Higher Persistence on Twice-yearly Lenacapavir Versus Daily F/TDF for PrEP in the UK and France in the PURPOSE 5 Study

O21

PURPOSE 5

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Conclusions

- At Week 52, pre-exposure prophylaxis (PrEP) persistence was significantly higher with twice-yearly subcutaneous (SC) lenacapavir (LEN) than daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) in people who would benefit from PrEP (PWBP) in the UK and France
  - This is consistent with the significantly higher persistence on LEN versus F/TDF in PURPOSE 1 and PURPOSE 2[1,2]
- LEN was generally safe and well tolerated
  - Safety, including injection experience, was similar to that observed in PURPOSE 1 and PURPOSE 2[3,4]
- There were no observed HIV acquisitions in participants receiving LEN
- Most participants expressed a strong preference for twice-yearly injection over a daily oral pill for PrEP
- Based on a rigorous, objective measure of persistence, PURPOSE 5 supports the potential public health impact of LEN in improving PrEP persistence, and consequently PrEP effectiveness, among PWBP not currently taking PrEP

Plain Language Summary

- Oral HIV pre-exposure prophylaxis (PrEP) can help to prevent HIV when taken every day as recommended. However, it may not work as well if people do not take it as recommended. Many people use PrEP in France and in the UK, but some communities are more affected by HIV and may face barriers to accessing or continuing PrEP
- Lenacapavir (LEN) is a PrEP option given as an injection under the skin twice a year. In two clinical studies, PURPOSE 1 and PURPOSE 2, LEN was shown to help prevent people getting HIV. LEN is approved for PrEP
- Because LEN is given as an injection only twice a year, it could help to overcome some of the challenges people face and make it easier for people to start and continue using PrEP as recommended
- The PURPOSE 5 study compared how consistently people continued taking their assigned PrEP as directed (on-time LEN injections or daily emtricitabine/tenofovir disoproxil fumarate [F/TDF] tablets) for 1 year. This is called persistence
- The study took place in France and the UK. It included only people who were not using PrEP when they joined the study
- After 1 year, more people in the LEN group (86%) were persistent with PrEP compared with the F/TDF group (46%)
- People preferred twice-yearly LEN injection over daily oral F/TDF for PrEP
- LEN was generally safe and well tolerated
- These results show that LEN could help people continue using PrEP as recommended over time, and therefore increase the effectiveness of PrEP

Introduction

- Although oral HIV PrEP is highly effective when taken daily, suboptimal adherence and discontinuations reduce effectiveness[3-5]
- Twice-yearly SC LEN was highly efficacious as PrEP in PURPOSE 1 and PURPOSE 2,[3,4] and has the potential to increase the uptake of, adherence to, and persistence on PrEP, thereby increasing effectiveness
- While overall PrEP use is high in France and the UK, many key populations remain underserved by oral PrEP and inequities remain between PrEP availability and uptake[6-12]
- PURPOSE 5 is a Phase 2, randomized, open-label study in France and the UK assessing the persistence on twice-yearly SC LEN or daily oral F/TDF for PrEP at 1 year

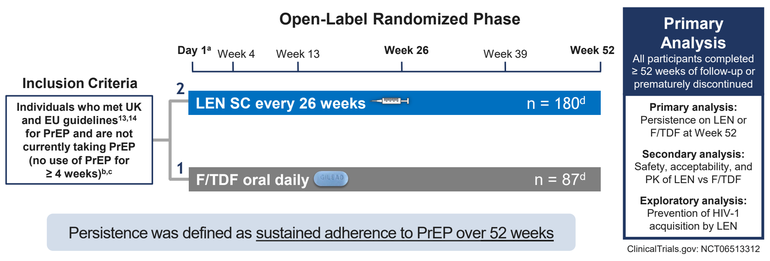
Objective

- To assess persistence at 1 year, defined as sustained adherence over time, on LEN or F/TDF in PWBP disproportionately affected by HIV not currently using PrEP in France and the UK

