Once-Yearly Lenacapavir for PrEP: Model-Informed Dose Determination and Phase 3 Trial Design

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PURPOSE 365

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Conclusions

- A once-yearly intramuscular (IM) dose of 3000 mg lenacapavir (LEN) with oral loading (600 mg on Days 1 and 2) was selected based on population pharmacokinetic (popPK) modeling
- Leveraging the totality of clinical and nonclinical data generated to date, we developed a model-informed drug development (MIDD) strategy to determine the appropriate dose and to support the efficacy of LEN as pre-exposure prophylaxis (PrEP) when administered intramuscularly once yearly without a large efficacy-powered Phase 3 study
- The Phase 3 PURPOSE 365 study is evaluating the safety, tolerability, and PK of once-yearly LEN for PrEP in a diverse participant population

Plain Language Summary

- Pre-exposure prophylaxis (PrEP) is very effective for preventing people from getting human immunodeficiency virus (HIV)
- Lenacapavir (LEN) is a long-acting form of PrEP. It is given as an injection under the skin every 6 months and was shown to work very well in preventing HIV in two large studies (PURPOSE 1 and PURPOSE 2)
- A new version of LEN has also been developed that can be given as an injection into a muscle once a year
- This approach used what we already know about how long LEN stays in the body when it is given under the skin every 6 months to build a model to figure out what dose should be used for the once-a-year injection into muscle so that LEN levels in the blood remain high enough at 1 year
- The model found that LEN levels in the blood at 1 year will be similar or higher when people received injections into a muscle once a year at a dose of 3000 mg versus under the skin every 6 months at a dose of 927 mg
- The once-a-year 3000-mg LEN injection into the muscle is being assessed in a larger study (called PURPOSE 365) to learn more about how safe it is and to see LEN concentrations after 1 year in people who would benefit from PrEP

Introduction

- The PK and tolerability of LEN following multiple routes of administration have been well characterized over many clinical studies, including evaluations in Phase 1 volunteers, people with HIV, and people who would benefit from PrEP (PWBP)
- Twice-yearly subcutaneous (SC) LEN (927 mg at 309 mg/mL with oral loading) demonstrated high efficacy and favorable safety in two Phase 3 trials (PURPOSE 1 [NCT04994509] and PURPOSE 2 [NCT04925752]) conducted in a diverse population of PWBP,[1,2] facilitating US and EU approval[3,4]
- Extending the LEN dosing interval to once yearly has the potential to further improve PrEP uptake and persistence. In a Phase 1 trial, two 5000-mg LEN IM formulations exceeded target concentrations of LEN for a once-yearly regimen. Both were safe and well tolerated[5]

Objective

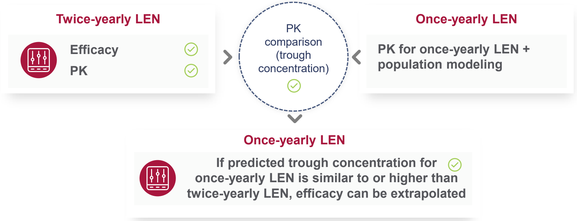
- To present our MIDD approach utilizing popPK modeling and simulation for the dose selection and design of a Phase 3 trial (PURPOSE 365) for once-yearly IM LEN for PrEP, which leveraged all clinical and nonclinical data for LEN

Methods

MIDD Approach

- In the absence of an efficacy-powered Phase 3 study, an MIDD approach utilizing popPK modeling is being used to determine the dose and to extrapolate efficacy of once-yearly LEN by an exposure-matching method (**Figure 1**)
- This approach will utilize PK and efficacy data from the PURPOSE 1 and 2 studies, and PK data with once-yearly LEN formulations

Figure 1. MIDD Efficacy Extrapolation



LEN, lenacapavir; MIDD, model-informed drug development; PK, pharmacokinetics.

