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Week 52 Subgroup Efficacy of Lenacapavir in Heavily Treatment-Experienced PWH

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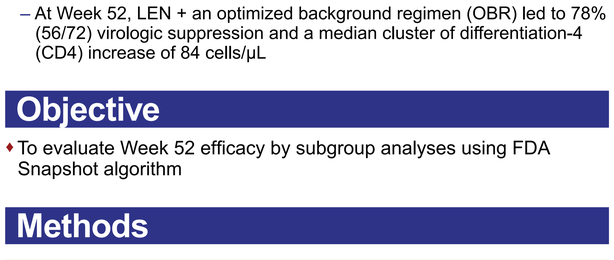
Introduction

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



EC_{50} = half-maximal effective concentration; Gag = group-specific antigen; LEN = lenacapavir; Pol = polymerase.

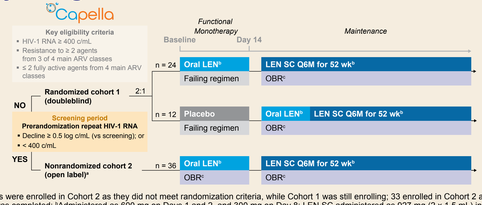
- LEN is a novel, highly potent, long-acting, first-in-class inhibitor of HIV-1 capsid protein approved in Canada, the EU, and the US for the treatment of HIV-1 infection in adults with multidrug resistance in combination with other antiretrovirals (ARVs)[3-5]
- LEN can meet significant unmet HIV treatment and prevention needs:
  - A new mechanism of action for people with multidrug-resistant (MDR) HIV-1 who are heavily treatment-experienced (HTE) and have 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 mutants resistant to nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), and entry inhibitors[6-9]
  - No observed preexisting resistance[10]
- The CAPELLA study (NCT04150068) is an ongoing Phase 2/3 study in people with HIV (PWH) who are HTE and viremic on their current regimen with MDR HIV-1[11]:
  - LEN achieved its primary endpoint as a functional monotherapy when added to a failing regimen:
    - Participants with ≥ 0.5-log decline: LEN 88% vs placebo 17% ($P < 0.001$)
    - HIV-1 RNA least-squares mean change: LEN -2.10 vs placebo 0.07 log ($P < 0.001$)
  - At Week 52, LEN + an optimized background regimen (OBR) led to 78% (56/72) virologic suppression and a median cluster of differentiation-4 (CD4) increase of 84 cells/μL

Objective

- To evaluate Week 52 efficacy by subgroup analyses using FDA Snapshot algorithm

Methods

Study Design



[a]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; [b]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; [c]Investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, tipranavir, and nevirapine were not allowed.

Results

Baseline Characteristics

	Randomized Cohort n = 36	Nonrandomized Cohort 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
No. of prior ARV agents, median (range)	9 (2-24)	13 (3-25)	11 (2-25)
No. of fully active agents in OBR, %			
0	17	17	17
1	39	36	38
≥ 2	44	47	46
Known resistance to ≥ 2 drugs in class, %			
NRTI	97	100	99
NNRTI	94	100	97
PI	78	83	81
INSTI	75	64	69
4-class resistance %	47	44	46

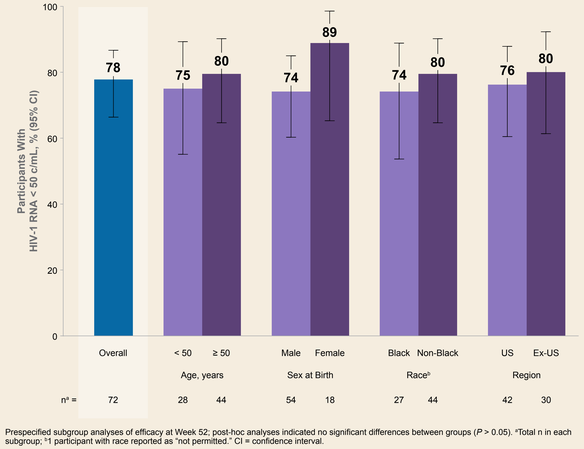
[a]Local regulators did not allow collection of race or ethnicity information for 1 participant.

