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PURPOSE 1

No Clinically Significant Drug–Drug Interactions Between Lenacapavir and Hormonal Contraceptives in PURPOSE 1

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Conclusions

- **Lenacapavir (LEN)** coadministration **did not result in clinically significant changes in the pharmacokinetics (PK) of progestin-type long-acting (LA) hormonal contraceptives**: medroxyprogesterone acetate (DMPA), norethindrone enanthate (NET-EN), or etonogestrel (ENG)
- **Similar findings were observed** when assessing potential for drug–drug interactions (DDIs) **between LEN and estradiol** coadministered in PURPOSE 2 for gender-affirming hormonal therapy (GAHT) (Blumenthal J, et al. IDWeek 2025, HIV: Treatment poster session, Poster 305)
- Taken together, these **data support the coadministration of LEN with commonly used LA or oral hormonal contraceptives** with no dose adjustments

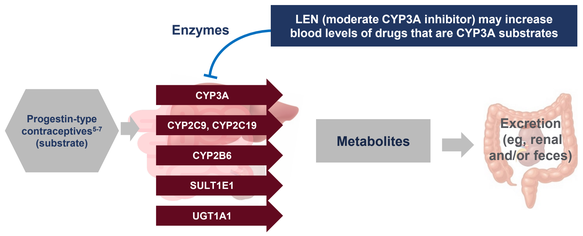
Plain Language Summary

- PrEP (pre-exposure prophylaxis) is a medication that helps prevent HIV before someone is exposed to the virus
- Many people who use PrEP also rely on hormonal contraception to prevent pregnancy
- LEN (lenacapavir) is a long-acting form of PrEP that's given as an injection twice a year (every 6 months). It was shown to be highly effective in preventing HIV in two large clinical trials (PURPOSE 1 and PURPOSE 2)
- This study looked at whether taking LEN affects the levels of hormonal contraceptives in the blood when both are used together
- The contraceptives studied were:
  - DMPA (medroxyprogesterone acetate) – an injectable contraceptive
  - Norethindrone enanthate – another injectable contraceptive
  - Etonogestrel – a hormone used in contraceptive implants
- These results showed that blood levels of these contraceptives were generally similar before and after LEN was given
- This means LEN and hormonal contraceptives can be safely used together, without needing to adjust the dose

Background

- Twice-yearly subcutaneous (SC) LEN demonstrated high efficacy and safety for PrEP in the Phase 3 randomized PURPOSE 1 (NCT04994509) trial in cisgender women[1]
- Since a substantial portion of the population who would benefit from PrEP also use contraception,[2] it is of interest to evaluate possible drug–drug interactions between LEN and commonly prescribed hormonal contraceptives
- The two primary classes of hormonal contraceptives are combined oral contraceptives, which include both an estrogenic and a progestin component, and progestin-only long-acting contraceptives, such as DMPA, NET-EN, and ENG[3]
- DMPA, NET-EN, and ENG are metabolized by cytochrome P450 3A (CYP3A) in addition to other pathways.[3-5] LEN is a moderate CYP3A inhibitor[6,7] and thus has the potential to increase concentrations of hormonal contraceptives metabolized by the CYP3A pathway (**Figure 1**)

Figure 1. Metabolism of Progestin-Type Contraceptives



CYP, cytochrome P450; LEN, lenacapavir; SULT1E1, estrogen sulfotransferase; UGT1A1, uridine diphosphate glucuronosyltransferase 1A.

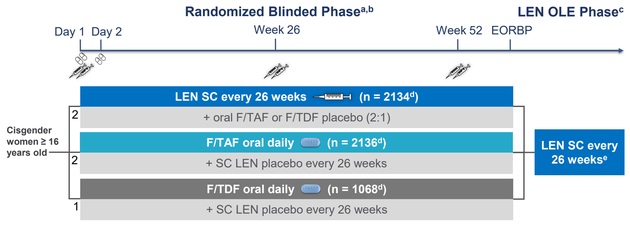
Objective

- To **assess drug–drug interactions between LEN and** commonly used progestin-type LA **hormonal contraceptives** (DMPA, NET-EN, or ENG) in a subset of PURPOSE 1 participants

Methods

- PURPOSE 1, a Phase 3, randomized, controlled trial, demonstrated the efficacy of twice-yearly LEN for PrEP in cisgender women. Participants were randomized 2:2:1 to SC LEN or oral emtricitabine/tenofovir alafenamide (F/TAF) or emtricitabine/tenofovir disoproxil fumarate (F/TDF) (**Figure 2**)[1]
- In PURPOSE 1, free contraception was provided but not required[1]
- We evaluated ENG, DMPA, and NET-EN concentrations based on observed levels at baseline and subsequent visit (after LEN was administered) in a selected subset of participants in the LEN group taking these contraceptives at baseline (prior to dosing) through at least 26 weeks
- Using a population PK model, we assessed the impact of hormonal contraceptives on LEN concentrations
- Adverse events (AEs) were assessed depending on concentration fluctuations