Methods

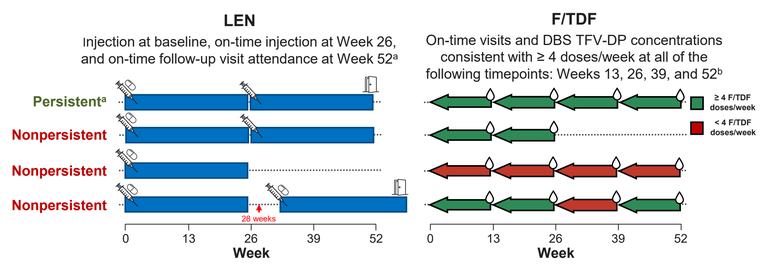
- PURPOSE 5 (NCT06513312) is a randomized, open-label study among people not currently taking PrEP in the UK and France. Participants were randomized 2:1 to receive twice-yearly LEN injection or daily oral F/TDF for 52 weeks (**Figure 1**)
- The primary endpoint of the study was persistence, which assessed continued adherence over time, through Week 52 (**Figure 2**)
  - LEN persistence was defined as injections at baseline, on-time injections (± 2 weeks) at Week 26, and on-time follow-up visit at Week 52
  - F/TDF persistence was defined as on-time visits and tenofovir-diphosphate (TFV-DP) concentration in dried blood spots (DBS) consistent with ≥ 4 doses/week at all of the following timepoints: Weeks 13, 26, 39, and 52
  - Persistence was compared using Fisher's exact test

Figure 1. PURPOSE 5 Evaluated Persistence on Twice-Yearly SC LEN vs Daily Oral F/TDF for PrEP in France and the UK



[a]On Days 1 and 2, all participants receiving LEN received a pharmacologic loading dose of 600 mg oral LEN.
[b]≥ 18 years of age, HIV-negative test, eGFR ≥ 60 mL/min. [c]HIV-negative status was confirmed by a local rapid HIV-1/2 antibody (Ab)/antigen (Ag) test, central HIV-1/2 Ab/Ag, and HIV-RNA NAAT at screening and on Day 1. [d]n numbers represent completed enrollment and received at least one dose of study drug.

Figure 2. Defining Annual Persistence on PrEP: Sustained Adherence to Study Drug and Follow-Up Visits Over 52 Weeks



Nonpersistence on PrEP included participants who discontinued study drug for any reason. The proportion of participants with persistence through Week 52 was reported for each study group with two-sided 95% exact CIs based on the Clopper-Pearson method. [a]On-time injection at Week 26 and on-time follow-up visit at Week 52 were defined as 26 weeks (± 2 weeks) after the last injection. [b]One DBS concentration could be missing if that visit still occurred on-time and DBS concentrations at the three other timepoints were consistent with ≥ 4 doses/week.

Results

- Baseline characteristics were balanced across study groups (**Table 1**)
- At Week 52, persistence on LEN was 39.3% higher than on F/TDF (**Figure 3**)
- Nearly twice as many participants persisted on LEN at Week 52 compared with F/TDF, with nonpersistence on F/TDF driven by low adherence (**Figure 4**)
  - Premature discontinuations occurred in a similar proportion of participants in the LEN (10%) and F/TDF groups (9%) (**Table 2**)
- No HIV acquisitions were reported in participants receiving LEN, while one participant in the F/TDF group acquired HIV (**Figure 5**)
  - At diagnosis, the participant who acquired HIV in the F/TDF group had evidence of low adherence by TFV-DP concentrations in DBS (< 2 doses of F/TDF per week on average)
- LEN was generally safe and well tolerated with no new safety concerns identified. Adverse events (excluding injection site reactions [ISRs]) were similar across groups (**Table 3**)
- Most ISRs with LEN were mild. ISR frequency and severity were similar to that observed in other LEN for PrEP studies[3,4] (**Figure 6**)
  - 169 (94%) of participants had ISRs. No severe (Grade 3 or 4) ISRs were reported
- Observed LEN concentrations at Week 26 in PURPOSE 5 were similar to those in PURPOSE 1 and PURPOSE 2 (**Table 4**). The mean C_{trough} 90% CI was above the target concentration of 15.5 ng/mL (IQ4)
- Most participants preferred a twice-yearly LEN injection over a once-daily pill for PrEP. A strong preference for injection increased from Day 1 to Week 26 in participants receiving LEN (**Figure 7**)

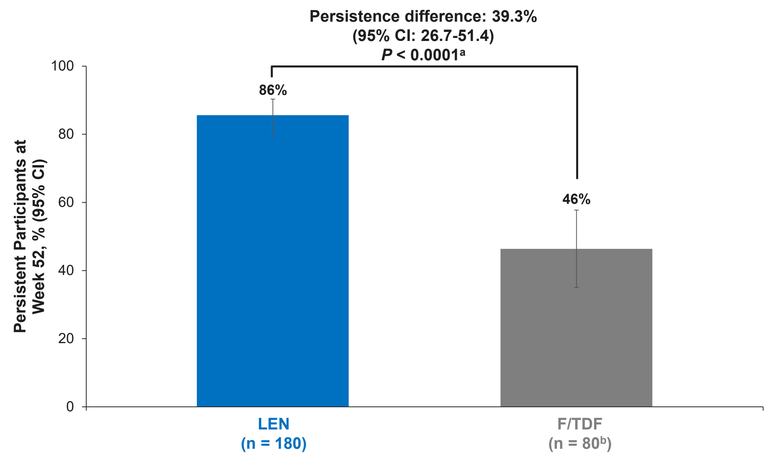
Results (cont.)

