Poster
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# Lenacapavir Sustained Delivery Formulation Supports 6-Month Dosing Interval

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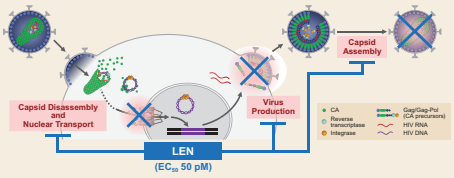
## Background

- 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 (Begley et al. 2019, Yant et al. 2019)
- 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 (Daar et al. 2020, Sager et al. 2019)
- Both oral (Begley et al. 2020) 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)




$EC_{50}$, 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/m² (range) | 28 (20–30) | 27 (24–29) | 25 (21–29) | 27 (20–30) |

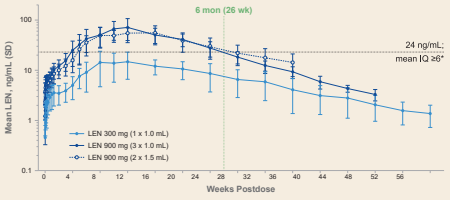
BMI, body mass index.

### 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 |
|---|---|---|---|
| $AUC_{inf}$, 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) |
| $\%AUC_{ext}$ | 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). $AUC_{\tau}$, area under curve from time 0 to ∞; $AUC_{inf}$, AUC extrapolated between $AUC_{\tau}$ and AUC to last measurable concentration ($AUC_{last}$).

### Mean LEN Single-Dose Plasma Concentration-Time Profiles




*Protein-adjusted $EC_{95}$: macrophages, 1.16 ng/mL; CD4+ T cells, 2.32 ng/mL; and MT-4 cells, 3.87 ng/mL.(Yant SR, 2019) IQ, ratio of LEN plasma concentration/$EC_{95}$; SD, standard deviation.

- Following administration of LEN 900 mg, concentrations were ≥24 ng/mL for 26 wk, corresponding to a mean IQ ≥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.

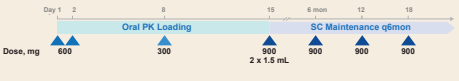
- Overall, LEN was well tolerated
- No serious or Grade 2, 3, or 4 AEs related to study drug
- No AEs leading to discontinuation
- Injection-site reactions were common (80%), but all were mild (Grade 1) and mostly lasted only a few days; induration and nodules were generally detectable only by clinicians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

## Results Cont'd

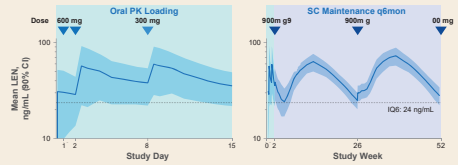
### Simulations Supporting Phase 2/3 LEN Dosing Regimen

- Based on observed antiviral activity, (Daar et al. 2020) 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 (Begley et al. 2020) 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

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