EPB240

Resistance Analysis of Long-Acting Lenacapavir in Highly Treatment-Experienced People With HIV After 52 Weeks of Treatment

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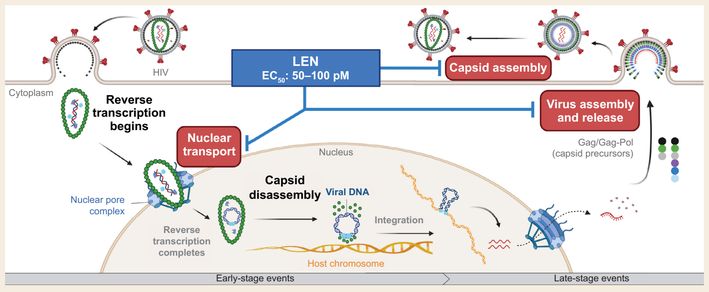
Introduction

Lenacapavir Targets Multiple Stages of HIV Replication Cycle[1,2]

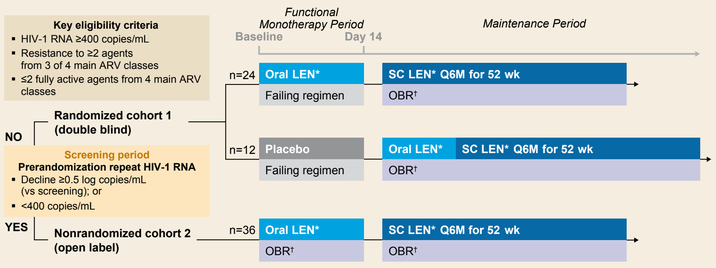


EC_{50}, half-maximal effective concentration; Gag, group-specific antigen; LEN, lenacapavir; Pol, polymerase.

LEN: Long-Acting Inhibitor of HIV-1 Capsid

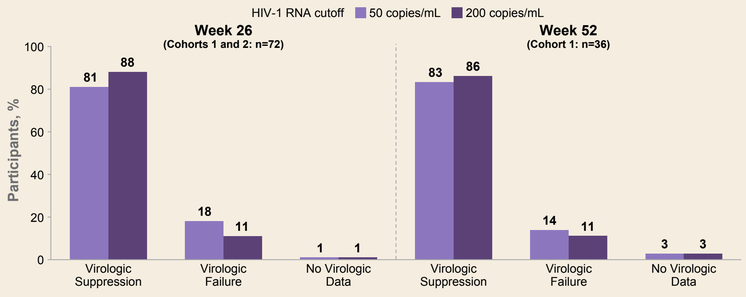
- Highly potent activity (EC_{50}: 50–100 pM), with low clearance and slow release kinetics[1]
  - Can be administered orally (daily or weekly) or subcutaneously (SC) every 6 months (Q6M)[3-5]
- Fully active against HIV with resistance to existing antiretroviral (ARV) classes (nucleoside reverse transcriptase inhibitors [NRTIs], non-NRTIs [NNRTIs], protease inhibitors [PIs], integrase strand transfer inhibitors [INSTIs], and entry inhibitors)[1,6,7]
- In vitro selected resistance-associated mutations (RAMs; L56I, M66I, Q67H, K70N, N74D/S, and T107N) had low replication capacity, except Q67H[1,8]
- In viremic heavily treatment-experienced people with HIV (PWH) with multidrug resistance (CAPELLA study; ClinicalTrials.gov NCT04150068[9-11]), LEN in combination with an optimized background regimen (OBR) led to 83% (n=30/36) virologic suppression at Week 52[12]
- In treatment naïve PWH (CALIBRATE study; ClinicalTrials.gov NCT04143594)[13,14]:
  - SC LEN, initially in combination with emtricitabine (FTC)/tenofovir alafenamide (F/TAF) and later with oral TAF or bictegravir (BIC), was well tolerated, and achieved and maintained high rates of virologic suppression through 1 year (90% and 85%, respectively)
  - Oral LEN in combination with F/TAF had similar efficacy (85%)

CAPELLA Study Design[9-11]



*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, and 300 mg on Day 22 for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15; †Investigational agents, such as fostemsavir (FTR), were allowed; atazanavir (ATV), ATV/cobicistat (c), ATV/ritonavir (r), efavirenz, entecavir, nevirapine, and tipranavir were not allowed.

