Lenacapavir Efficacy in CAPELLA Patients with No Fully Active Agents in Optimized Background Regimen

Poster 630

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Conclusions

- In heavily treatment-experienced (HTE) people with HIV-1 (PWH) with multidrug resistance, lenacapavir (LEN) combined with an optimized background regimen (OBR) led to sustained virologic suppression through Week 104 for most participants with no fully active antiretrovirals (ARVs) in their OBR
- A clinically meaningful increase in mean CD4 cell count was observed through Week 104
- Three participants had emergent LEN resistance, two of whom had virologic suppression at Week 104. No participants experienced treatment-emergent resistance to OBR through Week 104
  - A previous analysis demonstrated that emergence of LEN resistance is associated with inadequate OBR adherence, as well as OBRs lacking fully active agents[5,6]
- These data further support the role of LEN as an important treatment option for HTE PWH with limited treatment options due to multidrug resistance

Plain-Language Summary

Lenacapavir is a medicine approved for the treatment of HIV in people who have already received many different HIV medicines, and whose current medicines are not working. Lenacapavir was approved based on the results of the CAPELLA study. In this study, people had many HIV medicines that stopped working and they received lenacapavir combined with other HIV medicines picked by their doctor (known as an optimized background regimen). For some people in the CAPELLA study, none of the medicines in their optimized background regimen were fully effective against their HIV infection. We studied how well lenacapavir worked in these people in the CAPELLA study. We found that even when people had no fully effective medicines in their optimized background regimen, people who took lenacapavir had no virus found in their blood over a two-year period, and/or an increase in CD4 cell count over two years.

References: **1.** Sunlenca® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (Accessed February 2024). **2.** Segal-Maurer S, et al. *N Engl J Med.* 2022; 386:1793-803. **3.** Sunlenca® Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (Accessed February 2024). **4.** Ogbuagu O, et al. IDWeek 2023; Poster 1596. **5.** Margot N, et al. EACS 2023; Oral presentation PS8 04. **6.** Margot N, et al. *Antivir Ther* 2023; 28(6):13596535231220754.

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Background

- LEN is a highly potent, long-acting HIV-1 capsid inhibitor that has no overlapping resistance with other ARVs[1,2]
- LEN was approved for the treatment of HIV-1 infection, in combination with other ARVs, in HTE PWH with multidrug-resistant HIV-1 infection, based on the results of the Phase 2/3 CAPELLA study (NCT04150068)[1–3]
  - At Week 104, 82% (44/54) of participants had virologic suppression (HIV-1 RNA <50 copies/mL) by missing=excluded analysis[4]
- We explored the efficacy of LEN in CAPELLA within a subgroup of participants with no fully active agents in their OBR

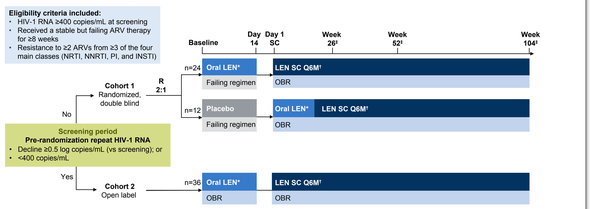
Objectives

- To assess LEN efficacy (including virologic outcomes and change from baseline in CD4 cell count) and emergence of resistance-associated mutations (RAMs) through Week 104 in CAPELLA participants whose OBR had no fully active ARVs

Methods

- In the Phase 2/3 CAPELLA study, HTE PWH with multidrug resistance received subcutaneous LEN every 6 months (following oral initiation dosing), combined with an OBR **(Figure 1)**[2,3]

Figure 1. CAPELLA Study Design



*Days 1 and 2: 600 mg; Day 8, 300 mg. [1]927 mg as two 1.5-mL injections in the abdomen on Day 15, then Q6M. †Following first SC LEN injection.
In both cohorts, the OBR was investigator selected. Investigational drugs were permitted in the OBR.
ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; LEN, lenacapavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; PI, protease inhibitor; Q6M, every 6 months; R, randomized; SC, subcutaneous.