Composition of Failing Regimen and OBR

	Total: N = 72	
	Failing Regimen	OBR
Class/agent		
NRTI	82%	85%
INSTI	68%	65%
PI	63%	63%
NNRTI	31%	33%
IMAB (CD4-directed postattachment inhibitor)	18%	24%
Maraviroc (CCR5 entry inhibitor)	14%	14%
FTR (attachment inhibitor)	6%	11%
Enfuvirtide (fusion inhibitor)	6%	7%
No. of fully active ARVs		
0	42%	17%
1	36%	38%
≥ 2	22%	46%
OSS, median[a]	1	2

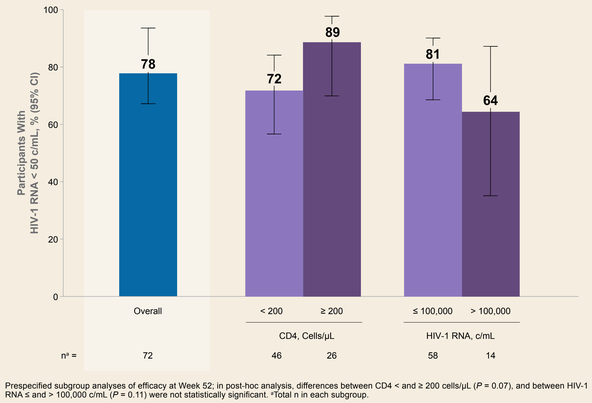
[a]Overall susceptibility scores (OSS; 1, 0.5, or 0 for full, partial, or no susceptibility, respectively) were determined based on proprietary algorithm (Monogram Biosciences Inc., South San Francisco, CA); for historical resistance reports, scores were derived from data provided by investigators; OSS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

Week 52 Efficacy by Demographics



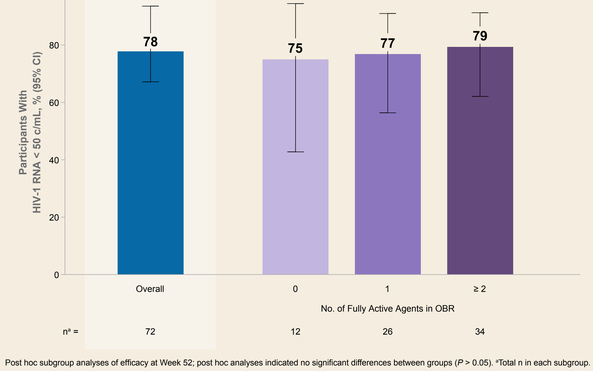
Prespecified subgroup analyses of efficacy at Week 52; post-hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup; [b]1 participant with race reported as "not permitted." CI = confidence interval.

Week 52 Efficacy by Baseline CD4 and HIV-1 RNA



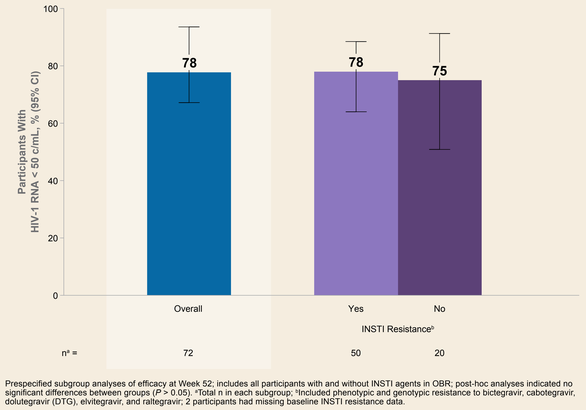
Prespecified subgroup analyses of efficacy at Week 52; in post-hoc analysis, differences between CD4 < and ≥ 200 cells/μL ($P = 0.07$), and between HIV-1 RNA ≤ and > 100,000 c/mL ($P = 0.11$) were not statistically significant. [a]Total n in each subgroup.

