Efficacy and Safety of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People With Multi-Drug Resistant HIV: Week 52 Results

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Disclosures

- O Ogbuagu: Gilead Sciences (advisor/consultant, honoraria), ViiV (advisor/consultant), Janssen (advisor/consultant)
- S Segal-Maurer: Gilead Sciences (advisor/consultant, grant/research support, honoraria), Janssen Therapeutics (honoraria), ViiV (honoraria)
- B Trottier: Gilead Sciences (advisor/consultant, honoraria), Merck (advisor/consultant, honoraria), ViiV Healthcare (advisor/consultant, honoraria)
- J Brunetta: Gilead Canada (advisor/consultant, honoraria, conference attendance sponsorship), ViiV Canada (advisor/consultant)
- H Wang, N Margot, H Dvory-Sobol, MS Rhee, JM Baeten: Gilead (employment, stocks/bonds)
- J-M Molina: Gilead (board member, grant/research support), Merck (board member, expert testimony), ViiV (board member)
- W Ratanasuwan, T Shirasaka, EL Koenig: Nothing to disclose

Introduction: Lenacapavir (LEN)

- LEN is a novel, highly potent, long-acting, first-in-class, HIV-1 capsid inhibitor
- LEN can satisfy or fulfill significant unmet medical needs:
  - A new drug class and mechanism of action for PWH, including those who are heavily treatment experienced (HTE) with multidrug resistance (MDR) and limited treatment options
  - Reduction of pill burden through less frequent dosing
- Highly desirable in vitro profile with picomolar antiviral activity (EC_{50}: 50-100 pM)
  - Retains full activity against NRTI-, NNRTI-, INSTI-, PI-, and entry inhibitor-resistant mutants[1-4]
  - No observed baseline resistance[5]

Calibrate	Phase 2 in TN PWH NCT04143594	Week 54[6]	LEN SC + (F/TAF → TAF)	90% virologic suppression
			LEN SC + (F/TAF → BIC)	85% virologic suppression
			Oral LEN + F/TAF	85% virologic suppression
Capella	Phase 2/3 in HTE PWH NCT04150068	Week 52[7]	LEN + OBR (randomized cohort)	83% virologic suppression

Objective: to assess efficacy and safety at Week 52 in both the randomized and nonrandomized cohorts

BIC = bictegravir; EC_{50} = half-maximal effective concentration; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor; PWH = people with HIV-1; TAF = tenofovir alafenamide; TN = treatment-naive.

1. Margot N, et al. *Antimicrob Agents Chemother.* 2021;65:e02057-20; 2. VanderVeen L, et al. CROI 2021, oral 128; 3. Yant SR, et al. CROI 2019, poster 480; 4. Margot N, et al. CROI 2022, poster 508; 5. Marcelin AG, et al. *J Antimicrob Chemother.* 2020;75:1588-90; 6. Gupta SK, et al. CROI 2022, abstr 138; 7. Ogbuagu O, et al. CROI 2022, abstr 1047.