Table 1. Baseline Characteristics

Characteristic	LEN (n = 180)	F/TDF[a] (n = 87)	Overall (N =267)
PrEP naïve, n (%)	68 (38)	33 (38)	101 (38)
Gender, n (%)[b]			
Cisgender men	130 (72)	63 (72)	193 (72)
Cisgender women	14 (8)	5 (6)	19 (7)
Transgender men	10 (6)	3 (3)	13 (5)
Transgender women	13 (7)	13 (15)	26 (10)
Gender nonbinary	12 (7)	3 (3)	15 (6)
Median age, years (IQR)	34 (28, 40)	34 (29, 43)	34 (28, 41)
Age ≤ 25 years, n (%)	30 (17)	15 (17)	45 (17)
Race or ethnic origin, n (%)			
White	110 (66)	62 (75)	172 (69)
Black	18 (11)	9 (11)	27 (11)
Asian	15 (9)	5 (6)	20 (8)
Other[c]	24 (14)	7 (8)	31 (12)
Not permitted[d]	13	4	17
Hispanic or Latino ethnicity, n (%)[e]	10 (6)	4 (5)	14 (6)
Born abroad, n (%)[f]	51 (29)	18 (21)	69 (26)
Diagnosis of bacterial STI in previous 12 months, n (%)	55 (31)	22 (25)	77 (29)
Engagement in sex work or transactional sex in previous 12 months, n (%)	17 (9)	10 (11)	27 (10)

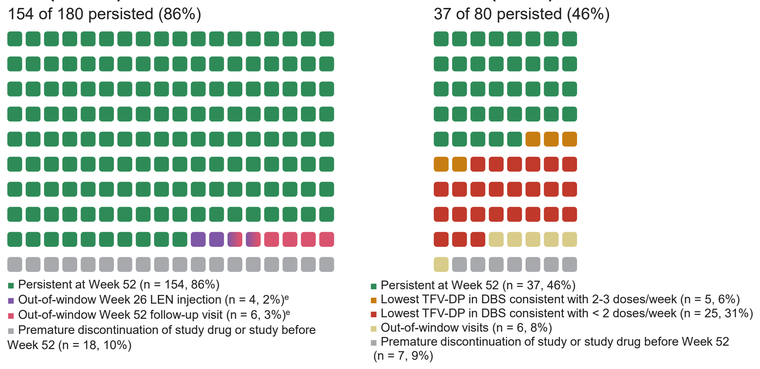
[a]88 participants were randomized and one participant discontinued before receiving study drug. [b]One participant identified as androgenous. [c]This includes one American Indian or Alaska Native participant and one Native Hawaiian or Pacific Islander participant in the LEN group. [d]'Not permitted' entered if information cannot be collected due to regulations or if the participant declines to provide information. [e]The denominator excluded participants with 'missing' or 'not permitted' entered. [f]Those with country of birth other than France or the UK. The denominator excluded participants with 'missing' or 'not permitted' country of birth (three with LEN and two with F/TDF).

Figure 3. Significantly More Participants Persisted on LEN vs F/TDF at Week 52



[a]*P* value for persistence difference is based on Fisher's exact test.
[b]Seven participants were excluded from the full analysis set due to no available DBS TFV-DP at any of the Week 13, 26, 39, or 52 visits.

Figure 4. Nonpersistence on F/TDF Was Primarily Driven by Low Adherence



[a]Percentages are of participants in each group. [b]Participants who were nonpersistent were categorized into early discontinuation versus nonadherence to the randomized PrEP regimen. If participants remained on study drug at 52 weeks, reasons for nonadherence were assessed. For participants in the F/TDF group, they were categorized by lowest TFV-DP concentration in DBS at Weeks 13, 26, 39, or 52, followed by out-of-window visits. If the six participants who were deemed nonpersistent due to out-of-window visits were considered persistent, 43 of 80 participants would be persistent on F/TDF at Week 52 (53.8%; *P* < 0.0001 vs LEN group). [c]Nonadherence in the F/TDF group was defined by TFV-DP concentrations in DBS and out-of-window visits. [d]Seven participants were excluded from the full analysis set due to no available DBS TFV-DP at any of the Week 13, 26, 39, or 52 visits. [e]Two participants had both out-of-window Week 26 LEN injection and Week 52 follow-up visit.

