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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,<sup>1,2</sup> facilitating US and EU approval<sup>3,4</sup>
- 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<sup>5</sup>

## Objective

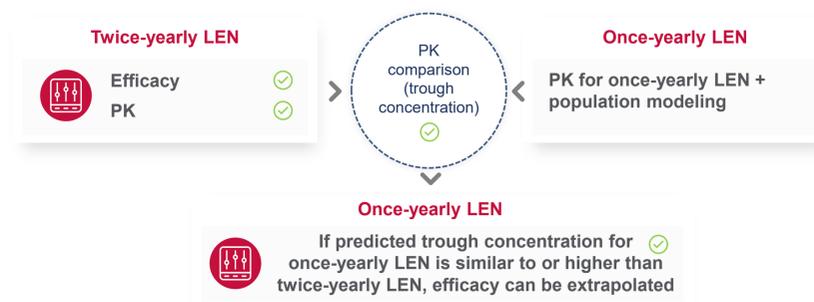
- To present our MIDD approach utilizing popPK modeling and simulation for the dose selection and design of a Phase 3 trial (PURPOSE 365) for once-yearly IM LEN for PrEP, which leveraged all clinical and nonclinical data for LEN

## 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

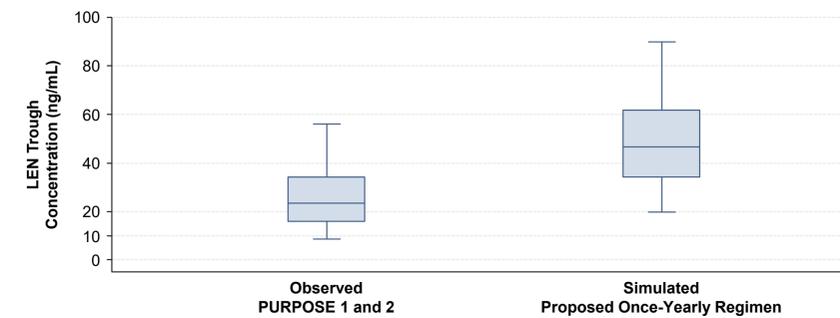
- A three-compartment popPK model was developed using data from four Phase 1 trials (151 participants, 3378 LEN concentration measurements). Oral data included 300- to 1800-mg doses and IM data included a single dose of 5000 mg
- We used this model to perform simulations investigating various oral loading 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  $\geq 52$  weeks (Figure 3)
  - Require oral loading (600 mg on Days 1 and 2) to achieve target concentrations rapidly by Day 2

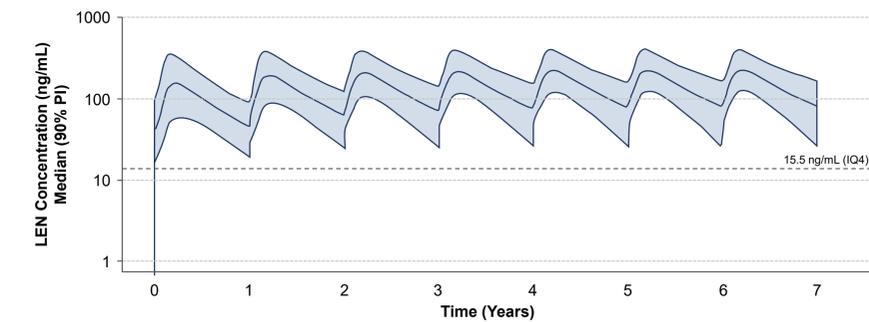
Figure 2. Simulated LEN Trough Concentration for Once-Yearly Regimen is Comparable to That Observed in PURPOSE 1 and 2



The observed data from the PURPOSE studies was recorded at Week 26 ( $\pm 2$  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)

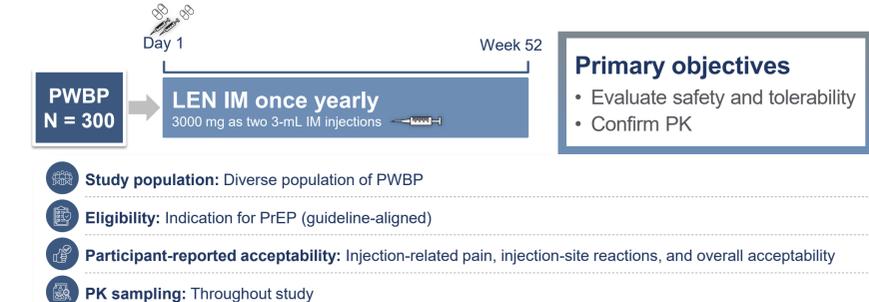


Central solid line = median concentration over time; shaded region = 90% PI. IQ4, inhibitory quotient 4; LEN, lenacapavir; PI, prediction interval.

### 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.

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Acknowledgments: We thank all study participants, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Medical writing support was provided by Jenna Steere, PhD (Aspire Scientific Ltd, Manchester, UK), and was funded by Gilead Sciences, Inc.

Disclosures: All authors are employees of, and own stocks in, Gilead Sciences, Inc.

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