Methods: Study Design

Key eligibility criteria

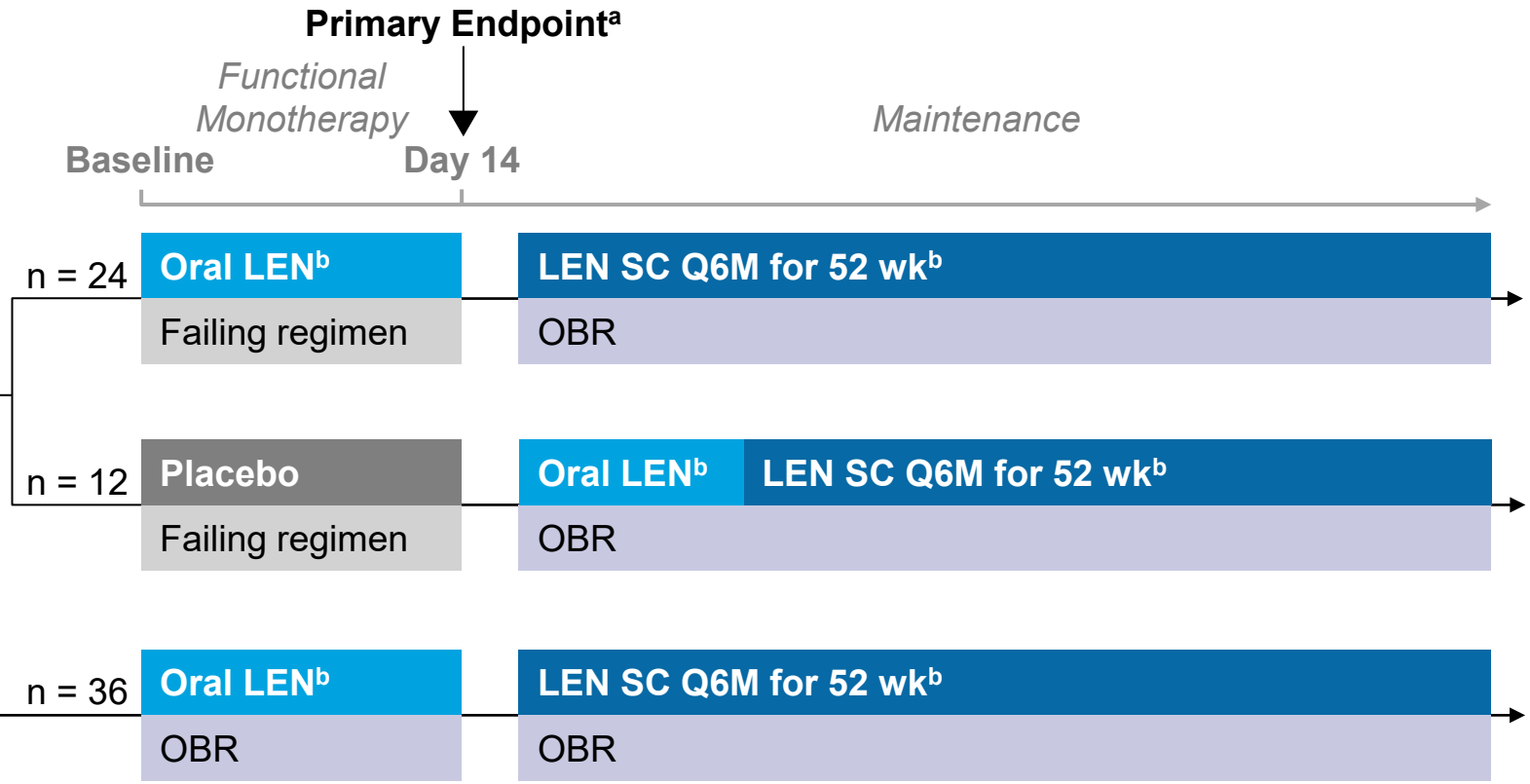
- HIV-1 RNA ≥ 400 c/mL
- Resistance to ≥ 2 agents from 3 of 4 main ARV classes
- ≤ 2 fully active agents from 4 main ARV classes

Screening period
Prerandomization repeat HIV-1 RNA

- Decline ≥ 0.5 log c/mL (vs screening); or
- < 400 c/mL

NO → **Randomized cohort (double blind)**

YES → **Nonrandomized cohort (open label)**



- In the nonrandomized cohort, 3 participants were enrolled due to not meeting the randomization criteria, while 33 were enrolled after enrollment to the randomized cohort was completed (of those, 28 still met the randomization criteria while 5 did not)
- Week 52 efficacy was previously summarized only for the randomized cohort (n = 36), as most participants in the nonrandomized cohort had not yet reached Week 52[1]

[a]Proportion of participants in the randomized cohort with HIV-1 RNA decrease ≥ 0.5 $\log_{10}$ copies/mL (Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793-1803)
[b]Administered as 600 mg on Days 1 and 2, and 300 mg on Day 8; subcutaneous lenacapavir (LEN SC) administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15
ARV = antiretroviral; c/mL = copies/mL; OBR = optimized background regimen; Q6M = every 6 months; wk = week.