Efficacy Through Weeks 26 and 52[12]

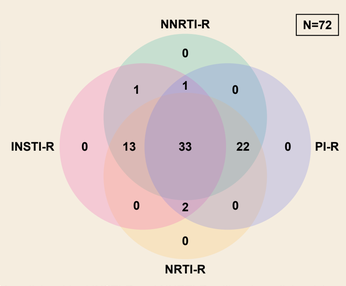


- Durable efficacy through Week 52
- Cohort 1 (randomized): mean increase in CD4 of 83 cells/μL at Week 52
- Cohort 2 (nonrandomized): mean increase in CD4 of 98 cells/μL at Week 26

Baseline Class Resistance[15]

4 Main ARV Classes

Resistance Within Classes				Participants, n (%)		
NRTI*	NNRTI	PI	INSTI	Cohort 1 n=36	Cohort 2 n=36	All 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)	1 (1)†



*M184V/I alone was not sufficient to fulfill NRTI-resistance (R) criteria in study; †1 participant had INSTI-R and NNRTI-R, with only partial resistance to 1 NRTI (didanosine) in presence of M184V/I (FTC-R and lamivudine [3TC]-R not counting in total NRTI-R when M184V/I was present per protocol requirement).

- **Entry Criteria:** resistance to ≥2 ARVs in ≥3 of 4 main ARV classes
- Nearly half of all participants had resistance to all 4 classes

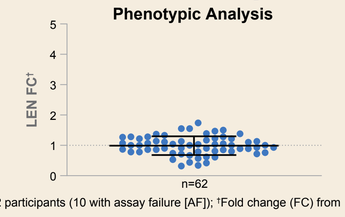
Absence of Baseline Resistance to Lenacapavir[15]

Genotypic Analysis

Participants With LEN RAMs*

L56I	M66I	Q67H	K70N	N74D/S	T107N
0	0	0	0	0	0

Phenotypic Analysis



*Mutations identified during in vitro resistance selections[1]; data available for 62 participants (10 with assay failure [AF]); †Fold change (FC) from wild-type control.

- Evaluated with PhenoSense® Gag-Pro (Monogram Biosciences, South San Francisco, California, USA)
  - No LEN-R mutations detected
  - Wild-type LEN phenotypic susceptibility: mean FC = 1.0 (range 0.3–1.7)

Objective

- To describe the resistance analyses conducted through Week 52 in CAPELLA

Methods

Virologic Failure (VF) Criteria

- Suboptimal virologic response: confirmed HIV-1 RNA ≥50 copies/mL and <1-log_{10} ↓ from LEN start (assessed at Week 4)
- Virologic rebound: after suppression, confirmed HIV-1 RNA ≥50 copies/mL or >1-log_{10} ↑ from nadir
- Viremia at last visit

On-Treatment Resistance Analyses: Participants With VF

- Initial or confirmatory VF visit analyzed for capsid protein (CA) resistance: PhenoSense Gag-Pro (genotypic and phenotypic assay) and alternate deep-sequencing assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) used for retest samples
- Confirmatory VF visit analyzed for protease (PR), reverse transcriptase (RT), and integrase (IN) resistance: PhenoSense GT, GenoSure® MG, PhenoSense Integrase, and GeneSeq® Integrase (Monogram)
- Drug plasma concentrations measured using liquid chromatography–tandem mass spectrometry

