PESUB23

Simulations for Once-Weekly Dosing of Oral Lenacapavir

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Introduction

- Oral long-acting antiretroviral regimens with less frequent dosing (eg, weekly oral dosing) have the potential to provide more convenient dosing options, and address challenges with suboptimal adherence and treatment fatigue associated with daily oral therapy, which can lead to improvement in treatment success rates while also helping to prevent HIV transmission
- Lenacapavir (LEN) is a novel, first-in-class, selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low human clearance, and physicochemical properties well suited for a long-acting injectable or oral formulation
- In addition to current dosing regimens, weekly oral LEN could be developed for use in combination with other oral antiretroviral agents for virologically suppressed people with HIV-1
- Mean trough concentration of 15.5 ng/mL, which is inhibitory quotient 4 (IQ4; ie, 4-fold greater than the in vitro protein-adjusted 95% effective concentration derived from MT-4 cells),[1] has been associated with high rates of virologic suppression in Phase 2/3 clinical studies
- The pharmacokinetics (PK) of LEN following single-dose administration of oral LEN 50–1800 mg has been characterized; oral LEN exposure increased less than dose proportionally over the evaluated dose range, with maximal plasma concentrations between 4 and 8 hours postdose, and a half-life of 10–13 days[2]
- Plasma LEN concentrations were well described by a 2-compartment population PK (PopPK) model with first-order absorption after oral administration, parallel-direct (first-order) and transit-compartment absorption after SC administration, and first-order elimination[3]

Objective

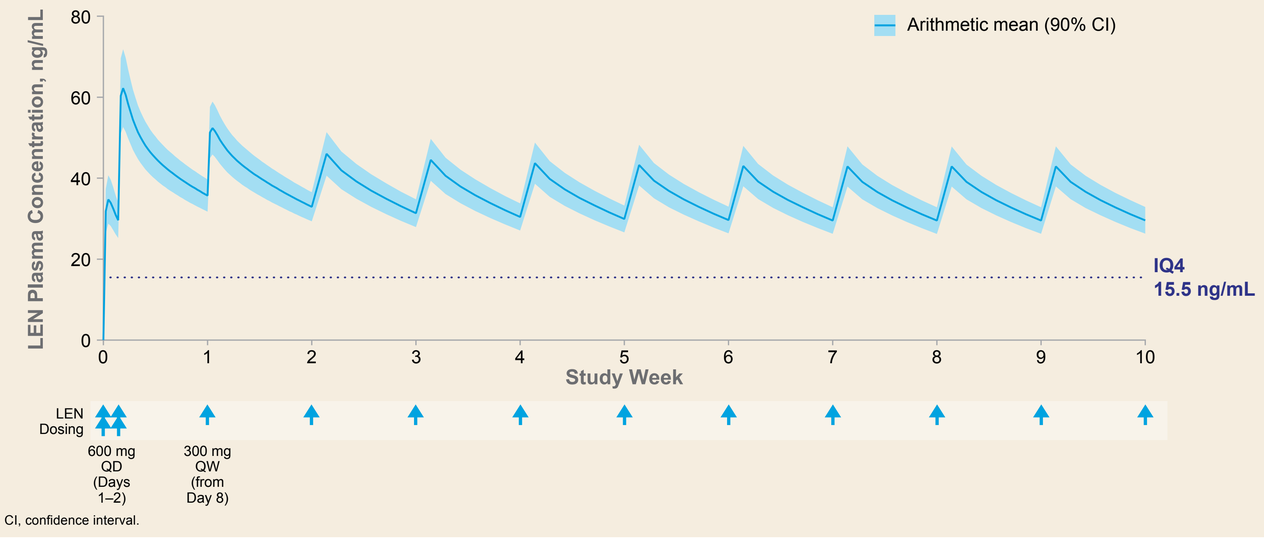
- To identify LEN dosing regimens that can be used in combinations with other antiretroviral agents by simulating various weekly dosing regimens that would rapidly achieve and maintain LEN concentrations above IQ4

Methods

- A previously developed 2-compartment LEN PopPK model with first-order absorption and linear elimination was utilized to simulate various weekly dosing regimens (loading + maintenance doses) that can achieve efficacious LEN concentrations rapidly and be maintained through the dosing interval[3]
- In addition, various scenarios including 1–3 weeks of missed oral dosing were simulated to evaluate the forgiveness window; these simulations were performed with the PopPK model incorporating variability and covariate effects