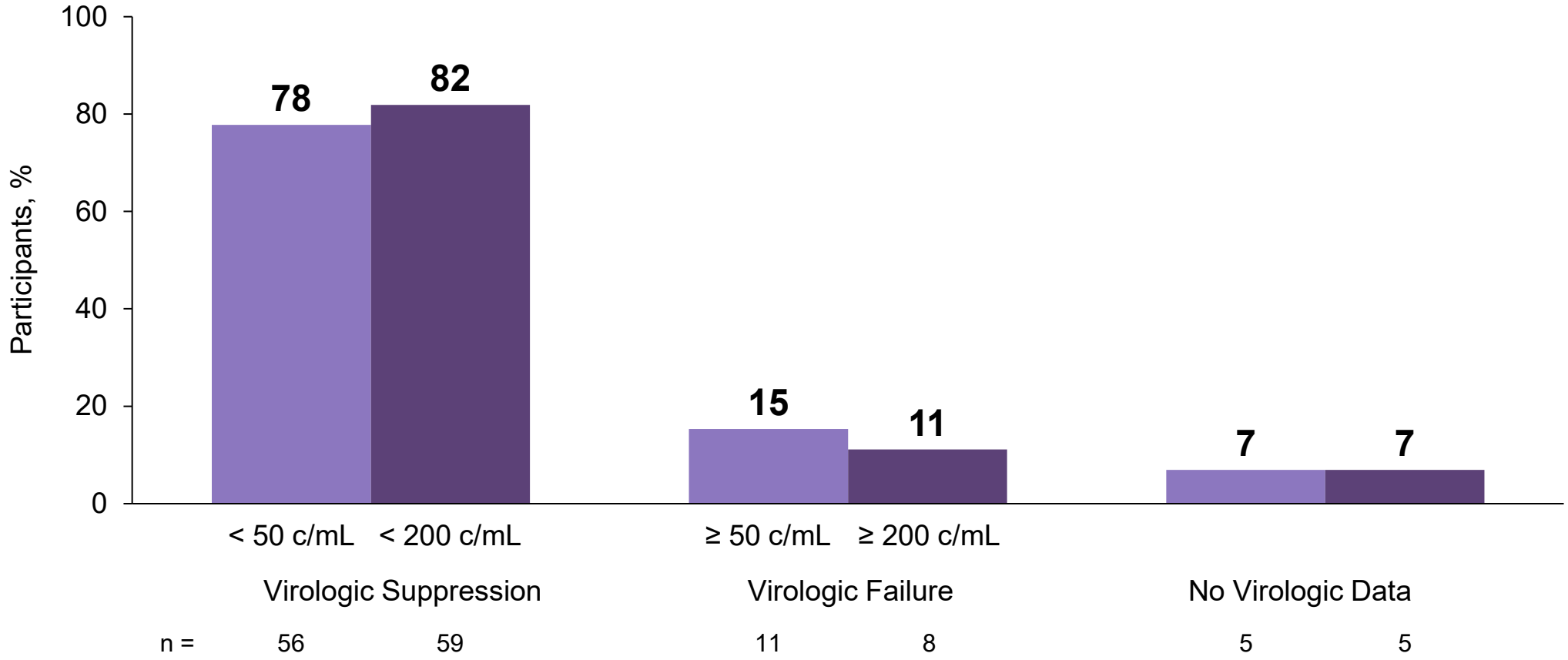
1. Ogbuagu O, et al. CROI 2022, abstr 1047.

