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

Long-Acting Lenacapavir in a Combination Regimen for Treatment Naïve PWH: Week 80

Debbie Hagins,[1]* Ellen Koenig,[2] Rachel Safran,[3] Lizette Santiago,[4] Michael Wohlfeiler,[5] Chiu-Bin Hsiao,[6] Shan-Yu Liu,[7] Laurie A. VanderVeen,[7] Hadas Dvory-Sobol,[7] Martin S. Rhee,[7] Jared Baeten,[7] Samir Gupta[8]

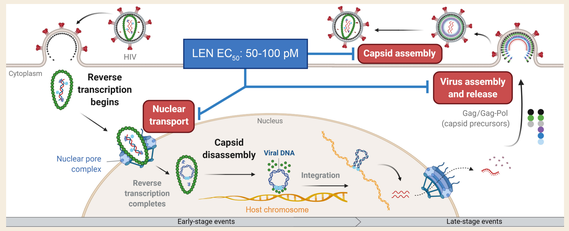
[1]Chatham County Health Department, Savannah, GA; [2]IDEV: Instituto Dominicano de Estudios Virologicos, Santo Domingo, Dominican Republic; [3]MultiCare Rockwood Internal Medicine & HIV Clinic, Spokane, WA; [4]Hope Clinical Research, Inc., San Juan, PR; [5]AIDS Healthcare Foundation-South Beach, Miami Beach, FL; [6]Allegheny Health Network, Pittsburgh, PA; [7]Gilead Sciences, Inc., Foster City, CA; [8]Indiana University-Purdue University, Indianapolis, IN

*Presenting author.

Introduction

- Lenacapavir (LEN) is a novel, highly potent, long-acting, first-in-class inhibitor of the HIV-1 capsid protein approved in Canada, the EU, and the US for the treatment of HIV-1 infection in adults with multidrug resistance in combination with other antiretrovirals[1-3]
  - Can be administered SC (2 x 1.5 mL [927 mg] in abdomen Q6M) or orally (daily or weekly)[4-6]
  - In development as a long-acting agent for treatment and prevention of HIV
- CALIBRATE (NCT04143594) is an ongoing, Phase 2, open-label, active-controlled study designed to generate exploratory clinical data to support the future development of LEN-containing regimens
- At the Week 54 primary endpoint, SC LEN Q6M or oral LEN QD in combination with oral tenofovir alafenamide (TAF), bictegravir (BIC; B), or emtricitabine (F)/TAF maintained high rates of virologic suppression (90%, 85%, and 85%, respectively) and was generally well tolerated[7]

Lenacapavir Inhibits Multiple Stages of HIV Replication Cycle[8,9]



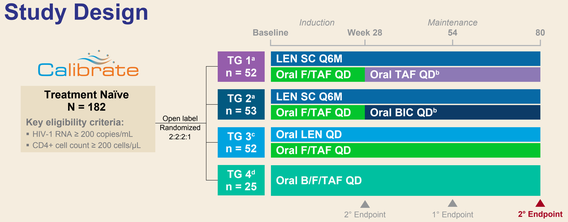
EC_{50} = half-maximal effective concentration; Gag = group-specific antigen; Pol = polymerase.

Objectives

- To report the secondary efficacy endpoint and safety at Week 80

Methods

Study Design



[a]LEN PO lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN 927 mg SC on Day 15; F/TAF 200/25 mg; [b]Participants in treatment groups (TGs) 1 and 2 needed to have 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 TG 1 and 1 in TG 2) discontinued due to having HIV-1 RNA ≥ 50 copies/mL prior to Week 28; [c]LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; [d]B/F/TAF 50/200/25 mg.

- There were no prespecified formal statistical comparisons between TGs

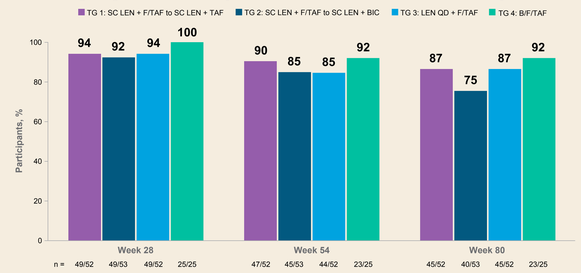
Results

Baseline Characteristics

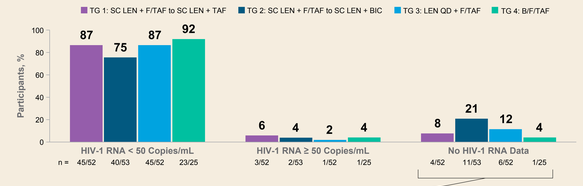
	LEN Total			B/F/TAF	
	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25	Overall N = 182
Age, median (range), years	31 (19-61)	28 (19-56)	28 (19-72)	29 (21-61)	29 (19-72)
Sex, % female at birth	10	2	12	0	7
Race, % Black	46	45	60	64	52
Ethnicity, % Hispanic/Latinx	48	40	46	48	45
HIV-1 RNA, median log_{10} copies/mL	4.27	4.32	4.53	4.37	4.37
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.86, 4.74
> 100,000 copies/mL, %	10	17	17	16	15
CD4 count, median cells/µL	404	450	409	482	437
Q1, Q3	320, 599	332, 599	301, 600	393, 527	332, 599
< 200 cells/µL, %	0	2	6	0	2

CD4 = cluster of differentiation-4; Q = quartile.

