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PURPOSE 2

No Clinically Significant Drug-Drug Interactions With Coadministration of Feminizing or Masculinizing Hormone Therapy and Twice-Yearly Lenacapavir PrEP in Gender-Diverse Persons

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Conclusions

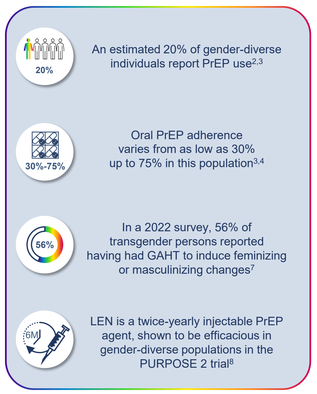
- In the most gender-diverse Phase 3 pre-exposure prophylaxis (PrEP) trial conducted to date, **lenacapavir (LEN)** had **no clinically significant impact on feminizing or masculinizing gender-affirming hormone therapy (GAHT) concentrations**
- Taken together with our prior finding that GAHT had no significant effect on LEN pharmacokinetics (PK)[1], these data **support the concurrent use** of twice-yearly **LEN for PrEP and feminizing or masculinizing GAHT without dose adjustments** in gender-diverse individuals, addressing a key barrier to PrEP uptake and adherence in a population that is disproportionately vulnerable to HIV acquisition
- Future studies may confirm these findings using intensive PK sampling

Plain Language Summary

- Gender-diverse people often face health challenges, including higher chances of getting HIV
- Pre-exposure prophylaxis (PrEP) is a highly effective medicine for preventing HIV, but some people worry that PrEP might interfere with their gender-affirming hormone therapy (GAHT)
- Lenacapavir (LEN) is a new type of PrEP taken twice a year (every 6 months) as an injection. Two large studies (PURPOSE 1 and PURPOSE 2) showed that it was very effective in protecting people from HIV, including gender-diverse individuals
- An earlier study found that LEN levels in the blood did not change with GAHT
- This study looked at whether LEN affects GAHT when taken together
- When GAHT and LEN were taken together, hormone levels stayed about the same before and after taking LEN
- These findings support that it is safe to take LEN for PrEP and GAHT at the same time without changing the dose of either, which may help more gender-diverse people feel comfortable taking PrEP while continuing their hormone therapy

Background

- Transgender and gender-diverse individuals are disproportionately vulnerable to HIV acquisition, yet PrEP uptake and adherence remain low[2,3]
- A **key barrier** to **PrEP uptake** and **adherence** among gender-diverse individuals is **concern about potential drug-drug interactions with GAHT**[4,5]
- GAHT agents – including estradiol and testosterone – are metabolized by multiple enzymes (eg, CYP3A4, CYP1A2, UGT1A1, aromatase, and 5α-reductase)[5]
- LEN is a substrate and moderate inhibitor of CYP3A[6]
- There is theoretical potential that LEN ***may*** **increase** blood **levels of GAHT** agents via **CYP3A inhibition**, but multiple metabolic pathways for GAHT may overcome this process
- **GAHT had no clinically significant effect on LEN PK** based on population PK modeling[1]



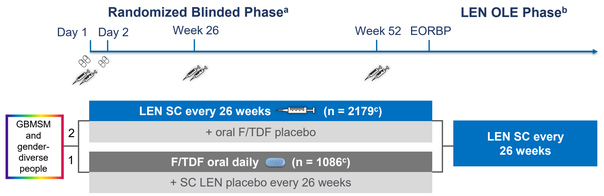
Objective

- To evaluate the **PK effects** of **coadministering feminizing and masculinizing GAHT** with twice-yearly subcutaneous (SC) **LEN for PrEP**

Methods

- PURPOSE 2 (NCT04925752) is a Phase 3, randomized controlled trial that demonstrated the efficacy of twice-yearly LEN PrEP in cisgender men, transgender women, transgender men, and gender nonbinary individuals (**Figure 1**)[8]
- Participant characteristics, including self-reported gender identity, were collected at baseline. GAHT use was queried at each study visit

