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Sunlenca® (lenacapavir) Inadequate Adherence to Background Regimen

This document is in response to your request for information regarding Sunlenca (lenacapavir [LEN]) efficacy in heavily treatment-experienced (HTE) people with HIV (PWH) with inadequate adherence to the optimized background regimen (OBR). Currently, there are no data to address this inquiry. Please see available information below regarding study participants who developed treatment-emergent resistance and had OBR adherence issues.

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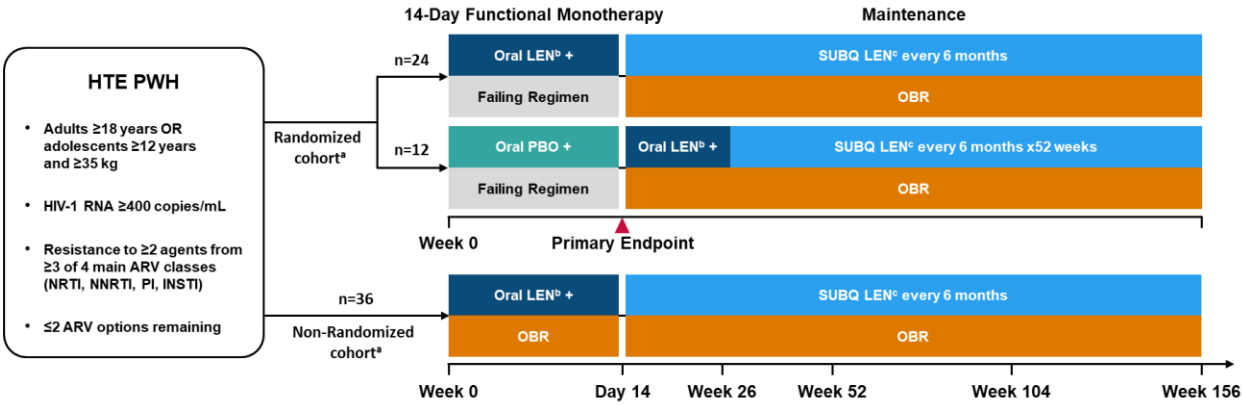
Clinical Studies: LEN and Inadequate Adherence to Background Regimen

CAPELLA: LEN in HTE PWH

Study design and demographics

CAPELLA (NCT04150068) is an ongoing, phase 2/3, double-blinded, PBO-controlled clinical study designed to evaluate LEN as add-on therapy to a failing regimen in HTE PWH with multidrug resistance. Participants on a failing regimen for ≥8 weeks who met the inclusion criteria entered a screening period. Those without a prespecified decline in viral load or change in HIV-1 RNA during the screening period were randomly assigned to receive either oral LEN or PBO in addition to their existing failing regimen. After this functional monotherapy phase, participants entered the open-label maintenance phase with subcutaneous LEN and a possible change in their failing regimen to OBR. Participants in the screening period who experienced prespecified improvements in HIV-1 RNA or who were enrolled after the randomized cohort was fully recruited, were enrolled into the nonrandomized cohort (Figure 1).[1,2]

Figure 1. CAPELLA: Study Design[1,3-5]



Abbreviations: ATV=atazanavir; SUBQ=subcutaneous.
[a]Participants with <0.5 log_{10} decline in HIV-1 RNA and HIV-1 RNA ≥400 c/mL were enrolled in the randomized cohort; participants were enrolled in the nonrandomized cohort if they had ≥0.5 log_{10} decline in HIV-1 RNA and/or had HIV-1 RNA <400 c/mL or were enrolled after the randomized cohort was fully recruited.
[b]Oral LEN dosing schedule: Day 1, 600 mg; Day 2, 600 mg; and Day 8, 300 mg.
[c]SUBQ LEN dosing schedule: 927 mg (2 × 1.5 mL) on Day 15 and then every 6 months.
Note: ATV, ATV/cobicistat, ATV/ritonavir, efavirenz, etravirine, nevirapine, and tipranavir were not permitted for use in OBR.