Efficacy by FDA Snapshot: HIV-1 RNA < 50 Copies/mL



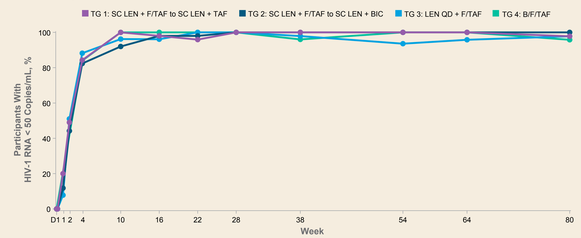
Efficacy by FDA Snapshot at Week 80



	TG 1	TG 2	TG 3	TG 4
Discontinued study drug due to AE/death	1 (2)	3 (6)	0	0
Discontinued study drug due to other reason (last available HIV-1 RNA < 50 copies/mL)	2 (4) • 1 investigator's discretion • 1 lost to follow-up	8 (15) • 4 participant decision • 2 investigator's discretion • 2 lost to follow-up	6 (12) • 5 participant decision • 1 lost to follow-up	1 (4) • 1 participant decision
Missing data during window, but on study drug	1 (2)	0	0	0

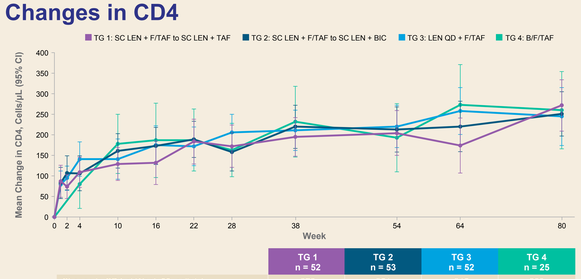
AE = adverse event.

Participants With HIV-1 RNA < 50 Copies/mL by Visit
Missing = Excluded (on Treatment)



	TG 1 n = 46	TG 2 n = 40	TG 3 n = 46	TG 4 n = 25
Participants with HIV-1 RNA < 50 copies/mL, % (n)	98 (45)	100 (40)	98 (45)	96 (23)

Changes in CD4



	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25
Change in CD4 at Week 80, cells/µL	272	251	245	260

CI = confidence interval.

- For participants in TGs 1-3, CD4 count increased by a mean of 256 cells/µL (minimum, maximum: -384, 843) at Week 80

Resistance Analysis

Participants, n	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25
Met resistance testing criteria	2	1	3	1
Emergent LEN resistance	1	1	1	0
Q67H	1	1	1	0
K70R	1	1	1	0

Genotypic and phenotypic resistance testing performed on any participants with confirmed HIV-1 RNA ≥ 50 copies/mL and < 1-log_{10} HIV-1 RNA reduction from Day 1 at Week 10 visit, any visit after achieving HIV-1 RNA < 50 copies/mL and rebound to ≥ 50 copies/mL, and any visit with > 1-log_{10} increase from nadir.

- Emergent LEN resistance in 3/157 participants (2%) through Week 80
  - 1 participant (TG 1) developed Q67H + K70R at Week 80
  - 1 participant (TG 2) developed M184M/I in reverse transcriptase prior to Q67H + K70R in capsid at Week 10[10,11]
  - 1 participant (TG 3) developed Q67H in capsid at Week 54 with subsequent emergence of K70R, and demonstrated nonadherence by pill count and drug levels[12,13]

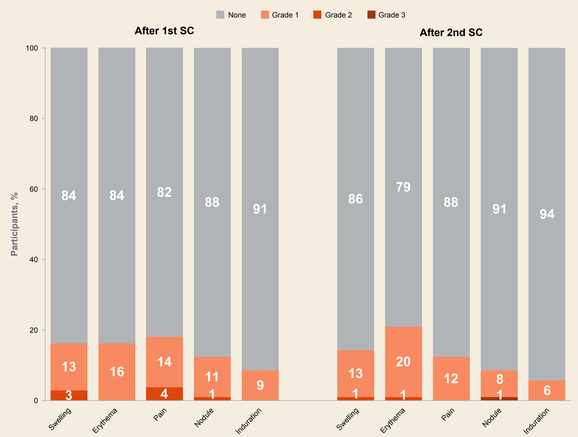
Adverse Events (Excluding ISRs)

≥ 10% of Participants in LEN total, %	LEN Total TGs 1-3 n = 157	B/F/TAF TG 4 n = 25
Headache	16	12
Nausea	13	4
COVID-19	13	16
Syphilis	11	16
Influenza	11	0
Diarrhea	10	8

ISRs = injection-site reactions.