- Baseline resistance was evaluated at Screening using genotypic and/or phenotypic assays (Monogram) or through historical resistance reports
- ARVs from the four main classes (NRTI, NNRTI, PI, INSTI) were assigned an individual susceptibility score: 0 (no susceptibility), 0.5 (partial susceptibility), and 1 (full susceptibility)
  - OBR overall susceptibility scores (OSS) were calculated as the sum of the individual susceptibility scores for OBR ARVs
- Plasma HIV-1 RNA was assessed at regular intervals throughout the study, with virologic suppression (HIV-1 RNA <50 copies/mL) evaluated per FDA Snapshot algorithm at Weeks 26, 52, and 104
- Change from baseline in HIV-1 RNA, CD4 cell count, and emergence of RAMs to LEN and OBR ARVs were assessed through Week 104
  - LEN and OBR resistance analyses were conducted at the time of virologic failure (virologic rebound ≥50 copies/mL or <1 $\log_{10}$ decline vs baseline)

Results

- This subgroup analysis presents results for 12 participants who had no fully active ARVs in their OBR (out of 72 total CAPELLA participants [17%]) **(Table 1)**
  - 5/12 participants had no partially active ARVs (OSS 0)
  - 6/12 participants had one partially active ARV (OSS 0.5)
  - 1/12 participants had two partially active ARVs (OSS 1)
- The 12 participants in this subgroup had a median of 4 agents in their OBR (range 2–6)
- The activity of participants' ARVs at baseline are shown in **Table 1**, with baseline resistance mutations reported in **Table 2**
- Participants' baseline HIV-1 RNA and CD4 cell count are shown in **Table 3**. At baseline, the 12 participants had:
  - Mean HIV-1 RNA: 4.02 $\log_{10}$ copies/mL (95% CI: 3.25; 4.79)
  - Mean CD4 cell count: 175 cells/μL (95% CI: 86; 265)
- Per FDA Snapshot algorithm, 10/12 participants had HIV-1 RNA <50 copies/mL at ≥1 of the three predefined visits (Week 26, Week 52, or Week 104), and 8/12 participants were suppressed at all three visits **(Table 3)**
- Viral and immunological responses for participants not suppressed at Weeks 26, 52, or 104, or with emergent LEN resistance, are shown in **Figure 2**
- From baseline to Week 104:
  - Mean decrease in HIV-1 RNA was 2.34 $\log_{10}$ copies/mL (95% CI: -3.25; -1.44)
  - Mean increase in CD4 cell count was 105 cells/μL (95% CI: -10; 220) **(Figure 3)**
- None of the 12 participants developed resistance to OBR agents, and none discontinued LEN

Results [continued]

Table 1. Participants' Baseline OBRs and ARV Activity Profiles

Participant	OBR	OBR OSS	Activity of antiretrovirals at baseline																											
			INSTIs					NNRTIs				NRTIs						PIs						EIs						
	No activity	Partial activity	BIC	DTG	EVG	RAL	DOR	EFV	ETR	RPV	3TC	FTC	ABC	d4t	TFV[a]	ZDV	FPV	ATV	DRV	LPV	TPV	FTR	MVC	ENF	IBA
1	3TC, DRVc, DTG, ENF, MVC	-	0																											
2	FTC, DOR, BIC, IBA	TAF	0.5																											
3	3TC, RPV, MVC, IBA	-	0																											
4	FTC, DRVc, DTG, IBA	TAF	0.5																											
5	FTC, TDF, DRVb, DTG	-	0																											
6	FTC, DRVc, DTG, IBA, FTR	TAF	0.5																											
7	FTC, DOR, DRVb	TAF	0.5																											
8	DOR, DTG	-	0																											
9	FTC	TAF, DRVc	1																											
10	DOR, IBA, FTR	-	0																											
11	DRVr, DTG	TDF	0.5																											
12	DOR	DTG	0.5																											

No activity | Partial activity | Full activity | No data

Resistance testing obtained for the agents stavudine, delavirdine, indinavir, nelfinavir, nevirapine, ritonavir, and saquinavir are not shown in the table. [a]Tenofovir (TFV) is the active drug moiety for both tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) prodrugs.
3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; BIC, bictegravir; c, cobicistat; d4t, didanosine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EI, entry inhibitor; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; FTR, fostemsavir; IBA, ibalizumab; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; OSS, overall susceptibility score; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; r, ritonavir boosting; TPV, tipranavir; ZDV, zidovudine.