Figure 1. PURPOSE 2 Study Design



[a]Participants randomized to LEN received loading doses of two 300-mg tablets of LEN on each of Days 1 and 2 and SC LEN 927 mg on Day 1 and then every 26 weeks (± 7 days); participants randomized to F/TDF received matched placebos. [b]Participants randomized to LEN in the RBP who chose to participate in the LEN OLE Phase received SC LEN every 26 weeks (± 7 days) and had study visits every 13 weeks (± 7 days). Participants randomized to F/TDF in the RBP who chose to participate in the LEN OLE Phase received SC LEN on LEN OLE Day 1 and every 26 weeks thereafter; these participants also received an oral LEN loading dose on LEN OLE Days 1 and 2 and had study visits at LEN OLE Day 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and then every 13 weeks (± 7 days) thereafter. [c]Included in the full analysis set for primary efficacy analyses (additional participants are included in the safety analysis).
EORBP, end of randomized blinded phase; F/TDF, emtricitabine/tenofovir disoproxil fumarate; GAHT, gender-affirming hormone therapy; GBMSM, gay, bisexual, and other men who have sex with men; LEN, lenacapavir; OLE, open-label extension; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; RBP, randomized blinded phase; SC, subcutaneous.

Methods (cont.)

- PK analyses were conducted in a subset of participants receiving LEN and feminizing (estradiol) or masculinizing (testosterone) GAHT
- Serum **estradiol**, plasma **testosterone**, and plasma dihydrotestosterone (DHT; testosterone active metabolite) **concentrations** were **measured** at **baseline** (**before LEN dosing**) **and** at available **post-dose visits**, from Week 4 and up to Week 52
- Values below the limit of quantitation (5 pg/mL for estradiol, 100 pg/mL for testosterone, and 50 pg/mL for DHT) were treated as zero for summary statistics

Results

- 2183 participants received LEN in PURPOSE 2 and **486** (**22.3%**) self-identified as **gender diverse** (**Table 1**)
- **253 participants (11.6%)** in the SC LEN arm reported **concomitant gender-affirming therapy** (**Table 2**)
- In a subset of participants taking gender-affirming estradiol (n = 115), serum **estradiol concentrations on Day 1** (baseline, before LEN dosing) were generally **comparable with post-dose** visits from Week 4 through Week 52, without adjusting for dose, frequency, or dosing changes (**Figure 2**)
- In a subset of participants taking gender-affirming testosterone (n = 25), plasma **testosterone and DHT concentrations on Day 1** (baseline, before LEN dosing) were generally **comparable with post-dose** visits from Week 4 through Week 52, without adjusting for dose, frequency, or dosing changes (**Figure 3**)

Table 1. Baseline Characteristics

	SC LEN N = 2183
Age, years, median (Q1, Q3)	28 (24, 34)
Sex assigned at birth, n (%)	
Male	2140 (98.0)
Female	43 (2.0)
Gender identity, n (%)	
Transgender woman	315 (14.4)
Cisgender man	1697 (77.7)
Transgender man	29 (1.3)
Nonbinary	136 (6.2)
Assigned male at birth	122 (5.6)
Assigned female at birth	14 (0.6)
Other (assigned male at birth)	6 (0.3)

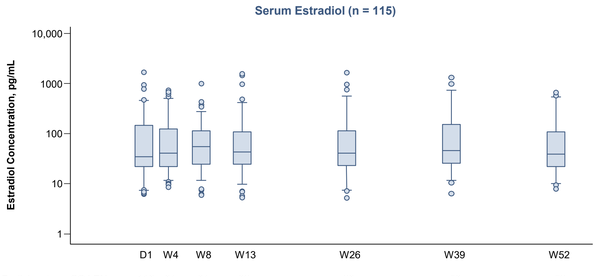
LEN, lenacapavir; Q, quartile; SC, subcutaneous.