- 1 participant (TG 1) had a serious AE of non-small-cell lung cancer with a fatal outcome and not related to study drug (Day 273)
- No serious AEs related to study drug
- No Grade 4 AEs related to study drug
- No discontinuations due to non-ISR AEs
- Gastrointestinal AEs: SC LEN (TG 1+2) vs oral LEN (TG 3)
  - Nausea: 14% vs 12%
  - Diarrhea: 10% vs 12%
  - Vomiting: 5% vs 10%

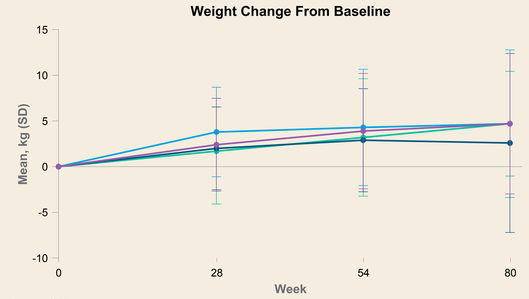
Injection-Site Reactions



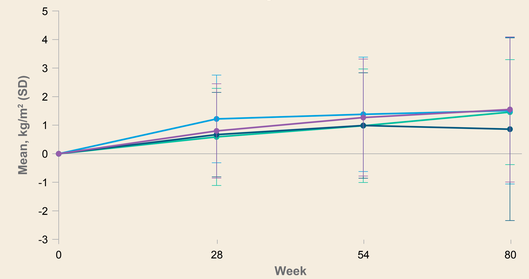
ISR types include those > 5% at both Weeks 1 and 26.

- LEN-related ISRs were mostly mild to moderate
  - 1 Grade 3 ISR (nodule) after the 2nd SC dose
- 4 participants discontinued due to ISRs:
  - 3 due to induration (all Grade 1; 2 after the 1st SC dose and 1 after the 3rd SC dose)
  - 1 due to erythema and swelling (Grade 1 after the 2nd SC dose)

Weight and BMI Changes



Mean change (n)			
TG 1: n = 52	2.4 (49)	3.9 (49)	4.7 (48)
TG 2: n = 53	2.0 (51)	2.9 (47)	2.6 (42)
TG 3: n = 52	3.8 (50)	4.3 (48)	4.7 (46)
TG 4: n = 25	1.7 (25)	3.2 (23)	4.7 (24)



Mean change (n)			
TG 1: n = 52	0.80 (49)	1.27 (49)	1.55 (48)
TG 2: n = 53	0.67 (51)	0.99 (47)	0.86 (42)
TG 3: n = 52	1.22 (50)	1.38 (48)	1.51 (46)
TG 4: n = 25	0.59 (25)	0.98 (23)	1.46 (24)

SD = standard deviation.

Conclusions

- In treatment-naïve people with HIV (PWH), SC LEN in combination with TAF or BIC and oral LEN with F/TAF maintained high rates of virologic suppression through Week 80
- LEN was well tolerated; discontinuations due to AEs were infrequent
- These long-term results support ongoing evaluation of LEN in combination with other long-acting partner agents for the treatment of HIV-1 infection, and support Gilead's long-acting oral and injectable development program

References: **1.** Sunlenca [package insert]. Foster City, CA: Gilead Sciences, Inc; 2022. **2.** Sunlenca [product monograph]. Mississauga, ON: Gilead Sciences Canada, Inc; 2022. **3.** Sunlenca [summary of product characteristics]. Carrigtohill, Ireland: Gilead Sciences Ireland UC; 2022. **4.** Begley R, et al. AIDS 2020, abstr PEB0265; **5.** Begley R, et al. CROI 2020, abstr 470; **6.** Daar EM, et al. CROI 2020, poster 3691; **7.** Gupta SK, et al. CROI 2022, abstr 1292; **8.** Link JO, et al. Nature 2020;584:614-8; **9.** Zila V, et al. Cell 2021;184:1032-46; **10.** Gupta SK, et al. IAS 2021, abstr OALB0302; **11.** VanderVeen L, et al. IDWeek 2021, oral 73; **12.** Gupta SK, et al. CROI 2022, oral 138; **13.** VanderVeen L, et al. AIDS 2022, abstr. EPB239.

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