Results

Postbaseline Resistance Analysis

Week 52 Interim Analysis

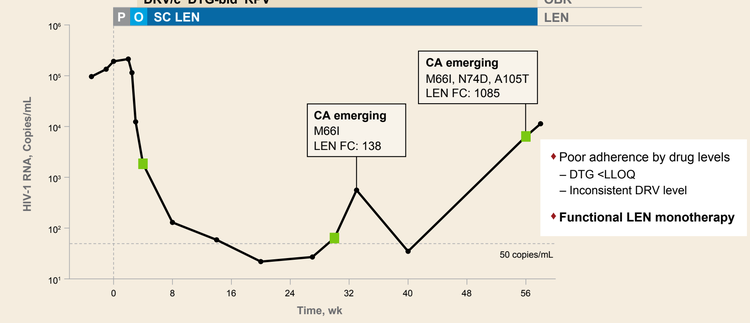
Resistance Category, n (%)	Cohort 1: n=36	Cohort 2: n=36	All: N=72
Resistance analysis population	11 (31)	10 (28)	21 (29)
With data	11 (31)	9 (25)	20 (28)
Resuppressed <50 copies/mL	4 (11)	4 (11)	8 (11)
With CA-R emerging	4 (11)	4 (11)	8 (11)
M66I, n	4	2	6
Q67H/K/N, n	1	2	3
K70H/N/R/S, n	1	3	4
N74D, n	3	0	3
A105S/T, n	3	1	4
*T107A/C/N, n**	1	3	4
No CA-R emergence	7 (19)	5 (14)	12 (17)

*1 participant had emergent T107A mutation in CA with no loss in LEN susceptibility before achieving HIV-1 RNA suppression; participant was not categorized as having CA-R emergence.

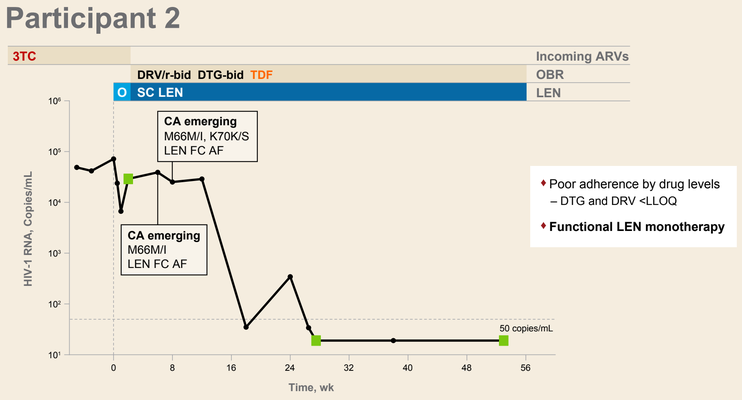
- 21 of 72 participants were analyzed for resistance
- 8 of 72 participants had CA-R emerging by Week 52, with no change since Week 26 interim analysis