The primary endpoint was the proportion of participants who achieved a ≥0.5-log_{10} c/mL reduction in HIV-1 RNA from baseline to the end of the functional monotherapy phase in the randomized cohort. Secondary endpoints included the percentage of participants in the randomized cohort with HIV-1 RNA <50 c/mL and <200 c/mL at Week 26.[2]
Baseline characteristics are provided in Table 1.[2,3] Twenty-two percent of all participants (16/72) did not have changes in their OBR before they entered the open-label maintenance phase; the ARV classes and agents that comprised the failing regimen and OBR are shown in Table 2.[6]

Table 1. CAPELLA Study: Baseline Demographics and Disease Characteristics[2,3]

Key Demographics and Characteristics[a]		Randomized Cohort		Non-Randomized Cohort	Total (N=72)
		LEN (n=24)	PBO (n=12)	LEN (n=36)	
Age, median (range), years		55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Female at birth, n (%)		7 (29)	3 (25)	8 (22)	18 (25)
Race or ethnicity,[b] n (%)	White	12 (50)	4 (36)	13 (36)	29 (41)
	Black	10 (42)	6 (55)	11 (31)	27 (38)
	Asian	2 (8)	1 (9)	12 (33)	15 (21)
	Data could not be collected	0	1 (9)	0	1 (1)
	Hispanic/Latinx ethnicity	6 (25)	4 (36)	5 (14)	15 (21)
Viral load[c]	HIV RNA, mean ± SD, log_{10} c/mL	3.97±0.92	4.87±0.39	4.06±1.16	4.17±1.03
	HIV 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)
	>100,000 c/mL, n (%)	1 (4)	6 (50)	7 (19)	14 (19)
CD4 count	Mean ± SD, cells/µL	199±166	85±63	258±273	210±224
	Median (range), cells/µL	172 (16–827)	85 (6–237)	195 (3–1296)	150 (3–1296)

Key Demographics and Characteristics[a]		Randomized Cohort		Non-Randomized Cohort	Total (N=72)
		LEN (n=24)	PBO (n=12)	LEN (n=36)	
Distribution, n (%)	<50 cells/µL	3 (12)	4 (33)	9 (25)	16 (22)
	50 to <200 cells/µL	13 (54)	7 (58)	10 (28)	30 (42)
	200 to <500 cells/µL	7 (29)	1 (8)	12 (33)	20 (28)
	≥500 cells/µL	1 (4)	0	5 (14)	6 (8)
Prior ARV regimens, median (range), n		9 (2–24)	9 (3–22)	13 (3–25)	11 (2–25)
Known resistance to ≥2 drugs in class, n (%)	NRTI	23 (96)	12 (100)	36 (100)	71 (99)
	NNRTI	22 (92)	12 (100)	36 (100)	70 (97)
	PI	20 (83)	8 (67)	30 (83)	58 (81)
	INSTI	20 (83)	7 (58)	23 (64)	50 (69)
	All four major classes	14 (58)	3 (25)	16 (44)	33 (46)
Resistance to entry inhibitors, n/N (%)	MVC	19/24 (79)	8/11 (73)	14/26 (54)	41/61 (67)
	IBA	8/23 (35)	3/10 (30)	6/25 (24)	17/58 (29)
	FTR	5/23 (22)	5/10 (50)	7/21 (33)	17/54 (31)
	T20	2/23 (9)	3/10 (30)	0/25 (0)	5/58 (9)

[a]Percentages may not equal 100 due to rounding.
[b]Race was reported by the participants. Collection of race or ethnicity data was prohibited by local regulators for 1 participant in the PBO group and was excluded from the denominator of the percentage calculation.
[c]Two participants in the non-randomized cohort had HIV-1 RNA >400 c/mL at screening but <50 c/mL at enrollment.

