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Lenacapavir Sustained Delivery Formulation Supports 6-Month Dosing Interval

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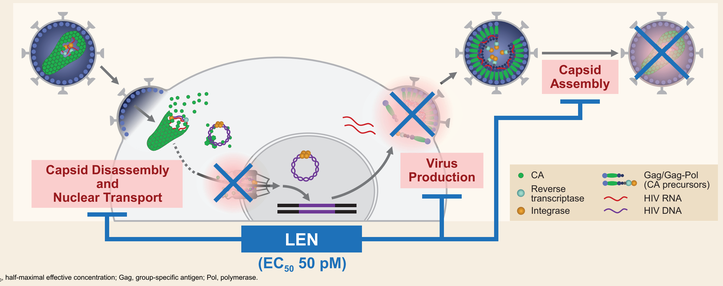
Introduction

- Lenacapavir (LEN; GS-6207) is a novel, first-in-class, selective inhibitor of HIV-1 capsid protein (CA)
- LEN is being developed as a component of a long-acting treatment regimen for people living with HIV (PLWH), including those with multiclass drug resistance[1,2]
- LEN has demonstrated potent antiviral activity in PLWH, with up to 2.3-$\log_{10}$ copies/mL decline in HIV RNA over 10 d after a single subcutaneous (SC) dose[3,4]
- Both oral[5] and SC LEN formulations are in clinical development
- The present study is the first to assess the safety and single ascending-dose pharmacokinetics (PK) of a new SC LEN formulation designed to support a 6-month (q6mon) dosing interval
- This new SC LEN formulation, combined with an oral PK loading regimen, is administered q6mon in the ongoing Phase 2 and 3 clinical studies (ClinicalTrials.gov NCT04143594 and NCT04150068)

LEN: 1st-in-Class HIV Capsid Inhibitor



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

- Inhibition of multiple CA-dependent functions essential for viral replication

Objectives

- To assess the safety, tolerability, and PK of escalating single doses of SC LEN injectable solutions compared with placebo (PBO)

Methods

Study Design

LEN Dose: 300-mg/mL SC Solution	Total Volume (injection no. and volume)	Participants, n (active:PBO)
300 mg	1.0 mL (1 x 1.0 mL)	8:2
900 mg	3.0 mL (3 x 1.0 mL)	8:2
900 mg	3.0 mL (2 x 1.5 mL)	8:2

- Phase 1, blinded, placebo-controlled, randomized (4:1), single ascending-dose study in HIV negative participants
- Blinded safety and available PK data reviewed between ascending single-dose cohorts
- Safety assessments: adverse event (AE) monitoring, clinical laboratory values, physical examination, and electrocardiographic evaluations performed throughout the study
- PK assessments and analysis:
  - PK sampling performed through 449 d postdose
  - Plasma concentrations of LEN determined using validated liquid chromatography–tandem mass spectrometry assays
  - LEN PK parameters estimated using noncompartmental methods (Phoenix® WinNonlin® Validation Suite™ 7.0, Certara USA, Inc., Princeton, New Jersey, USA) and summarized using descriptive statistics

Results

Participant Enrollment and Demographics

	LEN 300 mg or PBO (1 x 1.0 mL)	LEN 900 mg or PBO (3 x 1.0 mL)	LEN 900 mg or PBO (2 x 1.5 mL)	Total LEN or PBO
Enrolled/completed, n	10/10	10/10	10/10	30/30
Median age, y (range)	39 (26–45)	34 (21–44)	42 (25–44)	37 (21–45)
Men, n (%)	8 (80)	8 (80)	5 (50)	21 (70)
White, n (%)	4 (40)	9 (90)	8 (80)	21 (70)
Hispanic/Latino, n (%)	10 (100)	10 (100)	9 (90)	29 (97)
Median BMI, kg/m^2 (range)	28 (20–30)	27 (24–29)	25 (21–29)	27 (20–30)