Viral Response and Resistance: OBR Adherence Issue*

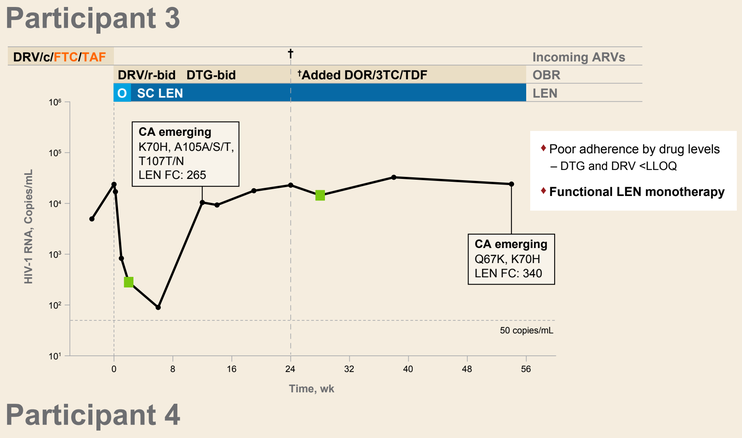
Participant 1



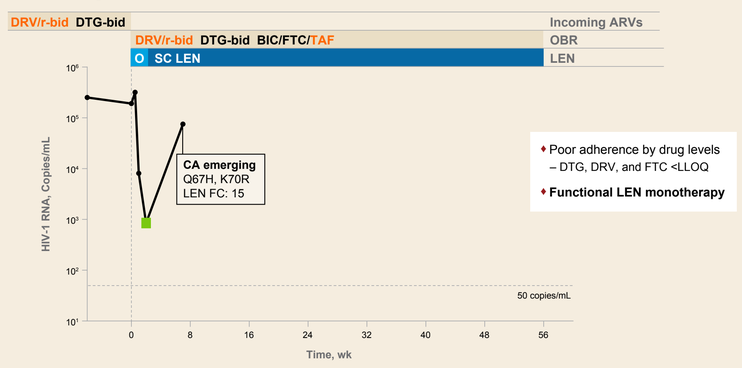
Participant 2



Participant 3



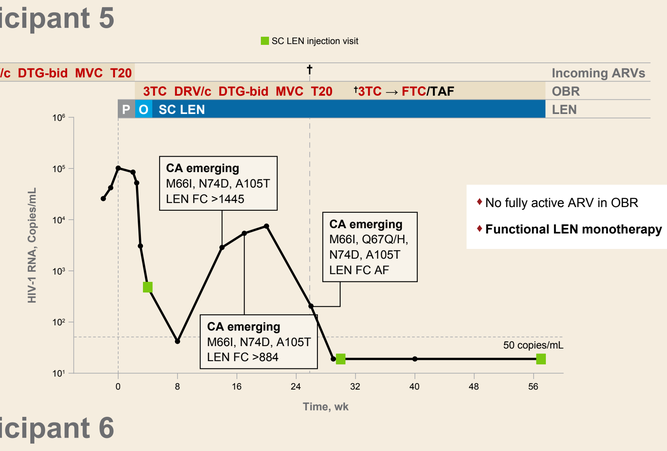
Participant 4



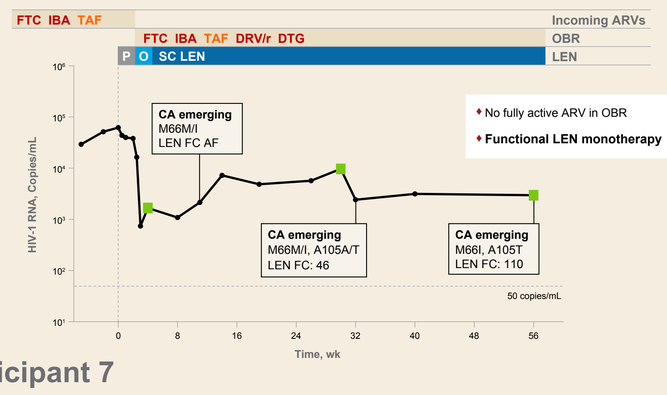
*Drugs in ***red*** are not active (overall susceptibility score [OSS]: 0); drugs in ***orange*** are partially active (OSS: 0.5); drugs in ***black*** are fully active (OSS: 1). DOR, doravirine; DRV, darunavir; DTG, dolutegravir; LLOQ, lower limit of quantification; O, oral; P, placebo; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