Results: Baseline Characteristics

	Randomized n = 36	Nonrandomized n = 36	Total N = 72
Age, median (range), years	54 (24-71)	49 (23-78)	52 (23-78)
Sex, % female at birth	28	22	25
Race, % Black	46[a]	31	38
Ethnicity, % Hispanic/Latinx	29[a]	14	21
HIV-1 RNA, median (range), log_{10} c/mL	4.5 (2.3-5.4)	4.5 (1.3-5.7)	4.5 (1.3-5.7)
> 100,000 c/mL, %	19	19	19
CD4 count, median (range), cells/μL	127 (6-827)	195 (3-1296)	150 (3-1296)
< 200 cells/μL, %	75	53	64
Number of prior ARV agents, median (range)	9 (2-24)	13 (3-25)	11 (2-25)
Number of fully active agents in OBR, %			
0	17	17	17
1	39	36	36
≥ 2	44	47	47
Known resistance to ≥ 2 drugs in class, %			
NRTI	97	100	99
NNRTI	94	100	97
INSTI	75	64	69
PI	78	83	81

[a]Local regulators did not allow collection of race or ethnicity information for 1 participant. ARV = antiretroviral; c/mL = copies/mL; INSTI = integrase strand-transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor.

Efficacy at Week 52: Both Cohorts (N = 72)

