EPB239

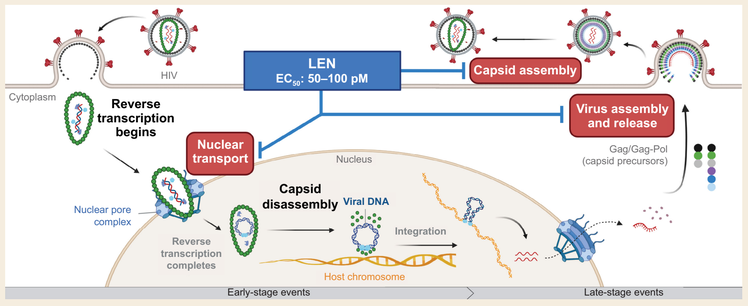
Resistance Analysis of Long-Acting Lenacapavir in Treatment-Naïve People With HIV at 54 Weeks

Laurie A. VanderVeen, Nicolas Margot, Vidula Naik, Hadas Dvory-Sobol, Martin S. Rhee, Christian Callebaut — Gilead Sciences, Inc., Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

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

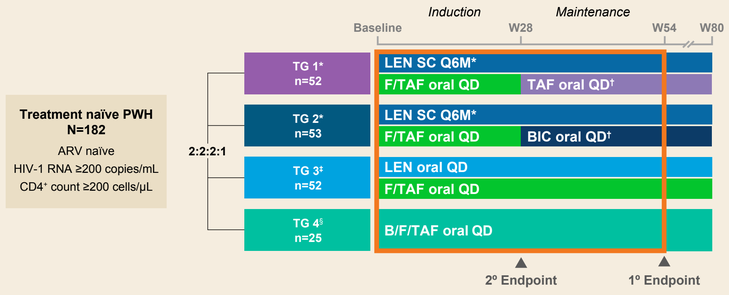


EC_{50}, half-maximal effective concentration; Gag, group-specific antigen; LEN, lenacapavir; Pol, polymerase.

Long-Acting Inhibitor of HIV-1 Capsid

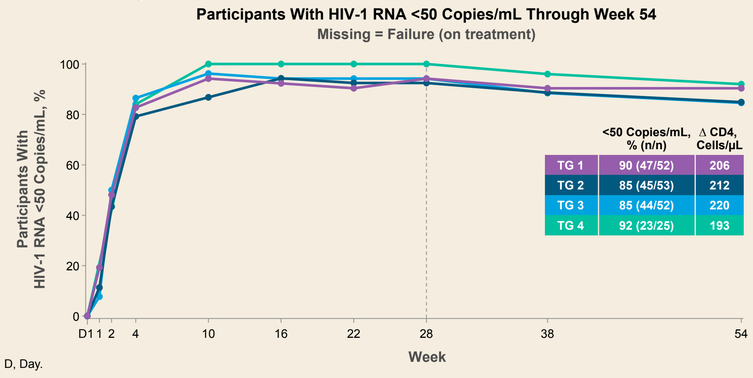
- Highly potent activity (EC_{50}: 50–100 pM), with low clearance and slow release kinetics[1]
  - Can be administered orally (daily or weekly) or subcutaneously (SC) every 6 months (Q6M)[3-5]
- In vitro selected resistance-associated mutations (RAMs; L56I, M66I, Q67H, K70N, N74D/S, and T107N) had low replication capacity (RC), except Q67H[1]
- In viremic heavily treatment-experienced people with HIV (PWH) with multidrug resistance (CAPELLA study; ClinicalTrials.gov NCT04150068[6,7]):
  - LEN in combination with an optimized background regimen led to 83% (n=30/36) virologic suppression at Week 52[8]
- In treatment-naïve PWH (CALIBRATE study; NCT04143594):
  - SC LEN, initially in combination with emtricitabine (FTC)/tenofovir alafenamide (TAF; F/TAF) and later with oral TAF or bictegravir (B or BIC), achieved and maintained high rates of virologic suppression through 1 year (90% and 85%, respectively)[9,10]
  - Oral LEN in combination with F/TAF had similar efficacy (85%)

CALIBRATE Phase 2 Study Design[9]



*LEN oral lead-in (600 mg on Days 1 and 2, and 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF 200/25 mg; †Participants needed HIV-1 RNA <50 copies/mL at Weeks 16 and 22 to initiate TAF 25 mg or BIC 75 mg at Week 28; participants with HIV-1 RNA ≥50 copies/mL discontinued study at Week 28; 3 participants (2 in treatment group [TG] 1 and 1 in TG 2) discontinued due to having HIV-1 RNA ≥50 copies/mL prior to Week 28; ‡LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; §B/F/TAF 50/200/25 mg. ARV, antiretroviral; CD4, cluster of differentiation-4; QD, once daily; W, week.

