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Long-Acting Lenacapavir in People With Multidrug-Resistant HIV-1: Week 52 Results

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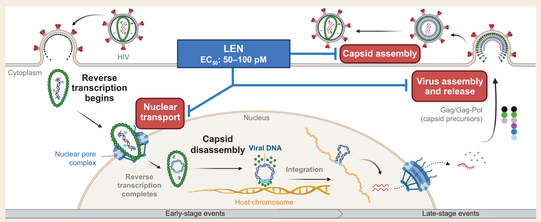
Introduction

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



EC_{50}, half-maximal effective concentration; Gag, group antigens; Pol, polyprotein.

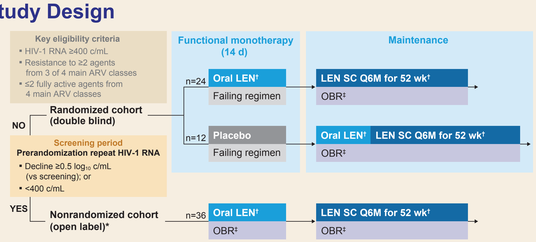
- LEN is a novel, highly potent, long-acting, first-in-class, HIV-1 capsid inhibitor
- LEN can meet significant unmet medical needs:
  - A new mechanism of action for heavily treatment-experienced (HTE) people with multidrug-resistant (MDR) HIV-1 and limited treatment options
  - Reduction of daily pill 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 (NNRTI)–, integrase strand transfer inhibitor (INSTI)–, and protease inhibitor (PI)–resistant mutants[3-5]
  - No observed preexisting resistance[6]
- In treatment-naïve people with HIV-1 (PWH), LEN + emtricitabine/tenofovir alafenamide led to 94% virologic suppression at Week 28[7]
- Previously in the CAPELLA Study (NCT04150068) in HTE people with MDR HIV-1:
  - LEN achieved its primary endpoint as a functional monotherapy when added to a failing regimen[8]:
    - Participants with ≥0.5-$\log_{10}$ decline: LEN 88% vs placebo 17% (p<0.001)
    - Mean HIV-1 RNA decline: LEN 1.9 vs placebo 0.3 $\log_{10}$ (p<0.001)
  - LEN + optimized background regimen (OBR) led to 81% virologic suppression at Week 26[9]

Objectives

- To evaluate the safety and efficacy (using the FDA Snapshot algorithm) of LEN in combination with an OBR at Weeks 26 and 52

Methods

Study Design



*3 participants were enrolled in Cohort 2 as they did not meet randomization criteria, while Cohort 1 was still enrolling; 33 enrolled in Cohort 2 after enrollment of Cohort 1 was completed; †Administered as 600 mg on Days 1 and 2, and 300 mg on Day 8; LEN SC 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, tipranavir, and nevirapine were not allowed. ARV, antiretroviral; d, day; Q6M, every 6 months; SC, subcutaneous; wk, week.

- Week 52 efficacy was summarized only for the randomized cohort (n=36), as most participants in the nonrandomized cohort have not yet reached Week 52
- Safety was summarized for both the randomized and nonrandomized cohorts (N=72)

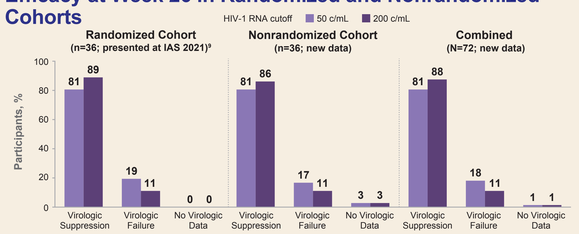
Results

Baseline Characteristics

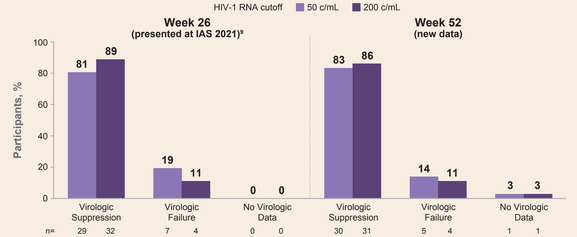
	Randomized		Nonrandomized	Total
	LEN: n=24	Placebo: n=12	LEN: n=36	N=72
Age, median (range), years	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), $\log_{10}$ c/mL	4.2 (2.3–5.4)	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 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
INSTI	83	58	64	69
PI	83	67	83	81

CD4, cluster of differentiation-4.

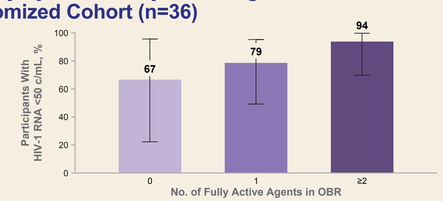
Efficacy at Week 26 in Randomized and Nonrandomized Cohorts



Efficacy in Randomized Cohort (n=36)



Efficacy by No. of Fully Active Agents in OBR at Week 52 in Randomized Cohort (n=36)



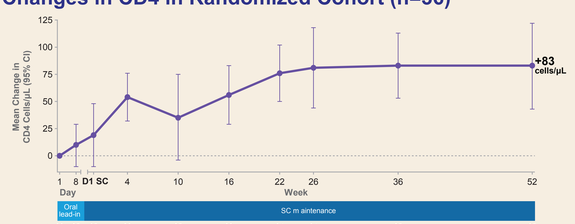
Emergent LEN Resistance*

n (%)	Randomized Cohort: n=36 (presented at IAS 2021, EACS 2021)[4,10]	Nonrandomized Cohort: n=36
Participants meeting criteria for resistance testing	11 (31)	10 (28)
Emergent LEN resistance†	4 (11)	4 (11)
M66I	4	2
Q67H/K/N	1	2
K70H/N/R/S	1	3
N74D/H/S	3	0
A105S/T	3	1
T107A/C/N	1	3

*Capsid genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥50 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; †Developed during maintenance period (Week 4 [n=5], Week 10 [n=2], and Week 26 [n=1]).