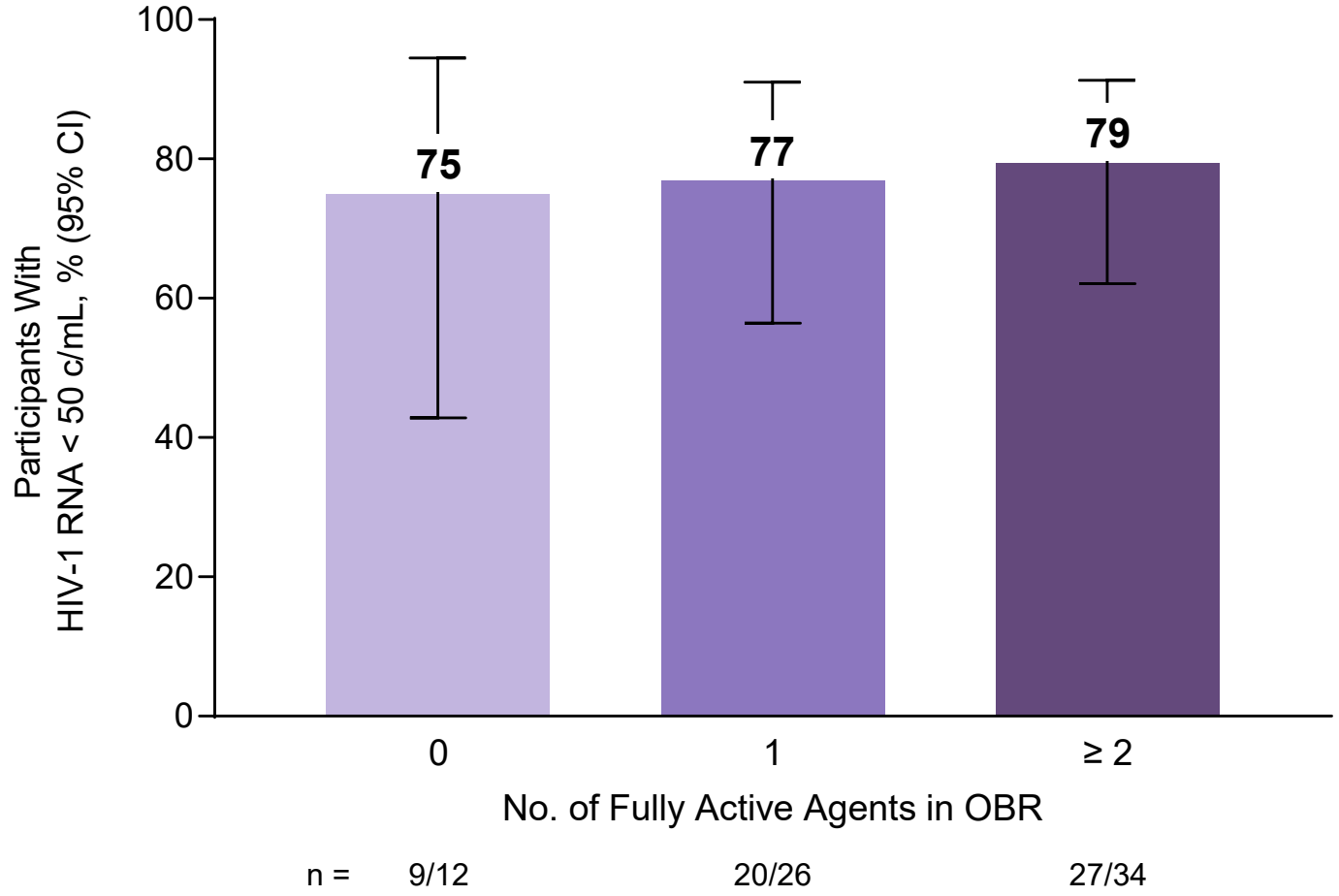


- Due to the clinical hold by FDA with SC LEN during the study, by Week 52, 17 participants took ≥ 1 dose of oral LEN bridging (300 mg QW)

SC LEN = subcutaneous lenacapavir; QW = once weekly.

Efficacy at Week 52

Number of Fully Active Agents in OBR (N = 72)



CI = confidence interval; OBR = optimized background regimen.

