P026

Week 52 Subgroup Efficacy Analyses of Long-Acting Subcutaneous Lenacapavir in Phase 2/3 in Heavily Treatment-Experienced People With Multidrug-Resistant HIV (CAPELLA Study)

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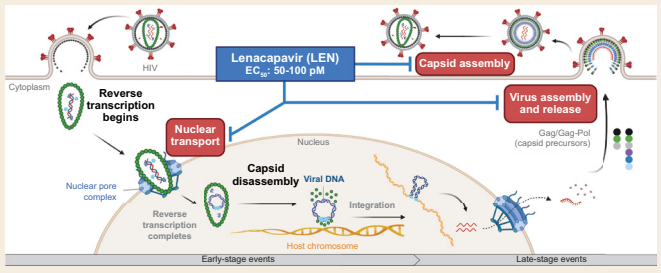
Introduction

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



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

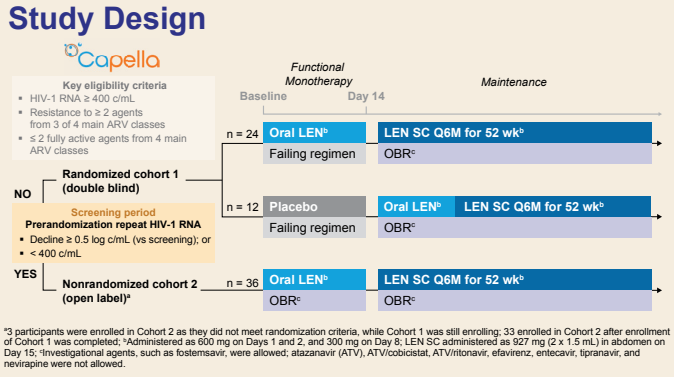
- LEN is a novel, highly potent, long-acting, first-in-class, HIV-1 capsid inhibitor
- LEN can meet significant unmet HIV treatment and prevention needs:
  - A new mechanism of action for people with multidrug-resistant (MDR) HIV-1 who are heavily treatment-experienced (HTE) and have limited treatment 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), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), and entry inhibitors[3-6]
  - No observed pre-existing resistance[7]
- LEN has been approved by the European Commission for the treatment of HIV-1 infection, in combination with other antiretrovirals (ARVs), in adults with MDR for whom it is otherwise not possible to construct a suppressive antiviral regimen
- Previously in the CAPELLA study (ClinicalTrials.gov NCT04150068) in people with HIV (PWH) who are HTE with MDR[8]:
  - 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 change, least-squares mean: LEN -2.10 vs placebo 0.07 log ($P < 0.001$)
  - LEN + optimized background regimen (OBR) led to 83% (30/36) virologic suppression at Week 52

Objective

- To evaluate Week 52 efficacy (assessed using U.S. Food & Drug Administration Snapshot algorithm) by subgroup analyses in a randomized cohort of PWH by demographics, and baseline HIV-1 RNA, CD4, OBR, and INSTI resistance

Methods

Study Design



a3 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; bAdministered 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; cInvestigational 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)
> 75,000 c/mL, %	28	28	28
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	36
≥ 2	44	47	47
Known resistance to ≥ 2 drugs in class, %			
NRTI	97	100	99
NNRTI	94	100	97
PI	78	83	81
INSTI	75	64	69

