Subgroup Efficacy Analyses of Long-Acting Subcutaneous Lenacapavir in Heavily Treatment-Experienced People With HIV in the Phase 2/3 CAPELLA Study

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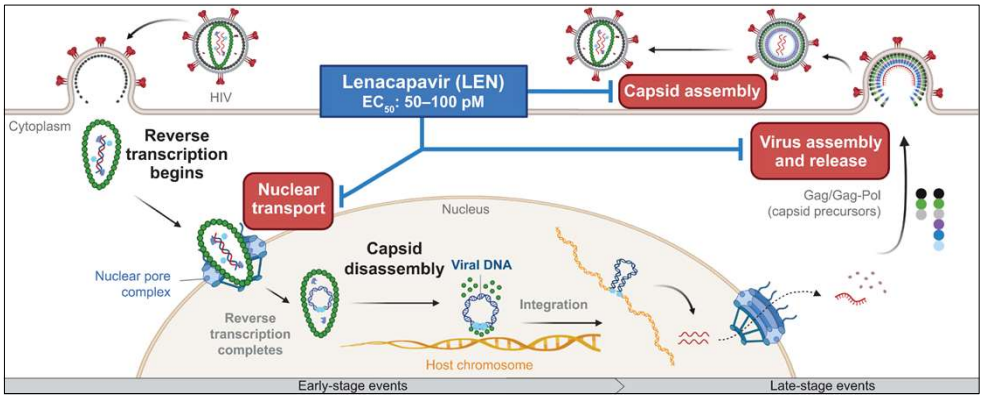
Introduction

- LEN is a novel, highly potent, long-acting, first-in-class, HIV-1 capsid inhibitor
- LEN can meet significant unmet medical needs:
  - A new mechanism of action for multidrug-resistant HIV-1
  - Reduction of daily pill burden through less frequent dosing for treatment and prevention
- Highly desirable in vitro profile with picomolar antiviral activity (EC_{50}: 50–100 pM)
  - Retains full activity against nucleoside reverse-transcriptase inhibitor (NRTI)–, non-NRTI–, integrase strand transfer inhibitor (INSTI)–, and protease inhibitor (PI)–resistant mutants[3-5]
  - No observed preexisting resistance[3,6]
- Subcutaneous (SC) LEN can be administered q6mo[7]
- LEN demonstrated potent antiviral activity in people with HIV (PWH), with up to 2.3 log decline[8]
- In treatment-naïve PWH, LEN + emtricitabine/tenofovir alafenamide led to 94% virologic suppression at Week 28[9]
- In heavily treatment-experienced (HTE) people with multidrug resistant HIV-1:
  - LEN achieved its primary endpoint as a functional monotherapy when added to a failing regimen[10]:
    - Participants with ≥0.5-log decline: LEN 88% vs placebo 17% (p<0.001)
    - HIV-1 RNA decline, mean: LEN 1.9 vs 0.3 log (p<0.001)
  - LEN + optimized background regimen (OBR) led to 81% virologic suppression at Week 26[11]

Lenacapavir (LEN, GS-6207) Targets Multiple Stages of HIV Replication Cycle[1,2]

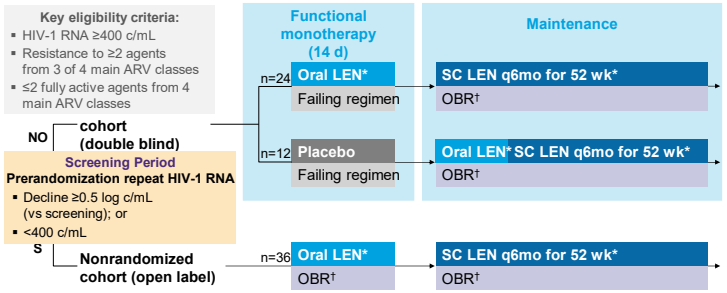


Objective

To evaluate Week 26 efficacy (assessed using U.S. Food & Drug Administration [FDA] Snapshot algorithm) by subgroup analyses in a randomized cohort by demographics and baseline HIV-1 RNA, cluster of differentiation-4 (CD4), INSTI resistance, and OBR

1. Bester SM, et al. Science 2020;370:360-4; **2.** Link JO, et al. Nature 2020;584:614-8; **3.** Margot N, et al. CROI 2020, poster 529; **4.** VanderVeen L, et al. CROI 2021, oral 01781; **5.** Yant SR, et al. CROI 2019, poster 480; **6.** VanderVeen L, et al. IDWeek 2021, oral 73; **7.** Begley R, et al. AIDS 2020, poster PEB0265; **8.** Daar E, et al. CROI 2020, poster 3691; **9**. Gupta SK, et al. IAS 2021, oral OALB0302; **10.** Segal-Maurer S, et al. CROI 2021, oral 2228. **11.** Molina JM, et al. IAS 2021, oral OALX01LB02.