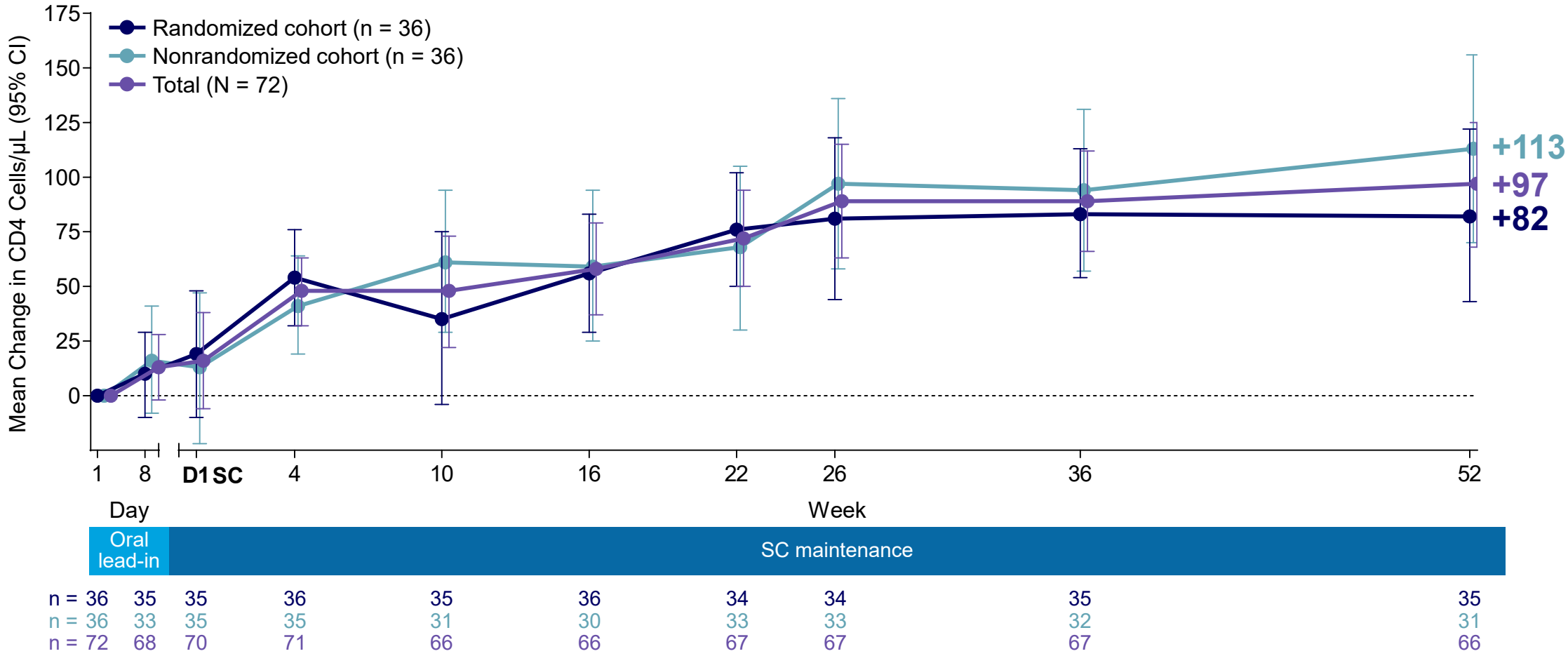
Emergent LEN Resistance by Week 52

n (%)	Randomized Cohort n = 36	Nonrandomized Cohort n = 36	Total N = 72
Participants meeting criteria for resistance testing	11 (31)	11 (31)	22 (31)
With data	11 (31)	10 (28)	21 (29)
Emergent LEN resistance	4 (11)	5 (14)	9 (13)
M66I	4	2	6
Q67H/K/N	1	3	4
K70H/N/R/S	1	3	4
N74D	3	0	3
A105S/T	3	1	4
T107A/C/N[a]	1	3	4

- Since Week 26, one additional participant had emergent LEN resistance: Q67H at Week 52
- All 9 participants with emergent LEN resistance remained on LEN
  - All 9 participants were at high risk of emergent LEN resistance: no fully active drugs in OBR (n = 4) or inadequate adherence to OBR (n = 5)[b]
  - 4 participants resuppressed at a later visit: 2 without and 2 with OBR change
- The most common pattern was M66I ± other mutations (n = 6, median LEN fold change = 234)

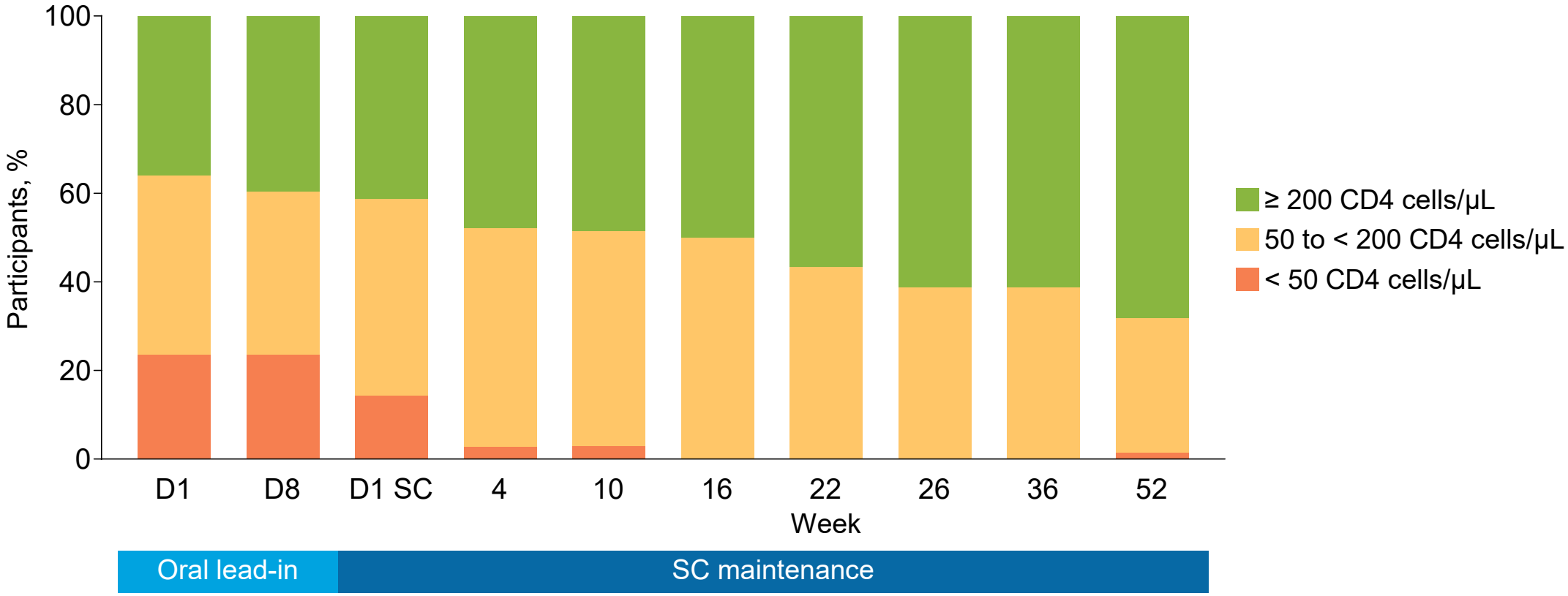
Capsid genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥ 50 copies/mL (c/mL) and < 1 $\log_{10}$ HIV-1 RNA reduction from Day 1 at Week 4 visit, at any visit after achieving HIV-1 RNA < 50 c/mL and rebound to ≥ 50 c/mL, and at any visit with > 1 $\log_{10}$ increase from nadir; HIV-1, protease, reverse transcriptase, and integrase genotypic and phenotypic testing were performed if rebound or suboptimal virologic response were confirmed. [a]1 participant had emergent T107A mutation in capsid protein with no loss in lenacapavir (LEN) susceptibility before achieving HIV-1 RNA suppression; participant was not categorized as having emergent capsid resistance; [b]OBR (optimized background regimen) adherence was assessed by plasma drug levels.