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

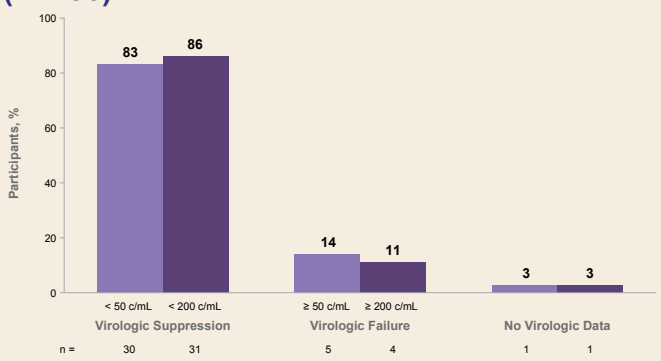
Composition of Failing Regimen and OBR

	Randomized Cohort: n = 36		Total: N = 72	
Class/agent, %	Failing Regimen	OBR	Failing Regimen	OBR
NRTI	83	89	82	85
INSTI	69	69	68	65
PI	56	58	63	63
NNRTI	25	28	31	33
Ibalizumab (CD4-directed postattachment inhibitor)	11	33	18	24
Maraviroc (CCR5 entry inhibitor)	11	17	14	14
Fostemsavir (attachment inhibitor)	6	8	6	11
Enfuvirtide (fusion inhibitor)	6	8	6	7
No. of fully active ARVs, %				
0	53	17	42	17
1	31	39	36	38
≥ 2	17	44	22	46
OSS, median[a]	0.8	1.8	1.0	2.0

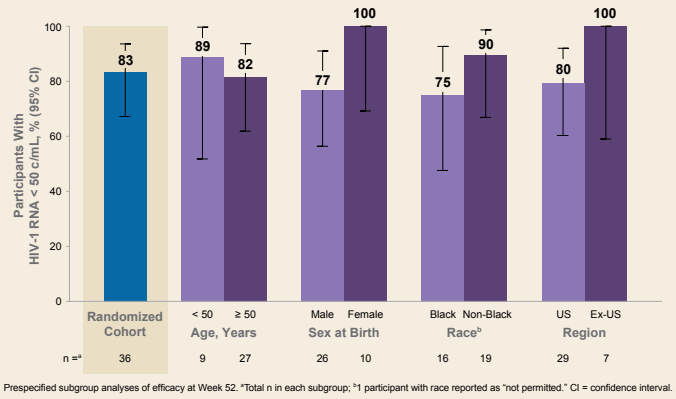
[a]Overall susceptibility scores (OSS; 1, 0.5, or 0 for full, partial, or no susceptibility, respectively) were determined based on proprietary algorithm (Monogram Biosciences Inc., South San Francisco, California, US); for historical resistance reports, scores were derived from data provided by investigators;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

- 16 of 72 participants (22%) had no changes in their OBR (12 of 36 [33%] in the randomized cohort)

Week 52 Efficacy: Randomized Cohort (n = 36)[9]

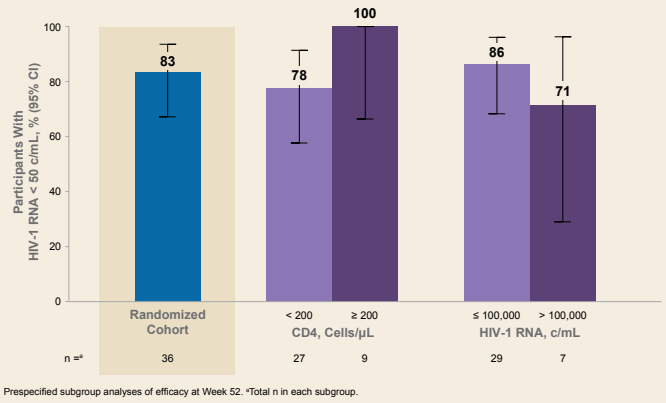


Week 52 Efficacy by Demographics



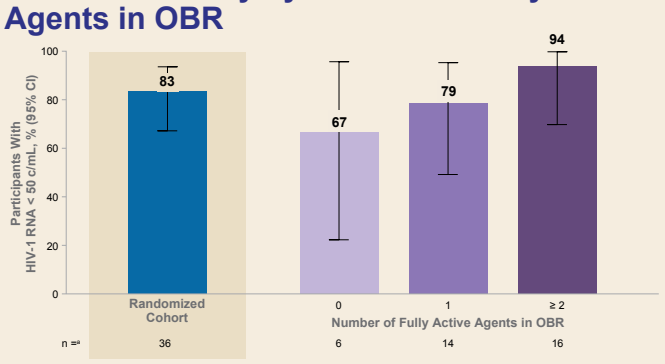
Prespecified subgroup analyses of efficacy at Week 52. *Total n in each subgroup; b1 participant with race reported as "not permitted." CI = confidence interval.

Week 52 Efficacy by Baseline CD4 and HIV-1 RNA



Prespecified subgroup analyses of efficacy at Week 52. *Total n in each subgroup.