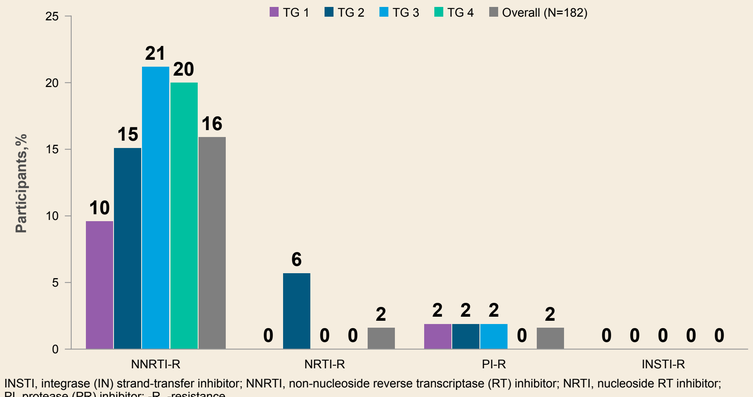
Efficacy at Week 54[9]



D, Day.

- Durable efficacy through Week 54
- Among TG 1 and 2 participants with HIV-1 RNA <50 copies/mL at Week 28, 94% (46/49) and 92% (45/49), respectively, maintained virologic suppression at Week 54

Preexisting Baseline Resistance to 4 Main ARV Classes[11]

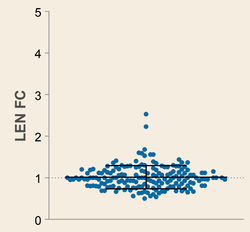


INSTI, integrase (IN) strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase (RT) inhibitor; NRTI, nucleoside RT inhibitor; PI, protease (PR) inhibitor; -R, -resistance.

- Most common NNRTI-R mutations were K103N/S (8%), followed by E138A/G/K/Q/R (4%)
- Primary NRTI-R mutations were thymidine analogue mutations

No Observed Baseline Resistance to LEN[11]

LEN RAM*	L56I	M66I	Q67H	K70N	N74D/S	T107N
Participants with RAM, n of 182	0	0	0	0	0	0



*Mutations identified during in vitro resistance selections.[1] FC, fold-change from wild-type (WT).

- No LEN RAMs detected in baseline samples
- WT susceptibility to LEN: mean EC_{50} FC: 1.0 (range: 0.5–2.5; data available for 175 participants)

Objective

- To describe resistance analyses in the CALIBRATE study in treatment-naïve PWH through the primary endpoint at Week 54

Methods

- Resistance analysis population:
  - Suboptimal virologic response: confirmed HIV-1 RNA ≥50 copies/mL and <1-log_{10} reduction from Day 1 at Week 10
  - Virologic rebound: confirmed HIV-1 RNA ≥50 copies/mL after achieving HIV-1 RNA <50 copies/mL or >1-log_{10} increase from nadir
  - HIV-1 RNA ≥50 copies/mL at last visit
- On-treatment resistance analyses:
  - Initial or confirmatory virologic failure visit analyzed for capsid protein (CA) resistance
    - Gag-Pro assay (genotypic and phenotypic assay, Monogram Biosciences, South San Francisco, CA)
    - Alternative deep-sequencing assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) used for retest samples and additional analyses
  - Confirmatory virologic failure visit analyzed for RT, PR, and IN resistance
    - PhenoSense® GT, GeneSeq® Integrase, and PhenoSense Integrase (Monogram)
- Drug plasma concentrations measured using liquid chromatography–tandem mass spectrometry
- In vitro infectious models:
  - Gag-PR fragments from clinical samples with CA-R mutations and corresponding site-directed mutants (SDMs) were cloned into the pXXLAI HIV molecular clone, followed by transfection into 293T cells
  - Viral supernatants were used in infection assays in the MT-2 cell line
  - Outputs included FC in LEN susceptibility and RC