Week 52 Efficacy by Number of Fully Active Agents in OBR



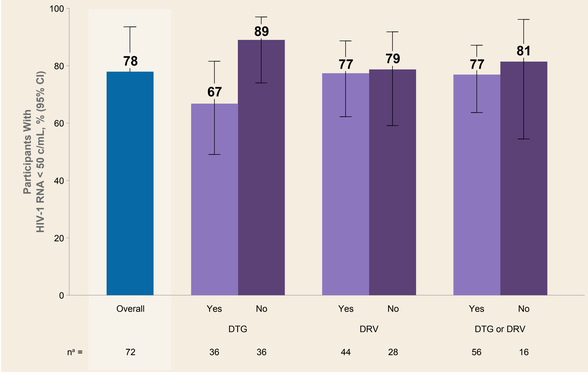
Post hoc subgroup analyses of efficacy at Week 52; post hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup.

Week 52 Efficacy by Baseline INSTI Resistance



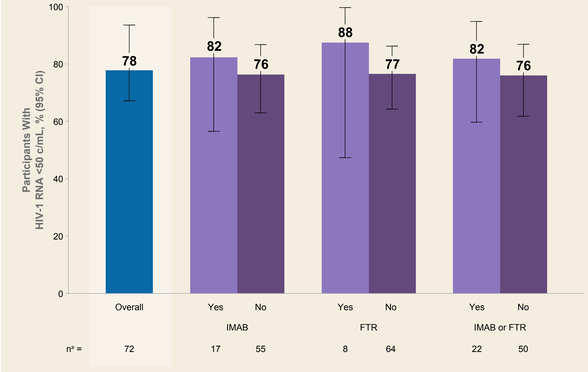
Prespecified subgroup analyses of efficacy at Week 52; includes all participants with and without INSTI agents in OBR; post-hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup; [b]Included phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir (DTG), elvitegravir, and raltegravir; 2 participants had missing baseline INSTI resistance data.

Week 52 Efficacy by Baseline Use of Dolutegravir or Darunavir



Post hoc subgroup analyses. [a]Total n in each subgroup. DRV = darunavir.

Week 52 Efficacy by Baseline Use of Ibalizumab or Fostemsavir



Prespecified subgroup analyses of efficacy at Week 52; post-hoc analyses indicated no significant differences between groups ($P > 0.05$). [a]Total n in each subgroup.

Conclusions

- In people with MDR HIV-1 and limited treatment options, LEN in combination with an OBR led to high rates of virologic suppression at Week 52 overall
- The efficacy of LEN in combination with an OBR was consistent across diverse demographics, baseline characteristics, and OBR
- LEN is an important option for people with MDR HIV-1 and limited treatment options
- These data support the ongoing evaluation of LEN for treatment and prevention of HIV

References: **1.** Link JO, *et al.* Nature 2020;584:614-8; **2.** Zila V, *et al.* Cell 2021;184:1032-46.e18; **3.** Sunlenca [package insert]. Foster City, CA: Gilead Sciences, Inc; 2022; **4.** Sunlenca [product monograph]. Mississauga, ON: Gilead Sciences Canada, Inc; 2022; **5.** Sunlenca [summary of product characteristics]. Carrigtohill, Ireland: Gilead Sciences Ireland UC; 2022; **6.** Margot N, *et al.* CROI 2020; poster 529; **7.** Margot N, *et al.* CROI 2022, poster 508; **8.** VanderVeen L, *et al.* CROI 2021, oral 01781; **9.** Yant SR, *et al.* CROI 2019, poster 480; **10.** VanderVeen L, *et al.* IDWeek 2021, oral 73; **11.** Segal-Maurer S, *et al.* N Engl J Med 2022;386:1793-1803.

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