CD4 Increases Observed in Both Cohorts (N = 72)



CI = confidence interval; D1 SC = 1st day subcutaneous lenacapavir was administered.

CD4 Changes by Category Observed in Both Cohorts (N = 72)



- LEN led to clinically meaningful improvement in CD4 cell count
- Proportion of participants with **very low CD4 (< 50 cells/μL) decreased from 24% (17/72) at baseline to 2% (1/66) at Week 52**
- Proportion of participants with **≥ 200 CD4 cells/μL increased from 36% (26/72) at baseline to 68% (45/66) at Week 52**

LEN = lenacapavir; SC = subcutaneous.

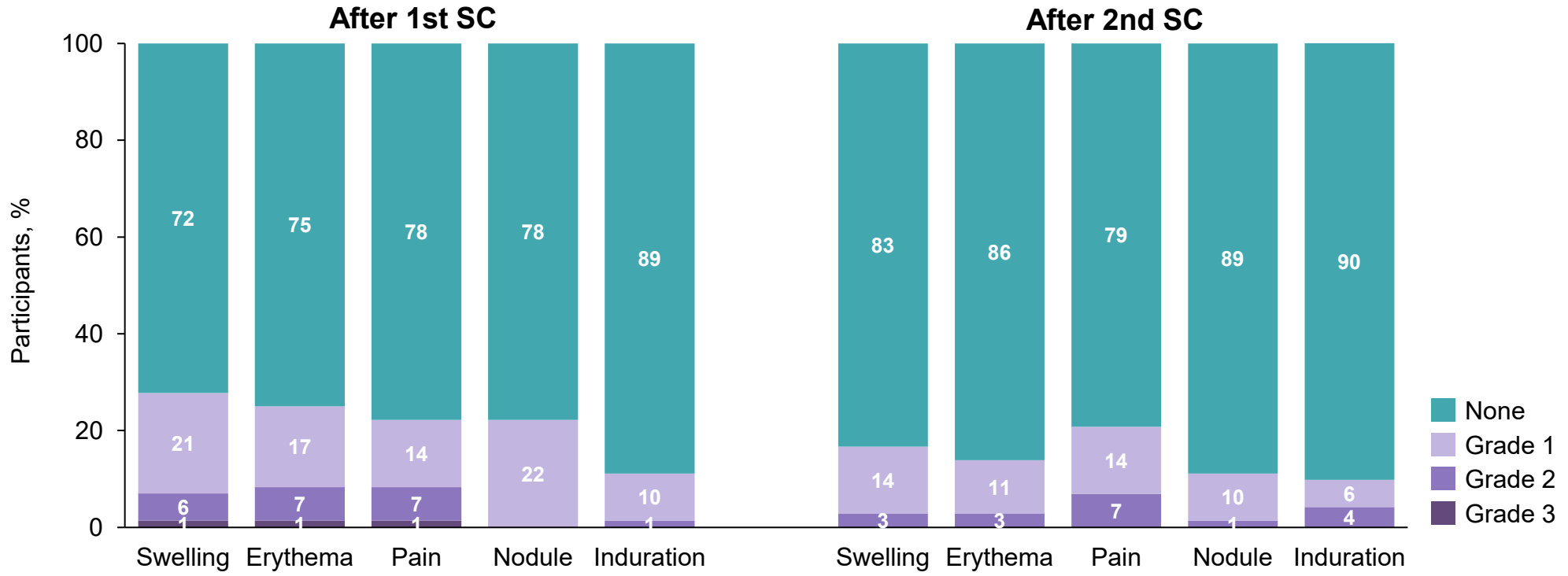
Adverse Events (excluding ISRs)