Methods: Study Design



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

*Administered as 600 mg on Days 1 and 2, and 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15; †Investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, ipranavir, and nevirapine were not allowed. ARV, antiretroviral.

Results: 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} c/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 c/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
No. of prior ARV agents, median (range)	9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
No. of ARV agents in failing regimen, median (range)	3 (1–7)	3 (2–6)	4 (2–7)	3 (1–7)
No. of ARV agents in OBR, median (range)	4 (2–6)	4 (2–7)	4 (2–6)	4 (2–7)
No. of fully active agents in OBR, %				
0	17	17	17	17
1	29	58	36	38
≥2	54	25	47	46
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

Composition of Failing Regimen and OBR

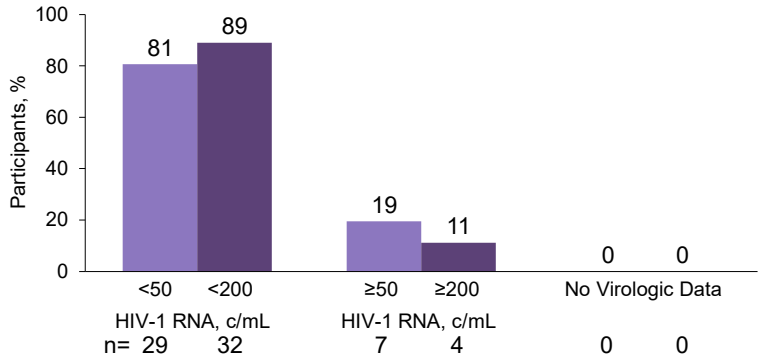
Class/Agent, %	Failing Regimen: N=72	OBR: N=72
NRTI	82	85
INSTI	68	65
PI	63	63
NNRTI	31	33
Ibalizumab (CD4-directed postattachment inhibitor)	19	24
Maraviroc (CCR5 entry inhibitor)	14	14
Fostemsavir (attachment inhibitor)	6	11
Enfuvirtide (fusion inhibitor)	6	7
No. of fully active ARV agents, %		
0	42	17
1	36	38
≥2	22	46
OSS, median*	1.0	2.0

- 17 of 72 participants (24%) had no changes in their OBR

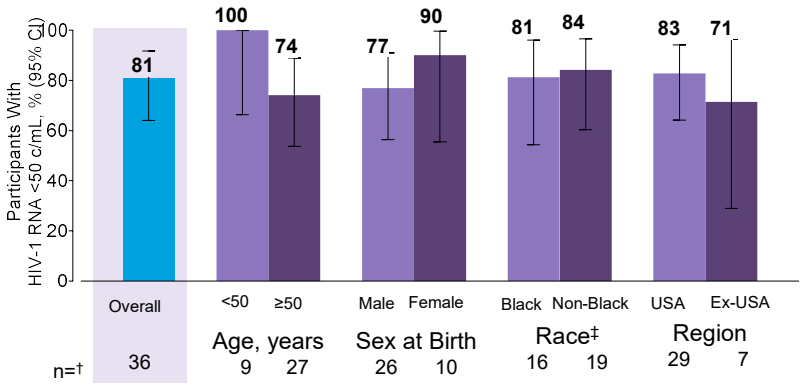
*Overall susceptibility scores (OSS; 1, 0.5, or 0 for full, partial, or no susceptibility, respectively) were determined based on proprietary algorithm (Monogram Biosciences Inc., South San Francisco, California, USA); for historical resistance reports, scores were derived from data provided by investigators; OSS of OBR was sum of individual scores. CCR5, C-C chemokine receptor type-5.

