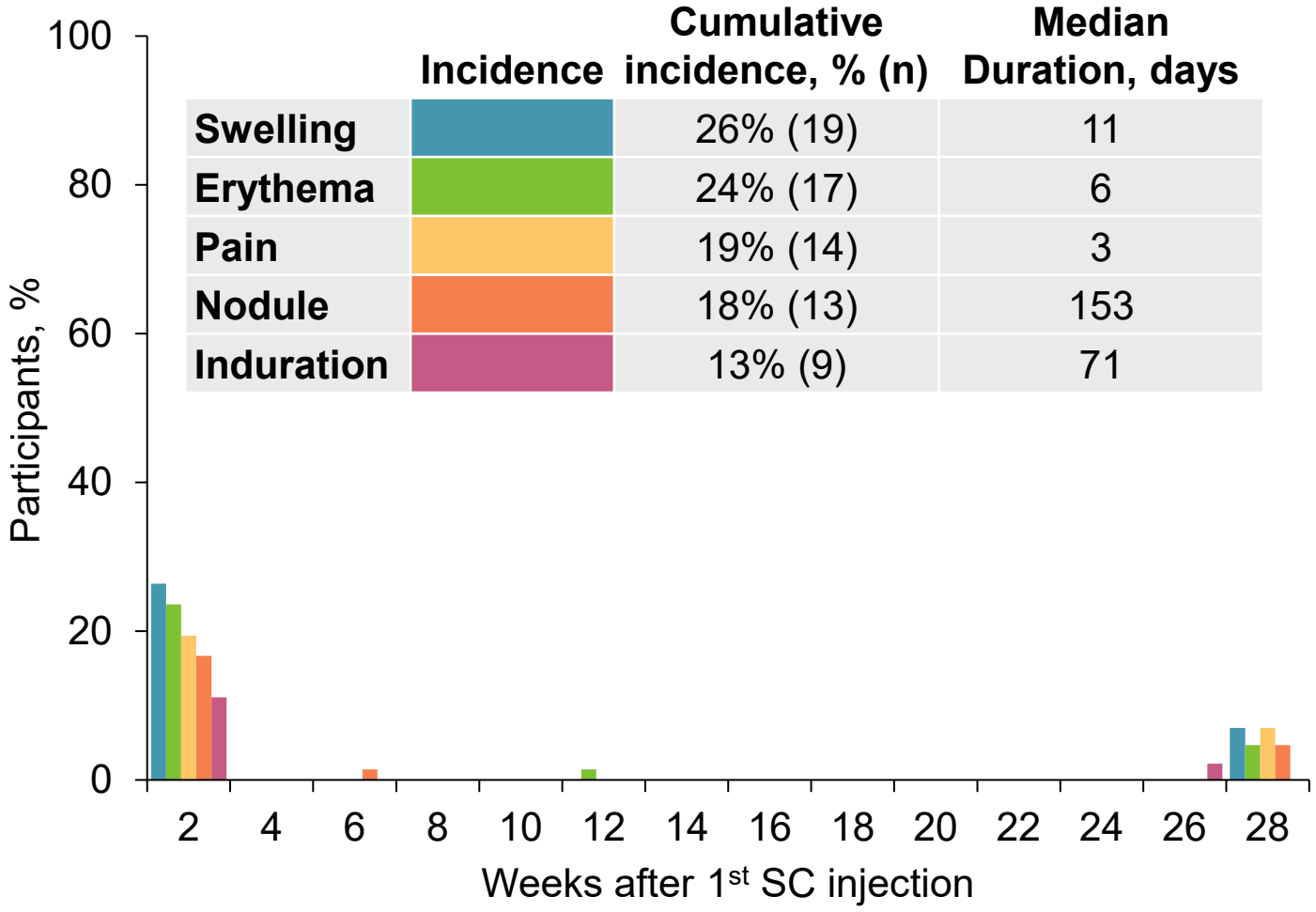
Adverse Events (excluding ISRs)

≥5% total in any Grade, (n)	Total LEN (N=72)
Diarrhea	8% (6)
Nausea	8% (6)
Cough	7% (5)
Headache	7% (5)
Pyrexia	7% (5)
Urinary tract infection	7% (5)
Abdominal distension	6% (4)
Arthralgia	6% (4)
Back pain	6% (4)
Constipation	6% (4)
Oral candidiasis	6% (4)
Rash	6% (4)

- No AEs leading to study drug discontinuation
- No SAEs related to study drug*
- One participant had an SAE of malignant neoplasm, not related to study drug with fatal outcome

*Serious adverse events (SAEs) not related to study drug: #1: malignant neoplasm, dizziness; #2: abdominal pain, pancreatic mass, *Clostridium difficile* infection; #3 proctalgia; #4: femoral neck fracture. ISR, injection site reaction.

Injection Site Reactions Related to SC LEN: Inciden



	Incidence	Cumulative incidence, % (n)	Median Duration, days
Swelling		26% (19)	11
Erythema		24% (17)	6
Pain		19% (14)	3
Nodule		18% (13)	153
Induration		13% (9)	71

Participants who received SC injection	72	39

- No ISRs reported in 44% (32/72)
- 56% (40/72) had ≥1 ISR related to LEN
  - Most ISRs were Grade 1 (70% [28/40]) and resolved within days
  - No Grade 4 ISRs occurred; two participants had Grade 3: one with swelling and erythema, which resolved in 4 and 8 days, respectively, and one with pain, which resolved in 1 day
- All nodules were Grade 1
- No participant discontinued due to ISRs
  - All 36 randomized and 3 of 36 nonrandomized participants received 2nd SC injection

*Only includes AEs related to LEN and excludes those not related to it (eg, T20).

Grade 3 or 4 Laboratory Abnormalities

≥5% in total, (n)	Total (N=72)
Any Grade 3 or 4 lab abnormality	26% (19)
Low creatinine clearance (eGFR)/high creatinine*	11% (8)
Glycosuria	6% (4)
Nonfasting/fasting hyperglycemia	6% (4)

- None of the Grade 3 or 4 lab abnormalities were clinically relevant
- Low creatinine clearance/eGFR and/or high creatinine were transient or unconfirmed abnormalities
- Hyperglycemia/glycosuria were transient, unconfirmed, or related to underlying diabetes

*Per DAIDS scale, Grade 3 creatinine clearance is <60–30 mL/min or 30–<50% decrease from baseline; Grade 3 creatinine is >1.8–<3.5 x upper limit of normal or increase to 1.5–<2.0 x baseline. eGFR, estimated glomerular filtration rate.

Conclusions

- In HTE PWH with MDR
  - LEN in combination with an OBR led to high rates of virologic suppression at Week 26 (81%)
  - LEN led to clinically meaningful increases in CD4 counts at Week 26
    - While 22% had CD4 <50 cells/μL at baseline, none did by Week 26
  - LEN was well tolerated with no AEs leading to discontinuation
  - All 36 randomized and 3 of 36 nonrandomized participants received 2nd SC injection
- LEN has the potential to become an important agent for HTE PWH with MDR
- These data support the ongoing evaluation of LEN for treatment and prevention of HIV