Results

Resistance Analysis Population at Week 54

Participants, n (%)	TG 1 LEN SC + F/TAF (→TAF) n=52	TG 2 LEN SC + F/TAF (→BIC) n=53	TG 3 LEN Oral + F/TAF n=52	TG-4 B/F/TAF n=25	TG 1+2+3 Pooled LEN Groups n=157
Met resistance testing criteria	1 (2)	1 (2)	3 (6)	1 (4)	5 (3)
Later resuppressed*	1 (2)	0	2 (4)	1 (4)	3 (2)
With emergent LEN-R	0	1 (2)†	1 (2)	0	2 (1)
With emergent NRTI-R	0	1 (2)†	0	0	1 (<1)
With emergent INSTI-R	0	0	0	0	0

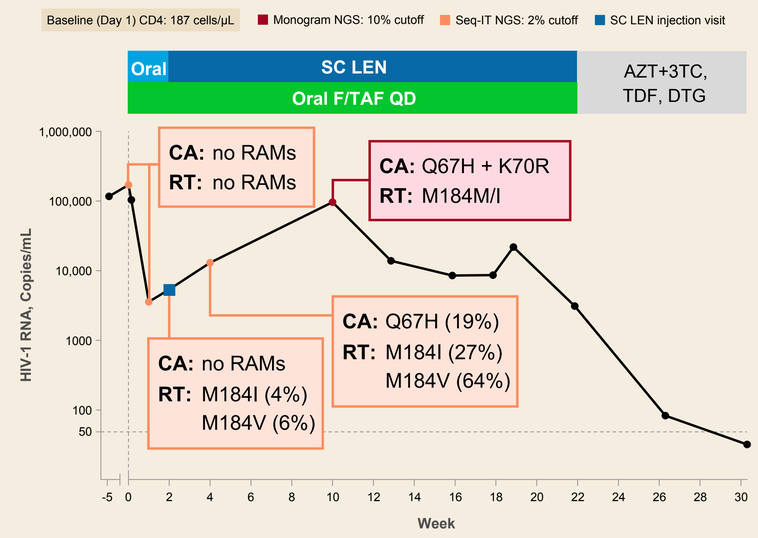
*Resuppressed HIV-1 RNA <50 copies/mL in absence of emergent resistance, while maintaining study drugs; †Single participant with LEN-R and NRTI-R.

- Emergent LEN-R in 2/157 participants (1.3%) receiving LEN
- No resistance development in TG 1 or 2 during maintenance period following switch from 3- to 2-drug regimen

Participants With Emergent Resistance Through Week 54

Participant	Time of Virology Analysis	LEN RAMs Q67	LEN RAMs K70	NRTI RAMs M184	Regimen at Time of LEN-R LEN	Regimen at Time of LEN-R F/TAF
1 (in TG 2)	Week 10	H	R	M/I	SC Q6M	Oral QD
2 (in TG 3)	Week 54	H	—	—	Oral QD	Oral QD

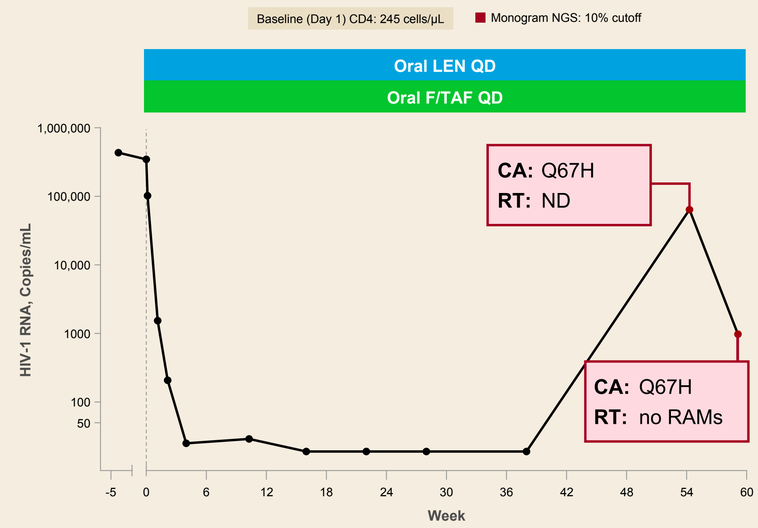
Participant 1 (in TG 2): M184I/V in RT Was First Mutation to Develop*