Table 2. Resistance Mutations at Baseline

Participant	Baseline Resistance Mutations			
	INSTIs	NNRTIs	NRTIs	PIs
1	M50I, T97A, S119R, E138K, G140S, Q148H	Y181I, Y188L	M41ML, M184V, T215F	V32I, I54M, Q58E, I84V, L90M
2	L74I/M, S119P, E138K/K, S147S/G, S153S/A/C/G, N155H, E157E/Q	V106M, V108I, Y181V	D67N, K70R, M184V, T215F, K219E	V32I, M46I, I54L, L76V, I84V, L90M
3	M50I, T97A, S119P, E138K, G140S, Q148H	L100I/V, G190Q	M41L, D67N,L74I/V, M184V, L210W, T215Y, K219R	V32I, M46I, I47V, I54L, I84V
4	T97A, E138K, G140S, Q148H	L100I, K103N, V108V/I	M41L, D67N, L74I, M184V, L210W, T215Y, K219N	M46I, I47V, I50V, L76V, V82T
5	E138K, G140A, S147G, Q148R, E157Q	K101H, Y181C, G190A	M41L, D67N, K70KR, M184V, T215F, K219Q	V32I, M46L, I54L, N83D, I84V
6	M50I/T, L74M, T97A, S119T, Y143C, S147G, N155H, E157Q	L100I/M, K103S, H221Y	T69(del), V75I, F77L, Y115F, F116Y, Q151M, M184V, K219Q	V32I, M46L, I54L, T74P, V82T, I84V, L90M
7	N155N/H	K101E, Y181I	M41L, M184V, T215F	V32V/I, I47V/I, I54I/M, Q58Q/E, I84V, L90M
8	M50M/I, T97A, S119R, S147G, N155H, E157Q	L100I, K103N	M41L, D67N, L74V, L210W, K219D/N	V32I, M46I, Q58E, I84V, L90M
9	M50I, G140S, Q148H, N155H	E138Q, Y181V, H221Y, M230L	M41L, M184V, T215F	V32I, M46I, I47V, I54L, Q58E, I84V, L90M
10	E138A, G140A, S147G, Q148R, N155H, E157Q	V106I/M, Y181C	M41L, V75I, F77L, F116Y, Q151M	V32I, I54L, Q58E, T74P, V82L, I84V, L90M
11	E138E/A, G140A, Q148R	K103N, E138Q	K70R, T215F, K219E	V32I, M46I, I54L, L76V, I84V
12	G140S, Q148H	K103N	M41L, D67N, L210W, T215Y, K219R	V32I, M46L, I54V, T74P, V82A, I84V, L90M

INSTI, integrase strand-transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

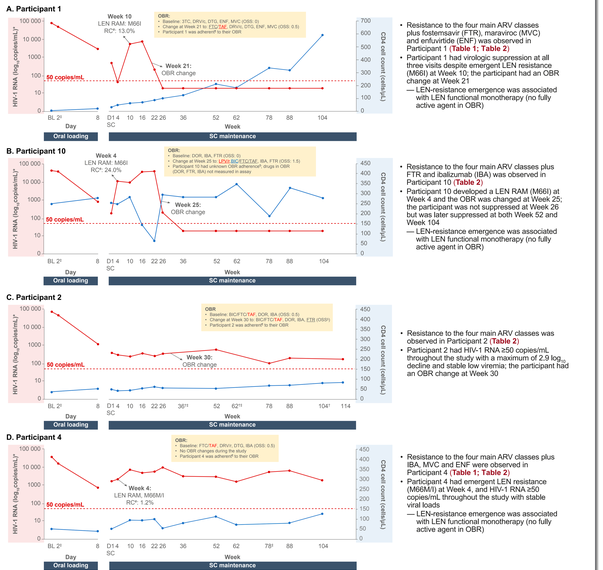
Table 3: Participants' Baseline Characteristics, HIV-1 RNA and CD4 cell count

Participant	Age (years)	Sex	Race	HIV-1 RNA, copies/mL				CD4 cell count, cells/μL	
				Baseline	Week 26	Week 52	Week 104	Baseline	Week 104
1*	27	F	Black or African American	85,100	<50	<50	<50	3	594
2	54	M	White	75,200	342	574	–	33	71
3	64	M	White	14,500	<50	<50	<50	176	181
4	58	M	Black or African American	38,300	2420	2970	1880	50	128
5	24	M	Asian	14,000	<50	<50	<50	189	273
6	61	M	Black or African American	1900	<50	<50	<50	84	98
7†	36	F	White	<50	<50	<50	<50	518	704
8	61	M	White	39,400	<50	<50	<50	159	278
9‡	60	M	Black or African American	91	<50	<50	<50	192	198
10	51	M	White	43,900	200	<50	<50	249	279
11§	41	F	Asian	69,500	<50	<50	–	137¶	–#
12	68	M	White	78,800	<50	<50	<50	313	319