Efficacy at Week 26 in Randomized Cohort (n=36)

FDA-Snapshot Algorithm[11]

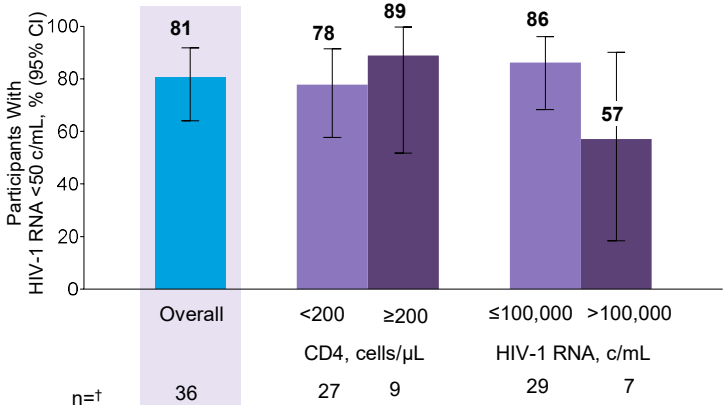


Efficacy by Demographics*



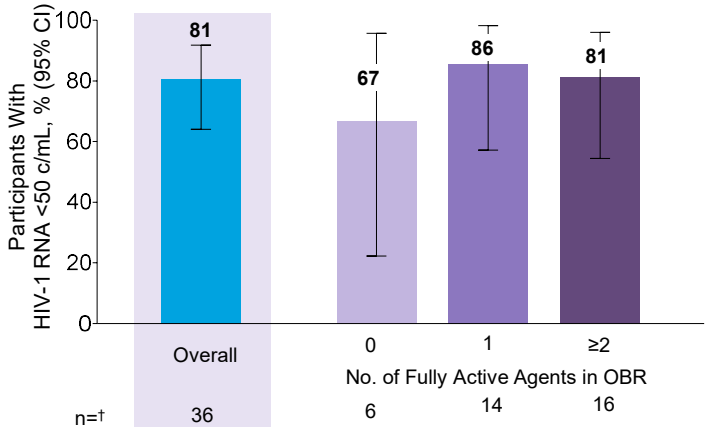
*Prespecified subgroup analyses; †Total n in each subgroup; ‡1 participant with race reported as "not permitted." CI, confidence interval.

Efficacy by Baseline CD4 and HIV-1 RNA*

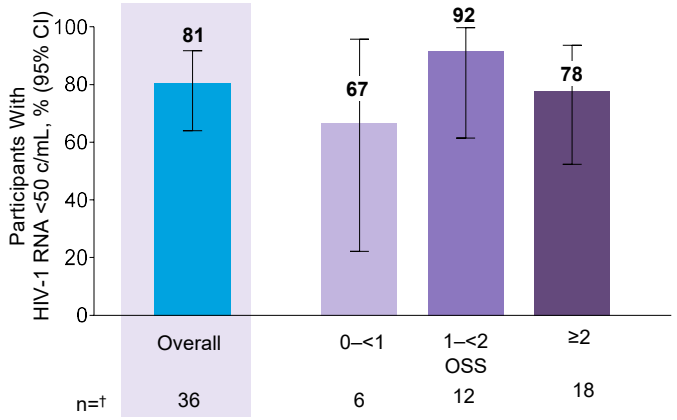


*Prespecified subgroup analyses; †Total n in each subgroup.