*Previously presented data[10,11]; †Lower bound of confidence interval above inhibitory quotient-4 (IQ4) based on protein-adjusted 95% effective concentration ($paEC_{95}$) from MT-4 cells; 3.87 ng/mL = IQ1; pharmacokinetic (PK) time points: predose and 1 h postdose on Days 1, 2, and 8, predose on Day 15, and single anytime on Day 5, and Weeks 4, 10, and 16. 3TC, lamivudine; AZT, zidovudine; DTG, dolutegravir; NGS, next-generation sequencing; TDF, tenofovir disoproxil fumarate.

- Directly observed therapy for LEN dosing
  - No missed LEN doses
  - Oral F/TAF dosing observed on Days 1, 2 and 8 only
- Plasma LEN concentrations were consistently in target range†
- Pattern of mutation emergence suggests incomplete adherence to F/TAF

Participant 2 (in TG 3): Emergent LEN Resistance at Week 54



*Lower bound of confidence interval above IQ4 based on $paEC_{95}$ from MT-4 cells; 3.87 ng/mL = IQ1; PK time points: single anytime on Days 1, 2, 5, 8, and 15, and Weeks 4, 10, 16, 22, 28, 38, and 54. ND, not determined.

- Poor adherence by pill count and drug levels at time of resistance emergence
  - Plasma LEN concentrations detected below target range*
  - Plasma tenofovir (TAF) <LLOQ

Phenotypic Characterization of LEN RAMs

Sample	Visit	LEN RAMs Q67	LEN RAMs K70	LEN FC in MT-2*	LEN FC in Gag-Pro*	RC in Gag-Pro (% WT)†
Clinical isolates						
1	Baseline	—	—	2.6	1.2	146
	Week 10	H	R	13	20	63
2	Baseline	—	—	0.9	1.0	163
	Week 54	H	—	12.8	7	49
SDMs						
SDM		H	—	7.7	4.8	58
SDM		—	R	ND	ND	9.7

*Ratio of mutant/WT EC_{50}; †Percentage of reference strain.

Conclusions

- In treatment-naïve PWH, LEN (with an oral lead-in and Q6M SC injections or an oral daily pill) in combination with other ARVs led to high rates of virologic suppression similar to B/F/TAF at 1 year
- Emergent resistance through 1 year of treatment was infrequent (1.3%) in participants receiving SC or oral LEN with other ARVs
  - Cases of treatment-emergent LEN resistance occurred in participants with likely or confirmed incomplete adherence to oral ARVs and were associated with functional LEN monotherapy
- These data support the ongoing evaluation of LEN in combination or coformulation with other ARVs 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; **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.** Molina J-M, et al. IAS 2021, abstr OALX01LB02; **7.** Segal-Maurer S, et al. CROI 2021, abstr 127; **8.** Ogbuagu O, et al. CROI 2022, abstr 1047; **9.** Gupta SK, et al. CROI 2022, abstr 138; **10.** Gupta SK, et al. IAS 2021, abstr OALB0302; **11.** VanderVeen L, et al. IDWeek 2021, oral 73.

Acknowledgments: We are grateful to all the individuals who participated in this trial, and their partners and families. Participating study investigators and their study teams: *Dominican Republic*: E Koenig; *USA*: P Benson, DS Berger, M Berhe, C Brinson, P Cook, DR Coulston, GE Crofoot, FA Cruickshank, D Cunningham, E DeJesus, C Dietz, V Drelichman, E Gardner, A Gaur, D Goldstein, SK Gupta, D Hagins, R Hengel, T Hodge, C-B Hsiao, A Khalsa, CA Kinder, P Kumar, C McDonald, A Mills, JO Morales-Ramirez, C Newman, G Oguchi, O Osiyemi, MN Ramgopal, PJ Ruae, W Sanchez, JL Santana-Bagur, L Santiago, A Scribner, J Sims, GI Sinclair, JL Stephens, M Wohlfeile, AK Wurapa. We also thank Monogram Biosciences for resistance analyses and Seq-IT for sequence analyses. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, New York, USA, funded by Gilead.