Figure 2. PURPOSE 1 Study Design[1]



[a]PK data were collected at Weeks 4, 8, 13, 26, and every 13 weeks thereafter.
[b]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/TAF or F/TDF received matched placebos.
[c]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/TAF of F/TDF in the RBP switched to SC LEN and had study visits at LEN OLE Day 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days). SC LEN was administered at LEN OLE Day 1 and Week 26 visits; these participants also received an oral LEN loading dose on LEN OLE Days 1 and 2. Participants whose last LEN injection was 13 weeks before LEN OLE Day 1 received LEN injections at LEN OLE Week 13 and 39 visits and completed the LEN OLE phase at Week 65.
[d]Included in the full analysis set for primary efficacy analyses.
[e]Or PK tail phase: participants who prematurely discontinued the study drug during the randomized blinded phase or LEN OLE phase, or those randomized to LEN in the randomized blinded phase who declined to participate in the LEN OLE phase upon unblinding, transitioned to the PK tail phase. Participants received oral F/TDF once daily for 78 weeks beginning 26 weeks after the last LEN injection.
EORBP, end of randomized blinded phase; F/TAF, emtricitabine/tenofovir alafenamide fumarate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; OLE, open-label extension; PK, pharmacokinetic; RBP, randomized blinded phase; SC, subcutaneous.

Results

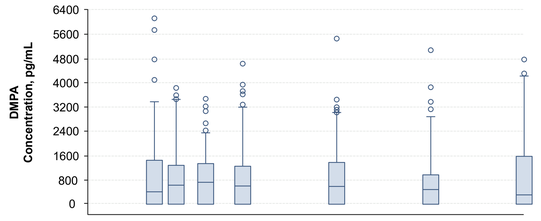
Concentrations of LA Hormonal Contraceptives

- Of 2140 participants in PURPOSE 1 receiving LEN, 226 had uninterrupted LA hormonal contraceptive exposure through at least Week 26
- Plasma concentrations of DMPA (**Figure 3**) and NET-EN (**Figure 4**) through Week 52 were generally comparable with baseline levels. With data pooled across various doses, frequencies, and dosing changes, no obvious trends were observed
- Median plasma ENG concentrations showed an upward trend between baseline and Week 13, before decreasing toward baseline levels at Week 26 (**Figure 5**)
- In a separate population PK analysis, progestin-type contraceptives had no impact on LEN exposures in PURPOSE 1[8]

Adverse Events

- Due to the observed fluctuations in median ENG concentrations, AEs were examined in depth for ENG only
- Rates of AEs commonly associated with ENG in participants taking concomitant ENG and not taking concomitant ENG are shown in **Table 1** and were comparable between LEN and oral PrEP treatment groups

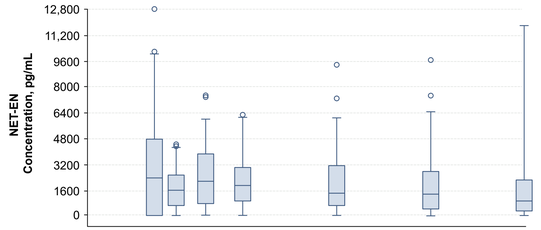
Figure 3. DMPA Concentration Remained Generally Comparable to Baseline Among Participants Receiving LEN



Participants on SC LEN, n	119	108	105	111	100	91	52

Concentrations observed are irrespective of form/dose/frequency/dosing changes of DMPA across the PK sampling duration. Values below the limit of quantitation (50 pg/mL) were treated as 0 for summary statistics. Summary statistics for a given time point displayed if sample size ≥ 5.
Boxes = first and third quartiles; horizontal lines inside boxes = median; whiskers = 5th and 95th percentiles; circles = outliers.
D, Day; DMPA, medroxyprogesterone acetate; LEN, lenacapavir; PK, pharmacokinetics; Q, quartile; SC, subcutaneous; W, Week.

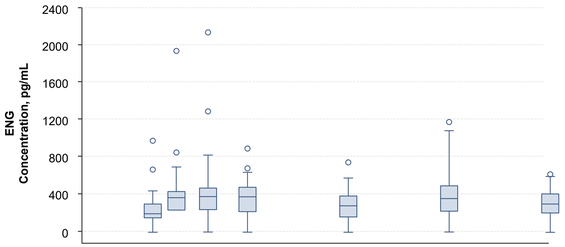
Figure 4. NET-EN Concentration Remained Generally Comparable to Baseline Among Participants Receiving LEN



Participants on SC LEN, n	55	52	48	55	46	35	19

Concentrations observed are irrespective of form/dose/frequency/dosing changes of NET-EN across the PK sampling duration. Values below the limit of quantitation (200 pg/mL) were treated as 0 for summary statistics. Summary statistics for a given time point displayed if sample size ≥ 5.
Boxes = first and third quartiles; horizontal lines inside boxes = median; whiskers = 5th and 95th percentiles; circles = outliers.
D, Day; LEN, lenacapavir; NET-EN, norethindrone enanthate; PK, pharmacokinetics; Q, quartile; SC, subcutaneous; W, Week.