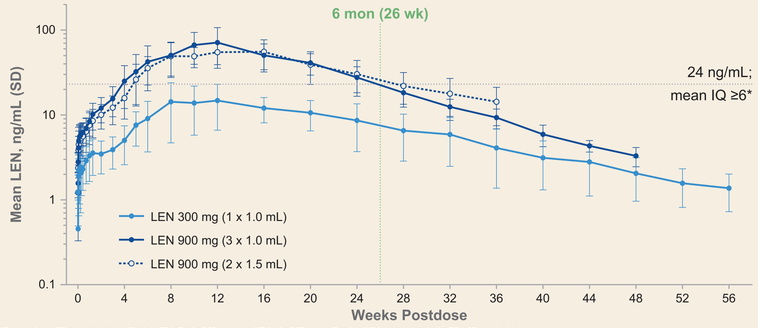
BMI, body mass index.

LEN Pharmacokinetic Parameters

PK Parameter Mean (%CV)*	300 mg (1 × 1.0 mL) n=8	900 mg (3 × 1.0 mL) n=8	900 mg (2 × 1.5 mL) n=8
AUC_{∞}, h·ng/mL	66,400 (27.8)	225,000 (33.6)	224,000 (31.5)
AUC_{last}, h·ng/mL	61,100 (28.8)	179,000 (53.4)	153,000 (47.6)
$\%AUC_{exp}$	8.06 (51.2)	5.79 (50.6)	21.5 (33.8)
C_{max}, ng/mL	17.7 (50.3)	67.0 (54.8)	61.2 (43.5)
T_{max}, d	97.9 (55.8, 140)	77.1 (70.0, 84.2)	84.2 (62.9, 112)
T_{last}, d	364 (334, 364)	280 (168, 280)	196 (196, 196)
$t_{1/2}$, d	175 (68.3, 93.8)	49.6 (46.7, 59.2)	64.6 (49.2, 80.0)

*Presented to 3 significant figures as mean and % coefficient of variation (CV), except time to maximal concentration (C_{max}; T_{max}), time of last measurable concentration (T_{last}), and half-life ($t_{1/2}$): median (quartiles 1, 3). AUC_{∞}, area under curve from time 0 to ∞; AUC_{exp}, AUC extrapolated between AUC_{∞} and AUC to last measurable concentration (AUC_{last}).

Mean LEN Single-Dose Plasma Concentration-Time Profiles



*Protein-adjusted EC_{90}: macrophages, 1.16 ng/mL; CD4+ T cells, 2.32 ng/mL; and MT-4 cells, 3.87 ng/mL.[2] IQ, ratio of LEN plasma concentration/EC_{90}; SD, standard deviation.

- Following administration of LEN 900 mg, concentrations were ≥24 ng/mL for 26 wk, corresponding to a mean IQ of ≥6 (range 6.2–20.3 across in vitro assays) throughout a 26-wk (6-mon) dosing interval

LEN Pharmacokinetic Results Summary

- LEN exposures increased in a generally dose-proportional manner from 300 to 900 mg
- LEN T_{max} was 11–14 wk postdose and apparent $t_{1/2}$ ranged from 7 to 11 wk
- A slow initial release of LEN was observed and target plasma concentrations were sustained for ≥6 mon after 900-mg single dose
- Similar PK was observed following 900-mg dose administered as 3 x 1.0-mL or 2 x 1.5-mL SC injection

LEN Safety Summary: Blinded Data*

AEs: ≥5 Participants, n (%)	LEN 300 mg or PBO (1 x 1.0 mL) n=10	LEN 900 mg or PBO (3 x 1.0 mL) n=10	LEN 900 mg or PBO (2 x 1.5 mL) n=10	Overall N=30
Injection-site induration	3 (30)	8 (80)	10 (100)	21 (70)
Injection-site pain	0	6 (60)	8 (80)	14 (47)
Injection-site erythema	1 (10)	5 (50)	4 (40)	10 (33)
Headache	3 (30)	4 (40)	3 (30)	10 (33)
Injection-site swelling	0	4 (40)	4 (40)	8 (27)
Injection-site nodule	2 (20)	3 (30)	0	5 (17)