Table 2. CAPELLA Study: Composition of Failing Regimens and OBR[7]

		Failing Regimen (N=72)	OBR (N=72)
Drug class/agent, %	NRTI	82	85
	INSTI	68	65
	PI	63	63
	NNRTI	31	33
	IBA	19	24
	MVC	14	14
	FTR	6	11
	T20	6	7
Number of fully active ARV agents, 0/1/≥2, %		42/36/22	17/38/46
OSS,[a] median		1	2

Abbreviation: OSS=overall susceptibility score.
[a]OSSs were calculated with a proprietary algorithm (Monogram Biosciences Inc.), and investigators provided data for scoring from historical resistance reports. An OSS of 1 indicated full susceptibility, 0.5 indicated partial susceptibility, and 0 indicated no susceptibility. The OSS of the OBR was the sum of the individual scores.

Baseline resistance analyses[8]

The study enrolled participants who had resistance to ≥2 ARVs in ≥3 of the four main ARV classes (NRTIs, NNRTIs, PIs, and INSTIs). Baseline resistance in these participants was assessed using genotypic and phenotypic assays (Monogram Biosciences) at screening or historical data provided by the investigators. Baseline HIV-1 capsid genotypic and phenotypic analyses were also performed. Table 3 summarizes the proportion of participants who had RAMs according to ARV class and the mean number of RAMs per ARV class. Table 4 summarizes the rates of baseline resistance to ARV classes according to study cohort and in the overall study population. At baseline, no RAMs associated with LEN resistance (eg, L56I, M66I, Q67H, K70N, K74D/S, and T107N) were found in the 62 participants for whom these data were available.

Table 3. CAPELLA Study: RAMs per ARV Class at Baseline[8]

	NRTI	NNRTI	PI	INSTI
Participants with RAMs, %	99	94	83	67
RAMs per ARV class, mean number per participant	3.8	2.4	4.1	1.3

Table 4. CAPELLA Study: Baseline Resistance to NRTI, NNRTI, PI, and INSTI Classes by Cohort and in the Overall Population[8,9]

Resistance[a] to ARV Class (Yes/No)				Participants, n (%)		
NRTI[b]	NNRTI	PI	INSTI	Randomized Cohort (n=36)	Non-Randomized Cohort (n=36)	Overall (N=72)
✓	✓	✓	✓	17 (47)	16 (44)	33 (46)
✓	✓	✓	–	9 (25)	13 (36)	22 (31)
✓	✓	–	✓	8 (22)	5 (14)	13 (18)
✓	–	✓	✓	2 (6)	0	2 (3)
–	✓	✓	✓	0	1 (3)	1 (1)
–	✓	–	✓	0	1 (3)[c]	1 (1)

[a]Resistance to ≥2 ARVs in the class. To be eligible for the study, participants had to have resistance to ≥2 ARVs from ≥3 of the four classes noted above.
[b]For this study, M184V/I alone was not sufficient to fulfill the NRTI resistance criteria.
[c]This participant had three-class resistance in the presence of NRTI mutation M184V/I only, which was not sufficient to fulfill the NRTI resistance criteria in this study.

Post-baseline resistance analyses[6,8-10]

An analysis of all participants with inadequate adherence to OBR was not conducted.

Post-baseline resistance analyses were conducted in participants with suboptimal virologic response (HIV RNA ≥50 c/mL and <1-$\log_{10}$ decrease in HIV RNA from LEN initiation; assessed at Week 4), virologic rebound (after suppression, HIV RNA ≥50 c/mL or >1-$\log_{10}$ increase from nadir), or viremia at their last visit.

Through Week 52, 11 participants from the randomized cohort were included in the post-baseline resistance analysis population. Of these 11 participants, 4 developed CAI resistance (LEN, n=1; PBO, n=3; Table 5). All 4 participants were receiving functional LEN monotherapy due to either a lack of active agents in the OBR or inadequate adherence to the OBR (Table 6).

Through Week 52, 10 participants from the non-randomized cohort were included in the post-baseline resistance analysis population. Of these 10 participants, 5 developed CAI resistance (Table 6). All 5 participants were at high risk of emergent LEN resistance due to either a lack of fully active drugs in the OBR or inadequate adherence to the OBR (Table 6).

All 9 participants with emergent LEN resistance remained on LEN, and 4 of these participants were resuppressed at a later visit (OBR was changed in 2 participants).