Figure 5. ENG Concentration Showed Upward Trend Between Baseline and Week 13 Before Decreasing to Baseline Levels Among Participants Receiving LEN



Participants on SC LEN, n	50	45	47	42	37	30	20

Concentrations observed are irrespective of form/dose/frequency/dosing changes of ENG across the PK sampling duration. Values below the limit of quantitation (25 pg/mL) were treated as 0 for summary statistics. Summary statistics for a given time point displayed if sample size ≥ 5.
Boxes = first and third quartiles; horizontal lines inside boxes = median; whiskers = 5th and 95th percentiles; circles = outliers.
D, Day; ENG, etonogestrel; LEN, lenacapavir; PK, pharmacokinetics; Q, quartile; SC, subcutaneous; W, Week.

Table 1. ENG-Related AEs[a] Were Comparable in Participants Taking[b] or Not Taking Concomitant ENG

AE, n (%)[c]	SC LEN		F/TAF		F/TDF	
	ENG n = 420	No ENG n = 1720	ENG n = 356	No ENG n = 1779	ENG n = 195	No ENG n = 875
Headache	46 (11.0)	239 (13.9)	60 (16.9)	292 (16.4)	28 (14.4)	127 (14.5)
Abnormal uterine bleeding	18 (4.3)	52 (3.0)	19 (5.3)	41 (2.3)	16 (8.2)	29 (3.3)
Heavy menstrual bleeding	15 (3.6)	50 (2.9)	18 (5.1)	60 (3.4)	12 (6.2)	26 (3.0)
Intermenstrual bleeding	9 (2.1)	17 (1.0)	8 (2.2)	19 (1.1)	7 (3.6)	7 (0.8)
Menstruation irregular	1 (0.2)	6 (0.3)	2 (0.6)	3 (0.2)	1 (0.5)	1 (0.1)
Abdominal pain	6 (1.4)	39 (2.3)	8 (2.2)	53 (3.0)	3 (1.5)	22 (2.5)
Vaginitis[d]	23 (5.5)	102 (5.9)	21 (5.9)	109 (6.1)	16 (8.2)	73 (8.3)
Weight increase	6 (1.4)	11 (0.6)	4 (1.1)	12 (0.7)	0	6 (0.7)
Acne	4 (1.0)	4 (0.2)	0	6 (0.3)	1 (0.5)	1 (0.1)
Breast pain	1 (0.2)	8 (0.5)	1 (0.3)	2 (0.1)	0	1 (0.1)
Pharyngitis[e]	4 (1.0)	52 (3.0)	9 (2.6)	59 (3.3)	2 (1.0)	18 (2.1)

[a]ENG-related AEs listed are those reported at > 10% in the etonogestrel implant prescribing information.[9]
[b]Concomitant etonogestrel (Standard Medication Name WHOGEN = ETONOGESTREL) used between first dose and last exposure dates of study drug (inclusive).
[c]AEs are treatment emergent in participants who received at least one dose of study drug; AEs coded according to the Medical Dictionary for Regulatory Activities, Version 27.0. Treatment-emergent events began on or after study drug first dose date up through last exposure date for the study phase after permanent discontinuation of study drug, or led to premature study drug discontinuation.
[d]Includes vulvovaginitis, trichomonal vulvovaginitis, chlamydial vulvovaginitis, gonococcal vulvovaginitis, vaginitis chlamydial, and bacterial vulvovaginitis.
[e]Includes, nasopharyngitis, viral pharyngitis, bacterial pharyngitis, and pharyngitis.
AE, adverse event; ENG, etonogestrel; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SC, subcutaneous.

References: **1**. Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92. **2**. de Dieu Tapsoba J, et al. *AIDS Care*. 2021;33:712-20. **3**. Bick AJ, et al. *Pharmacol Ther*. 2021;222:107789. **4**. Li L, et al. *Drug Metab Dispos*. 2023;51:718-32. **5**. Zhang N, et al. *Clin Transl Sci*. 2018;11:251-60. **6**. Yeztugo (lenacapavir) USPI, Gilead Sciences, Inc., June 2025. **7**. Begley R, et al. Oral 89 presented at: CROI, March 6-10, 2021; Virtual. **8**. Imperial M, et al. Poster I-109 presented at: PAGE; June 4-6, 2025; Thessaloniki, Greece. **9**. Nexplanon (etonogestrel implant) USPI, Organon, September 2023.

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