Viral Response and Resistance: No Fully Active ARV in OBR*

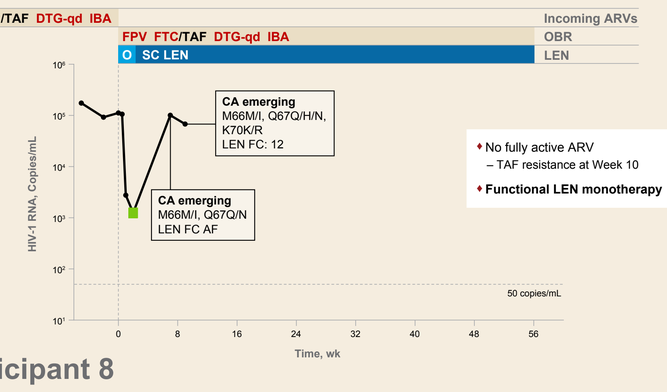
Participant 5



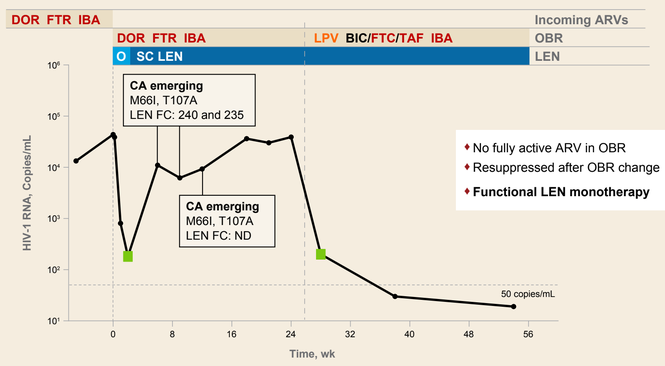
Participant 6



Participant 7



Participant 8



*Drugs in ***red*** are not active (OSS: 0); drugs in ***orange*** are partially active (OSS: 0.5); drugs in ***black*** are fully active (OSS: 1). FPV, fosamprenavir; IBA, ibalizumab; LPV, lopinavir; MVC, maraviroc; ND, not determined; T20, enfuvirtide.

Summary of Participants With CA Resistance

Participant	1st Visit With CA-R	CA RAMs	LEN FC	No. of Fully Active Drugs	Reason for Functional LEN Monotherapy
1	Week 26	M66I	138	3	OBR adherence issue*
2	Week 4	M66M/I, K70K/S	ND	2	
3	Week 10	K70H, A105A/S/T, T107T/N	265	2	
4	Week 4	Q67H, K70R	15	3	
5	Week 10	M66I, N74D, A105T	>1445	0	No fully active ARVs in OBR
6	Week 4	M66M/I	46	0	
7	Week 4	M66M/I, Q67Q/H/N, K70K/R	12	1†	
8	Week 4	M66I, T107A	240	0	

*Adherence based on drug plasma concentrations; †TAF was fully active at baseline (PhenoSense GT), but was inactive at Week 10 (GenoSure).

Conclusions

- In heavily treatment-experienced PWH with baseline multidrug resistance:
  - LEN + OBR led to durable high rates of virologic suppression (83%) and increases in CD4 count through Week 52
  - LEN was well tolerated, with no adverse events leading to discontinuation
- Postbaseline emergence of LEN RAMs was observed in 8 of 72 participants
- All 8 cases with LEN RAM emergence were associated with functional LEN monotherapy at the time of resistance emergence
- Absence of postbaseline emergence of LEN RAMs was observed in 12 of 72 participants with viremia
- Minimal emergence of resistance to OBR drugs was observed, with no adverse virologic effects (participants resuppressed after OBR drug-resistance emergence)

References: **1.** Link JO, et al. Nature 2020;584:614-8; **2.** Zila V, et al. Cell 2021;184:1032-46; **3.** Begley R, et al. AIDS 2020, abstr PEB0265; **4.** Begley R, et al. CROI 2020, abstr 470; **5.** Daar EM, et al. CROI 2020, poster 3691; **6.** Margot N, et al. Antimicrob Agents Chemother 2021;65:e02057-20; **7.** Margot N, et al. CROI 2022, abstr 508; **8.** Margot N, et al. J Antimicrob Chemother 2022;77:989-995; **9.** Molina J-M, et al. IAS 2021, abstr OALX01LB02; **10.** Segal-Maurer S, et al. CROI 2021, abstr 127; **11.** Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803; **12.** Ogbuagu O, et al. CROI 2022, abstr 1047; **13.** Gupta SK, et al. CROI 2022, abstr 138; **14.** Gupta SK, et al. IAS 2021, abstr OALB0302; **15.** Margot N, et al. EACS 2021, oral OS1/1.

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