Table 5. CAPELLA Study: Emergent LEN Resistance Through Week 52[6]

	Randomized Cohort (n=36)	Non-Randomized Cohort (n=36)
Participants who met criteria for resistance testing, n (%)	11 (31)	11 (31)
Participants with available data, n (%)	11 (31)	10 (28)

	Randomized Cohort (n=36)	Non-Randomized Cohort (n=36)
Emergent CAI resistance,[a] n (%)	4 (11)	5 (14)
M66I, n	4	2
A105S/T, n	3	1
N74D, n	3	0
K70H/N/R/S, n	1	3
Q67H/K/N, n	1	3
T107A/C/N, n	1	3

[a]Developed during the maintenance period.

Table 6 describes the 5 participants in the analysis with OBR adherence issues. Additionally, there were participants in the post-baseline resistance analysis population who developed resistance due to not having fully active ARVs in OBR.

Table 6. CAPELLA Study: Participants With CAI Resistance and OBR Adherence Issues (Week 52 Interim Analysis)[6,8-10]

Pt.	First Visit With CAI Resistance (CAI RAMs)	LEN Susceptibility: Fold Change from WT	Number of Fully Active Agents in OBR	Cohort	Comments
1	Week 26 (M66I)	138	3	R	• Functional LEN monotherapy[a] • Incoming ARVs: DRV/c (fully active), FTC (not active), and TAF (partially active) • OBR: DRV/c, DTG twice daily, and RPV • An adherence issue was noted with OBR. DTG levels were <LLOQ, and DRV levels were inconsistent
2	Week 4 (M66M/I, K70K/S)	Not determined	2	R	• Functional LEN monotherapy[a] • Incoming ARVs: DRV/r, DTG, and 3TC (not active) • OBR: DRV/r twice daily, DTG twice daily, and TDF • An adherence issue was noted with OBR. DRV/r and DTG were both fully active, but drug levels were <LLOQ. TDF was partially active • Pt achieved HIV RNA <50 c/mL between Weeks 24 and 32, and this was maintained through Week 56

Pt.	First Visit With CAI Resistance (CAI RAMs)	LEN Susceptibility: Fold Change from WT	Number of Fully Active Agents in OBR	Cohort	Comments
3	Week 10 (K70H, A105A/S/T, T107T/N)	265	2	NR	• Functional LEN monotherapy[a] • Incoming ARVs: DRV/c (fully active), FTC (partially active), and TAF (partially active) • OBR: DRV/r twice daily, DTG twice daily through Week 24; after Week 24 DOR/3TC/TDF was added • An adherence issue was noted with OBR. DTG and DRV levels were <LLOQ • Pt did not achieve HIV RNA <50 c/mL through Week 56
4	Week 4 (Q67H, K70R)	15	3	NR	• Functional LEN monotherapy[a] • Incoming ARVs: DRV/r twice daily (partially active) and DTG twice daily (fully active) • OBR: DRV/r twice daily, DTG twice daily through Week 24; after Week 24 DOR/3TC/TDF was added • An adherence issue was noted with OBR: DTG and DRV levels were <LLOQ
5	Week 52 (Q67H)	Not reported	Not reported	NR	• Pt was at high risk of emergent LEN resistance due to inadequate adherence to OBR

Abbreviations: 3TC=lamivudine; DOR=doravirine; DRV=darunavir; DRV/c=darunavir/cobicistat; DRV/r=darunavir/ritonavir; DTG=dolutegravir; FTC=emtricitabine; LLOQ=lower level of quantification; NR=non-randomized; Pt=participant; R=randomized; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.
[a]Developed during the maintenance period.

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Abbreviations

ARV=antiretroviral
BIC=bictegravir
c/mL=copies per mL
CAI=capsid protein inhibitor
CD4=clusters of differentiation 4
FTR=fostemsavir
HTE=heavily treatment-experienced
IBA=ibalizumab
INSTI=integrase strand transfer inhibitor
LEN=lenacapavir
MVC=maraviroc
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
OBR=optimized background regimen
PBO=placebo
PI=protease inhibitor
PWH=people with HIV
RAM=resistance-associated mutation
T20=enfuvirtide

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Sunlenca US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.

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