Table 2. Concomitant Gender-Affirming Therapy Use Reported by 253 Participants in the SC LEN Arm

	SC LEN N = 2183
Total Participants who received ≥ 1 gender-affirming therapy, n (%)	**N = 2183** 253 (11.6)
Transgender women Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 315** 190 (60.3)
Transgender men Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 29** 22 (75.9)
Cisgender men Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 1697** 23 (1.4)
Gender nonbinary – assigned male at birth Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 122** 7 (5.7)
Gender nonbinary – assigned female at birth Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 14** 8 (57.1)
Other – assigned male at birth Participants who received ≥ 1 gender-affirming therapy, n (%)	**n = 6** 3 (50.0)

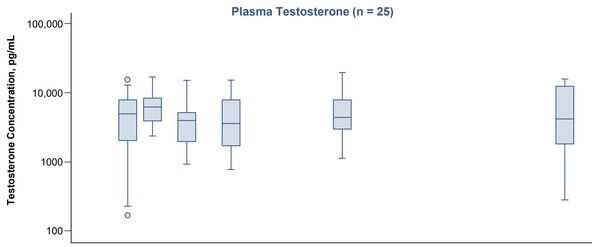
Gender-affirming therapies include Standard Medication Name (WHOGEN) for testosterone and estradiol based on WHODrug BMAR24 or investigator report of feminizing hormone therapy, masculinizing hormone therapy, non-hormonal gender-affirming therapy or other gender-affirming medical therapy.
LEN, lenacapavir; SC, subcutaneous.

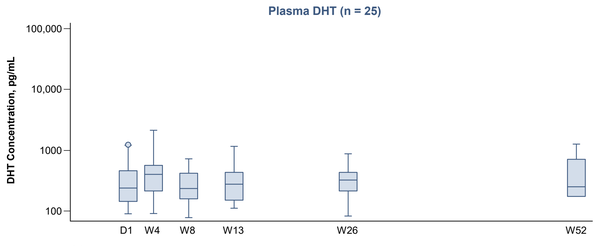
Figure 2. Serum Estradiol Concentrations Remained Generally Comparable to Baseline Among Participants Receiving LEN



Three participants receiving feminizing GAHT were missing evaluable hormone concentrations at baseline. Subsequent levels, if available, were included at other timepoints. Boxes = first and third quartiles; horizontal lines inside boxes = median; whiskers = 5th and 95th percentiles; circles = outliers.
D, Day; GAHT, gender-affirming hormone therapy; LEN, lenacapavir; SC, subcutaneous; W, Week.

Figure 3. Plasma Testosterone and DHT Concentrations Remained Generally Comparable to Baseline Among Participants Receiving LEN





Two participants receiving masculinizing GAHT were missing evaluable hormone concentrations at baseline. Subsequent levels, if available, were included at other timepoints. Data at W39 were not presented since the evaluable number of participants were < 5 at that visit (n = 3). At Week 52, the 5th percentile (concentration of 0 on log scale) of plasma DHT could not be plotted. Boxes = first and third quartiles; horizontal lines inside boxes = median; whiskers = 5th and 95th percentiles; circles = outliers. The PK cohort included 1 participant who self-identified as cisgender man at baseline. D, Day; DHT, dihydrotestosterone; GAHT, gender-affirming hormone therapy; LEN, lenacapavir; PK, pharmacokinetics; SC, subcutaneous; W, Week.

References: **1.** Imperial M, et al. Poster I-109 presented at: 33rd Population Approach Group Europe (PAGE) Meeting; June 4-6, 2025; Thessaloniki, Greece. **2.** Zarwell M, et al. *AIDS Behav*. 2021;25:1063-71. **3.** Zamantakis A, et al. *Prev Sci*. 2025;26:798-813. **4.** Ogunbajo A, et al. *AIDS Behav*. 2021;25:2301-15. **5.** Senneker T. *Br J Clin Pharmacol*. 2024;90:2366-82. **6.** Yeztugo USPI, Gilead Sciences, Inc., June 2025. **7.** Rastogi A, et al. https://transequality.org/sites/default/files/2025-06/USTS_2022Health%20Wellbeing%20Report_WEB.pdf (accessed Aug. 7, 2025). **8.** Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76.

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