Results

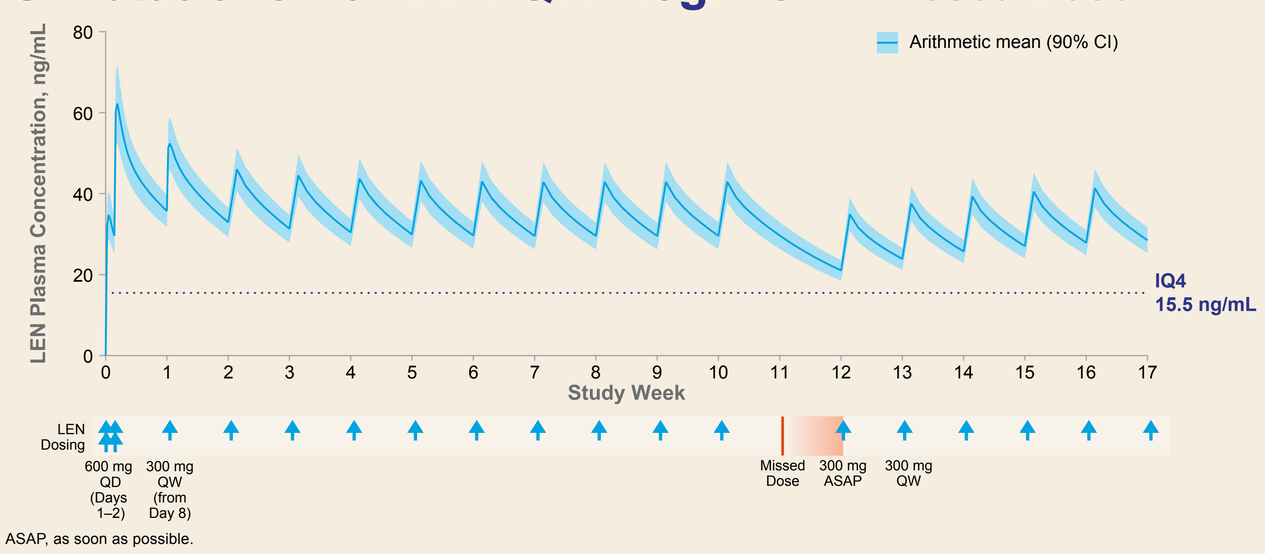
LEN QW Dosing Regimen Following Oral Loading
600 mg QD on Days 1–2, Then 300 mg QW From Day 8



CI, confidence interval.

- Simulations showed that an oral loading dose of 600 mg on Days 1 and 2 followed by oral 300-mg QW doses maintained the lower bound of the 90% CI of mean trough concentration above IQ4 (15.5 ng/mL) through the dosing interval; this regimen reached IQ4 rapidly within 4 hours

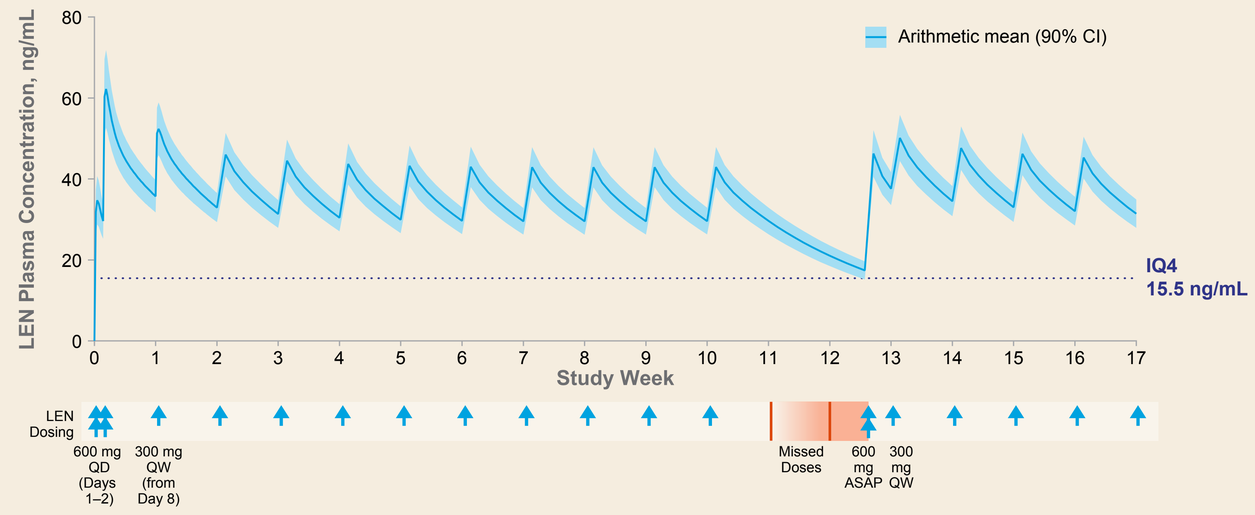
Simulations For LEN QW Regimen 1 Missed Dose



ASAP, as soon as possible.

- Simulations suggested that LEN 300 mg QW allows for a 7-day forgiveness window
- If 1 oral LEN dose is missed, it should be taken as soon as possible and then normal dosing regimen can be resumed (ie, taking 1 dose on the scheduled day) to maintain mean LEN concentrations above IQ4

Simulations for LEN QW Regimen 2 Missed Doses



- If 2 oral LEN doses are missed, simulations indicated taking 2 doses as soon as possible and then resuming the normal regimen on the scheduled day will result in concentrations above IQ4 and within the safety margin
  - If taking doses on the scheduled dosing day, only 2 doses should be taken; never take 3 doses on the same day

Conclusions

- The oral LEN QW regimen (600 mg on Days 1 and 2, followed by 300 mg QW) is expected to rapidly achieve and then maintain LEN concentrations above IQ4 for the dosing interval
- LEN 300 mg QW dosing allows for a 7-day forgiveness window for people with HIV after the last missed dose
- LEN is well suited to be part of a QW oral regimen

Reference: **1.** Daar E, et al. CROI 2020, poster 3691; **2.** Dvory-Sobol H, et al. Curr Opin HIV AIDS 2022;17:15-21; **3.** Shaik N, et al. AIDS 2022, poster EPB174. **Acknowledgments:** 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.

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