Efficacy by No. of Fully Active Agents in OBR*

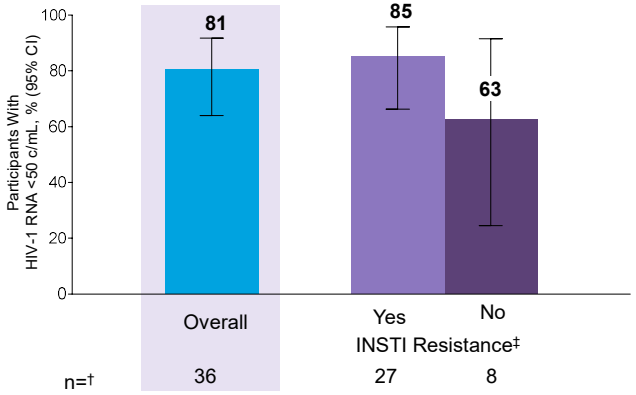


Efficacy by Baseline OBR Sensitivity Score*



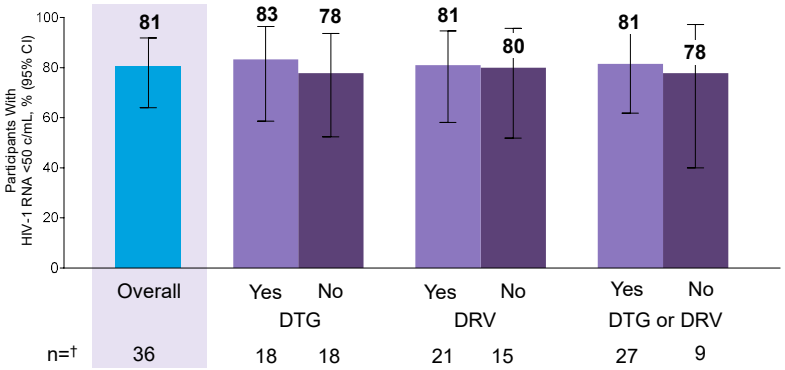
*Prespecified subgroup analyses; †Total n in each subgroup.

Efficacy by Baseline INSTI Resistance*



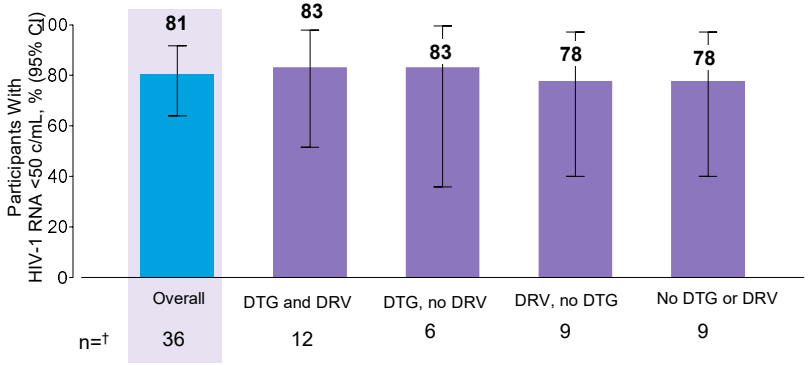
*Prespecified subgroup analyses; †Total n in each subgroup; ‡Included phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir (DTG), elvitegravir, and raltegravir; 1 participant had missing baseline INSTI resistance data.

Efficacy by Baseline Use of Dolutegravir and/or Darunavir*

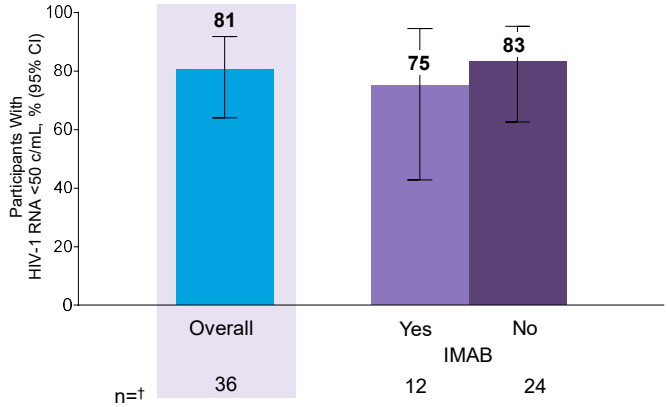


*Post hoc subgroup analyses; †Total n in each subgroup. DRV, darunavir.

Efficacy by Baseline Use of Dolutegravir and/or Darunavir*



Efficacy by Baseline Use of Ibalizumab*



*Post hoc subgroup analyses; 3 participants were on fostemsavir and all had HIV-1 RNA <50 c/mL at Week 26; †Total n in each subgroup.

Conclusions

- In HTE PWH with limited treatment options due to multidrug resistance, LEN demonstrated a clinically meaningful contribution towards virologic suppression in combination with an OBR
- No clinically relevant differences were seen in efficacy among subgroups who were considered more difficult to treat (eg, those with low CD4 count, INSTI resistance, no fully active agents, or no DTG or DRV in the OBR)
- LEN has the potential to become an important agent for HTE PWH with multidrug resistance
- These data support the ongoing evaluation of LEN for treatment and prevention of HIV

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