Week 52 Efficacy by Number of Fully Active Agents in OBR

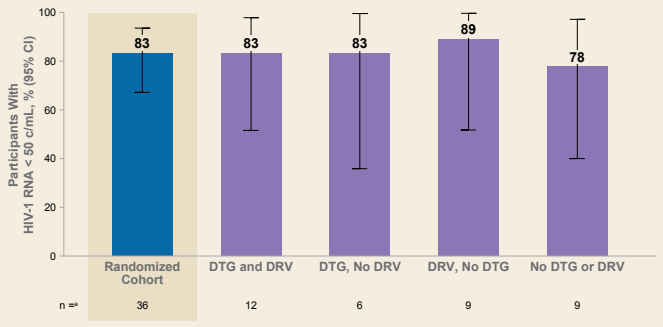


Post hoc subgroup analyses of efficacy at Week 52. *Total n in each subgroup.

Week 52 Efficacy by Baseline INSTI Resistance

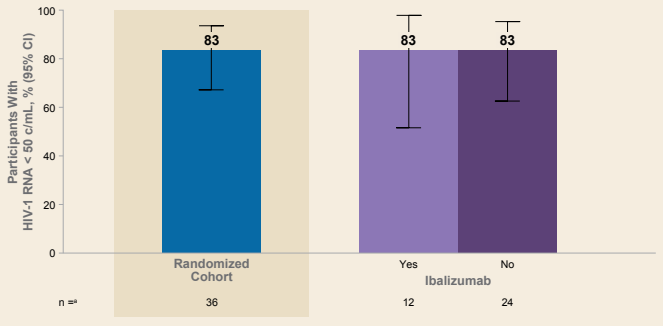
Prespecified subgroup analyses of efficacy at Week 52; includes all participants from randomized cohort with and without INSTI agents in OBR. *Total n in each subgroup; bIncluded phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir (DTG), elvitegravir, and raltegravir; 1 participant had missing baseline INSTI resistance data.

Week 52 Efficacy by Baseline Use of Dolutegravir and/or Darunavir



Post hoc subgroup analyses. *Total n in each subgroup. DRV = darunavir.

Week 52 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 PWH who were HTE with limited treatment options due to MDR, LEN in combination with an OBR led to high rates of virologic suppression
- No clinically relevant differences were seen in efficacy among subgroups who were considered more difficult to treat (eg, those with high HIV-1 RNA, low CD4 count, INSTI resistance, no fully active agents in the OBR, or no DTG or DRV in the OBR)
- LEN has the potential to become an important agent for PWH who are HTE with MDR
- 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.** Margot N, et al. CROI 2020, poster 529; **4.** Margot N, et al. CROI 2022, poster 508; **5.** VanderVeen L, et al. CROI 2021, oral 01781; **6.** Yant SR, et al. CROI 2019, poster 480; **7.** VanderVeen L, et al. IDWeek 2021, oral 73; **8.** Segal-Maurer S, et al. *N Engl J Med.* 2022;386:1793-1803; **9.** Ogbuagu O, et al. CROI 2022, poster 1047.

Acknowledgments: We extend our thanks to the study participants and their families, and the participating study investigators and staff: *Canada:* J Brunetta, B Trottier; *Dominican Republic:* E Koenig; *France:* J-M Molina, S Ronot-Bregigeon, Y Yazdanpanah; *Germany:* H-J Stellbrink; *Italy:* A Antinori, A Castagna, F Castelli; *Japan:* T Shirasaka, Y Yokomaku; *South Africa:* M Rassool; *Spain:* J Mallolas; *Taiwan:* C-C Hung; *Thailand:* A Avihingsanon, P Chetchotisakd, K Siripassorn, W Ratanasuwan; *US:* DS Berger, M Berhe, C Brinson, CM Creticos, GE Crofoot, E DeJesus, D Hagins, T Hodge, K Lichtenstein, JP McGowan, O Ogbuagu, O Osiyemi, GJ Richmond, MN Ramgopal, PJ Ruane, W Sanchez, S Segal-Maurer, J Sims, GI Sinclair, DA Wheeler, A Wiznia, K Workowski, C Zurawski. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by Aaron Katzman of BioScience Communications, New York, NY, funded by Gilead.