Methods

PopPK Model Development and Dose Selection

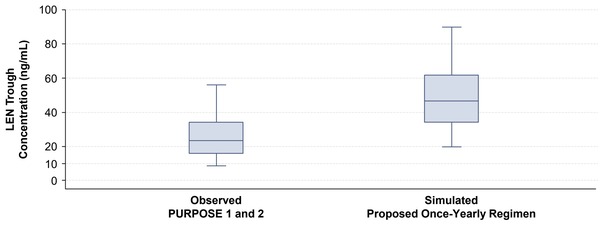
- A three-compartment popPK model was developed using data from four Phase 1 trials (151 participants, 3378 LEN concentration measurements). Oral data included 300- to 1800-mg doses and IM data included a single dose of 5000 mg
- We used this model to perform simulations investigating various oral loading frequencies and potential IM doses. Simulations leveraged the large size and diverse population characteristics of PURPOSE 1 and 2 to select a regimen
- A regimen was selected based on exposure matching, where target concentrations are reached rapidly and projected trough concentrations (Week 52 C_{trough}) are equivalent to or greater than that observed in PURPOSE 1 and 2 (Week 26 C_{trough}), where twice-yearly LEN was shown to be efficacious as PrEP

Results

Dose Selection

- PopPK simulations predicted that an IM dose of 3000 mg would:
  - Result in a Week 52 C_{trough} exceeding the observed Week 26 C_{trough} in PURPOSE 1 and 2 (**Figure 2**)
  - Maintain median LEN concentration (and 90% prediction interval) at more than four times the *in vitro* inhibitory quotient 4 (IQ4; 15.5 ng/mL) for ≥ 52 weeks (**Figure 3**)
  - Require oral loading (600 mg on Days 1 and 2) to achieve target concentrations rapidly by Day 2

Figure 2. Simulated LEN Trough Concentration for Once-Yearly Regimen is Comparable to That Observed in PURPOSE 1 and 2

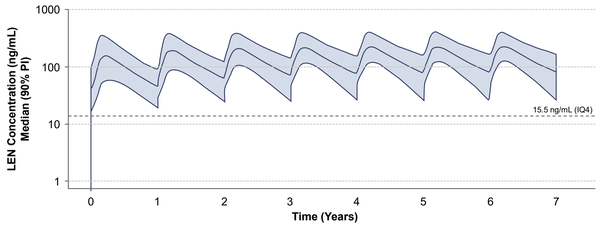


The observed data from the PURPOSE studies was recorded at Week 26 (± 2 weeks) and the simulated data at Week 52.
Boxes = first and third quartiles; horizontal lines inside boxes = medians; whiskers = 5th and 95th percentiles. LEN, lenacapavir.

Results

Figure 3. Simulated Concentration of LEN for 3000-mg Once-Yearly IM Administration Over 7 Years

Median (90% PI)

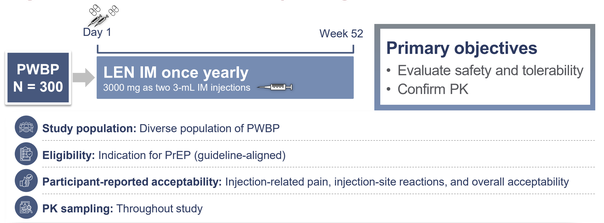


Central solid line = median concentration over time; shaded region = 90% PI.
IQ4, inhibitory quotient 4; LEN, lenacapavir; PI, prediction interval.

Phase 3 Trial (PURPOSE 365)

- The formulation and dose for PURPOSE 365 was selected based on popPK modeling and formulation considerations
- While efficacy can be extrapolated, further study among PWBP is needed to assess the safety of the novel formulation and route of administration
- To assess safety and facilitate MIDD-based efficacy extrapolation, we initiated a single-arm, open-label Phase 3 study (PURPOSE 365; NCT07047716) in which 300 diverse PWBP will receive 3000 mg of LEN (two 3-mL, ventrogluteal IM injections) once yearly, with 600-mg oral loading on Days 1 and 2
- The study design for the ongoing PURPOSE 365 study is shown in **Figure 4**

Figure 4. PURPOSE 365 Study Design



IM, intramuscular; LEN, lenacapavir; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; PWBP, people who would benefit from PrEP.

References: **1.** Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92. **2.** Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76. **3.** Yeztugo (lenacapavir) USPI, Gilead Sciences, Inc., June 2025. **4.** Yaytuo (lenacapavir) EU SmPC, Gilead Sciences, Inc., September 2025. **5.** Jogiraju V, et al. *Lancet*. 2025;405:1147-54.

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