*Developed resistance at Week 10 and resuppressed at Week 26; †HIV-1 RNA at screening was 687 copies/mL; ‡HIV-1 RNA at screening was 4800 copies/mL; §Participant 11 was suppressed at Weeks 26 and 52, but missing virologic data in the Week 104 window and was suppressed at a later visit (Week 114); ¶Value from the screening visit as Participant 11 had missing data for Day 1. #Missing at Week 104, 321 cells/μL at Week 114.
F, Female; M, Male.

- Through Week 104, Participant 1 and 10 developed resistances to LEN and were re-suppressed with OBR change; Participant 2 was not suppressed with low-level viremia; Participant 4 was not suppressed and developed resistance to LEN **(Table 3)**

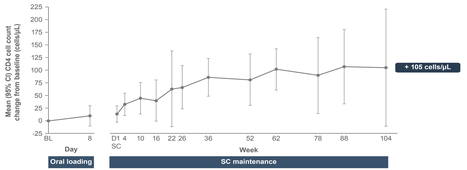
Figure 2. Viral and Immunological Response for Participants Not Suppressed at Weeks 26, 52, or 104, or with LEN-Resistance Emergence



- Resistance to the four main ARV classes plus fostemsavir (FTR), maraviroc (MVC) and enfuvirtide (ENF) was observed in Participant 1 **(Table 1; Table 2)**
- Participant 1 had virologic suppression at all three visits despite emergent LEN resistance (M66I) at Week 10; the participant had an OBR change at Week 21
  - LEN-resistance emergence was associated with LEN functional monotherapy (no fully active agent in OBR)
- Resistance to the four main ARV classes plus FTR and ibalizumab (IBA) was observed in Participant 10 **(Table 2)**
- Participant 10 developed a LEN RAM (M66I) at Week 4 and the OBR was changed at Week 25; the participant was not suppressed at Week 26 but was later suppressed at both Week 52 and Week 104
  - LEN-resistance emergence was associated with LEN functional monotherapy (no fully active agent in OBR)
- Resistance to the four main ARV classes was observed in Participant 2 **(Table 2)**
- Participant 2 had HIV-1 RNA ≥50 copies/mL throughout the study with a maximum of 2.9 $\log_{10}$ decline and stable low viremia; the participant had an OBR change at Week 30
- Resistance to the four main ARV classes plus IBA, MVC and ENF were observed in Participant 4 **(Table 1; Table 2)**
- Participant 4 had emergent LEN resistance (M66M/I) at Week 4, and HIV-1 RNA ≥50 copies/mL throughout the study with stable viral loads
  - LEN-resistance emergence was associated with LEN functional monotherapy (no fully active agent in OBR)

Red text indicates OBR ARVs with susceptibility score: 0.5. Blue text indicates OBR ARVs with susceptibility score: 1.0. Underlined text indicates the addition of an agent to the OBR. *For illustrative purposes, HIV-1 RNA samples with <50 copies/mL are shown on Figure as 19 copies/mL. †No virologic data; ‡No immunological data; §Overall susceptibility score unavailable as no susceptibility for fostemsavir (FTR) was recorded. ¶OBR agents measured: dolutegravir (DTG), darunavir (DRV), emtricitabine (FTC), tenofovir alafenamide (TAF), tenofovir (TFV) from TAF only; #Replication capacity (RC) of clone with full mutation is expressed as % of wild-type control. [a]TC, lamivudine; BL, baseline; BIC, bictegravir; c, cobicistat; D, day; DOR, doravirine; ENF, enfuvirtide; IBA, ibalizumab; LEN, lenacapavir; LPV, lopinavir; MVC, maraviroc; OBR, optimized background regimen; OSS, overall susceptibility score; r, ritonavir; RAM, resistance-associated mutation; SC, subcutaneous; TDF, tenofovir disoproxil fumarate.

Figure 3. Mean CD4 Cell Count Change from Baseline (n=12)



BL, baseline; CI, confidence interval; D, day; SC, subcutaneous.