- No additional participants with LEN resistance were observed in the randomized cohort after Week 26
- All 8 participants with emergent LEN resistance remained on LEN
  - All 8 participants were at high risk of emergent LEN resistance: no fully active drugs in OBR (n=4) or inadequate adherence to OBR (n=4)
  - 3 participants resuppressed at a later visit: 1 without and 2 with OBR change

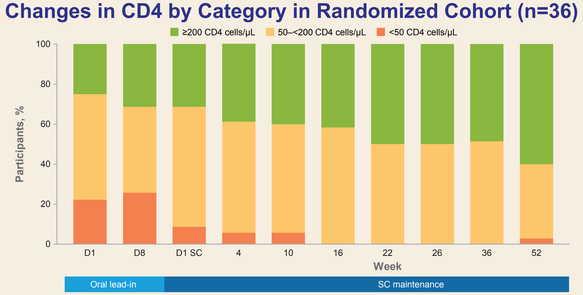
Changes in CD4 in Randomized Cohort (n=36)



D1 SC, 1st d LEN SC was administered. CI, confidence interval.

- Randomized cohort: mean change in CD4, cells/µL (95% CI): 81 (44, 118) at Week 26; 83 (43, 122) at Week 52
- Nonrandomized cohort: mean change in CD4, cells/µL (95% CI): 98 (59, 136) at Week 26

Changes in CD4 by Category in Randomized Cohort (n=36)



- LEN led to clinically meaningful improvement in CD4 cell count
- Proportion of participants with very low CD4 (<50 cells/µL) decreased from 22% (8/36) at baseline to 3% (1/36) at Week 52
- Proportion of participants with ≥200 CD4 cells/µL increased from 25% (9/36) at baseline to 60% (21/36) at Week 52

Adverse Events (excluding ISRs)*

≥10% Total in Any Grade, % (n)	Total LEN: N=72
Diarrhea	13 (9)
Nausea	13 (9)
COVID-19	11 (8)

*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); and septic shock, renal impairment, and shock (n=1). ISRs, injection-site reactions.

- Duration of follow up: median 376 d (interquartile range: 306, 501)
- 70 participants with ≥197 d of follow-up and 36 participants with ≥379 d of follow-up
- No serious AEs were related to study drug
- 1 participant had a serious AE of malignant neoplasm with a fatal outcome and not related to study drug

Incidence of ISRs Related to SC LEN*

ISR Types, %	After 1st SC Dose at Week 1 N=72	After 2nd SC Dose at Week 26 n=70	Median Duration, d
Swelling	26	13	12
Erythema	24	11	6
Pain	22	21	3
Nodule	22	11	180
Induration	11	10	118

*Only includes AEs related to LEN and excludes those not related to it.

- Mostly Grade 1 or 2 ISRs
- No Grade 4 ISRs, but 2 participants had Grade 3: 1 participant with swelling and erythema, which resolved in 4 and 8 d, respectively, and 1 participant with pain, which resolved in 1 d
- 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 d)
- 1 participant discontinued study drug at Week 52 due to an ISR (nodule; Grade 1)

Grade 3 or 4 Laboratory Abnormalities

Laboratory Abnormality, % (n)	Total: N=72
Any Grade 3 or 4	29 (21)
≥5% in total	
Low creatinine clearance (eGFR)*	14 (10)
Elevated creatinine†	13 (9)
Glycosuria	6 (4)
Nonfasting/fasting hyperglycemia	6 (3)

*Per Division of AIDS 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.

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

Conclusions

- In HTE PWH with limited treatment options due to MDR:
  - LEN in combination with an OBR led to high rates of virologic suppression at Week 52 (83%)
  - 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 and prevention of HIV-1 infection
  - In HTE people with MDR HIV
  - In treatment-naïve and -experienced PWH in combination with other agents
  - In people who could benefit from pre-exposure prophylaxis

References: **1.** Link JO, et al. Nature 2020;584:614-8; **2.** Zila V, et al. Cell 2021;184:1032-46.e18; **3.** Margot N, et al. Antimicrob Agents Chemother 2021;65:e02057-20; **4.** VanderVeen L, et al. CROI 2021, oral 128; **5.** Yant SR, et al. CROI 2019, poster 480; **6.** Marcelin AG, et al. J Antimicrob Chemother 2020;75:1588-90; **7.** Gupta SK, et al. IAS 2021, oral OALB0302; **8.** Segal-Maurer S, et al. CROI 2021, oral 127; **9.** Molina JM, et al. IAS 2021, oral OALX01LB02; **10.** Margot N, et al. EACS 2021, oral OS1/1.

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