Any grade AEs ≥ 10%	LEN + OBR, % (n) Total: N = 72
Diarrhea	14% (10)
Nausea	14% (10)
Constipation	13% (9)
Cough	11% (8)
Pyrexia	11% (8)

- Duration of follow up: median 498 days (interquartile range: 421, 612)
- No serious AEs were related to study drug
- No study drug-related AEs occurred in more than 5%
- 2 deaths: 1 serious AE of malignant neoplasm; 1 AE of acute respiratory failure; neither related to study drug

Serious adverse events (AEs) not related to study drug: malignant neoplasm and dizziness (n = 1); abdominal pain, pancreatic mass, Clostridium difficile colitis, and angina pectoris (n = 1); anal squamous cell carcinoma, proctalgia, impaired healing, and anal cancer (n = 1); femoral neck fracture (n = 1); COVID-19 (n = 2); pneumonia (n = 1); septic shock, renal impairment, and shock (n = 1); pneumonia mycoplasmal, pancytopenia, dehydration, and acute respiratory failure (n = 1); genital herpes simplex (n = 1); AE of COVID-19 in 13% (n = 9) is not included in the table. ISRs = injection site reactions; LEN = lenacapavir.

Incidence of ISRs Related to SC LEN



- Most ISRs were Grade 1 or 2
- No Grade 4 ISRs, but 3 participants had Grade 3: 1 participant with swelling and erythema, which resolved in 4 and 8 days, respectively, and 1 participant with pain, which resolved in 1 days
- All nodules were Grade 1, except in 1 participant who had 2 AEs of Grade 2 nodules, each after the 2nd and 3rd injections (both resolved after 3 days)
- From the 1st to 2nd doses of LEN SC, the incidence of ISRs generally declined
- 1 participant discontinued study drug at Week 52 due to an ISR (nodule; Grade 1)

Only includes adverse events (AEs) related to lenacapavir (LEN) and excludes those not related to it. ISR = injection site reaction; SC = subcutaneous.

Conclusions

- In HTE PWH with limited treatment options due to MDR:
  - LEN in combination with an OBR led to high and sustained rates of virologic suppression at Week 52 (78%)
  - LEN led to clinically meaningful increases in CD4 counts at Week 52
  - LEN was well tolerated, with only 1 ISR leading to discontinuation
- These data support the ongoing evaluation of LEN for treatment of HIV-1 infection
  - In HTE people with MDR HIV
  - In treatment-naïve and -experienced PWH in combination with other agents

HTE = heavily treatment experienced; ISR = injection site reaction; LEN = lenacapavir; MDR = multidrug resistance; OBR = optimized background regimen; PWH = people with HIV.

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