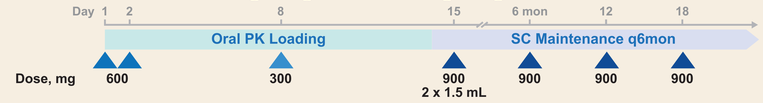
*1 participant had Grade 3 AEs of abscess (serious AE), cellulitis, and methicillin-resistant *Staphylococcus aureus* infection, none of which were related to LEN.

- Overall, LEN was well tolerated
- No serious or Grade 2, 3, or 4 AEs related to study drug
- No AEs leading to discontinuation
- Injection-site reactions were common (80%), but all were mild (Grade 1) and mostly lasted only a few days; induration and nodules were generally detectable only by clinicians and lasted several weeks
- 7 participants (23%) had Grade 3 or 4 laboratory abnormalities; none were clinically relevant

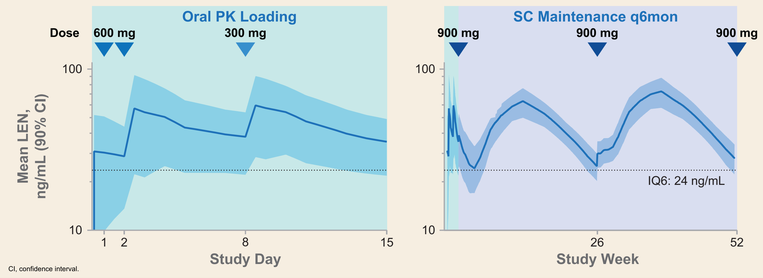
Simulations Supporting Phase 2/3 LEN Dosing Regimen

- Based on observed antiviral activity,[3] the mean LEN target concentration is 24 ng/mL, corresponding to a mean IQ ≥6 (range 6.2–20.3)
- The new LEN 300-mg/mL SC injection formulation exhibits a slow initial release necessitating an oral PK loading regimen prior to the first injection
- PK simulations were performed using single-dose oral LEN tablet PK[5] and SC injection PK from the present study
- The regimen was predicted to achieve target concentrations within a few days of initiation of dosing and maintain them with a 26-wk (6-mon) dosing interval

LEN Oral + SC Dosing Regimen in Ongoing Phase 2 and 3 Studies



Predicted LEN PK for Phase 2/3 Oral + SC Combination Regimen



CI, confidence interval.

Conclusions

- Single LEN SC doses up to 900 mg were generally safe and well tolerated
  - Injection-site reactions were common, but all were mild
- LEN 900 mg SC maintained target concentrations for 26 wk (6 mon), supporting its use as a q6mon antiretroviral agent
- PK simulations support LEN regimen with oral PK loading, followed by q6mon SC maintenance in ongoing Phase 2 and 3 clinical studies
  - 14-d oral loading: 600 mg on Days 1 and 2, and 300 mg on Day 8
  - SC maintenance: 900 mg on Day 15, followed by 900-mg q6mon

References: **1.** Begley R, et al. EACS 2019, oral PS-13/1; **2.** Yant SR, et al. CROI 2019, poster 480; **3.** Daar E, et al. CROI 2020, poster 3691; **4.** Sager JE, et al. CROI 2019, abstr 141; **5.** Begley R, et al. CROI 2020, poster 3670.

Disclosures: **R. Begley, J. Lutz, M. Rhee, H. Dvory-Sobol, A. Chiu, S.K. West, J. Corpus, J. Ling,** and **P. German:** Gilead. **Acknowledgments:** We extend our thanks to the participants. This study was funded by Gilead Sciences, Inc.

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