Table 2. Premature Discontinuations Occurred in a Similar Proportion of Participants in the LEN and F/TDF Groups

n (%)	LEN (n = 180)	F/TDF (n = 80[a])
Premature discontinuation of study drug or study prior to Week 52	18 (10)	7 (9)
Investigator's discretion	1 (< 1)[b]	0
AEs	0	0
Participant's decision or withdrawal of consent	13 (7)[c]	2 (3)
Nonadherence to study drug	1 (< 1)	0
Lost to follow-up	2 (1)	4 (5)
HIV-1 acquisition	0	1 (1)
Missing	1 (< 1)	0

[a]Seven participants were excluded from the full analysis set due to no available DBS TFV-DP at any of the Week 13, 26, 39, or 52 visits; two of these seven participants discontinued prior to Week 13 due to AEs with F/TDF. [b]One participant was discontinued at the discretion of the investigator due to participant experiencing macular urticaria, which was assessed as related to LEN. The investigator discontinued LEN but reported discontinuation as at their discretion rather than due to AE. [c]Participant reasons for discontinuing LEN injections or withdrawing consent included: ISRs (n = 3), did not like/did not want further injections (n = 3), relocated (n = 3), lifestyle changes (n = 1), and no additional rationale documented (n = 3).

Figure 5. No HIV Acquisitions Were Reported in Participants Receiving LEN

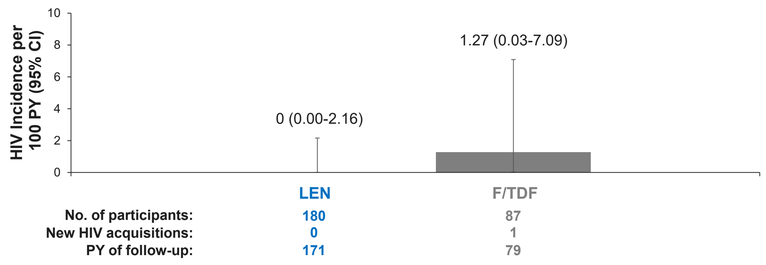
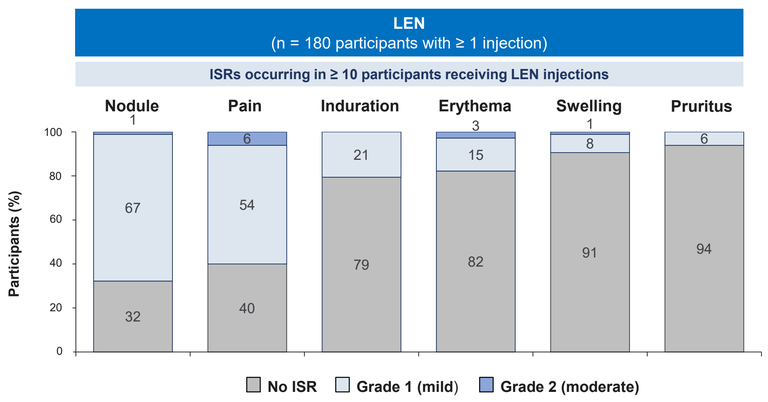


Table 3. Adverse Events and STIs Were Similar Across Groups

n (%)	LEN (n = 180)	F/TDF (n = 87)
Any AE (excluding ISRs)	157 (87)	71 (82)
Grade ≥ 3	8 (4)	6 (7)
Serious AEs	7 (4)	3 (3)
AEs leading to discontinuation of study drug	0	2 (2)
Death	0	0
AEs occurring in ≥ 10% of participants in either group (excluding ISRs)		
Anal gonococcal infection	20 (11)	12 (14)
Anal chlamydia infection	19 (11)	9 (10)
Diarrhea	14 (8)	13 (15)
Oropharyngeal gonococcal infection	20 (11)	3 (3)
Nausea	7 (4)	9 (10)
Sexually transmitted infections (STIs)[a]		
Gonorrhea, chlamydia, or *Trichomonas vaginalis*	48 (27)	25 (29)
Gonorrhea	26 (15)	18 (21)
Chlamydia	30 (17)	11 (13)
Trichomonas vaginalis	2 (8)	0
Syphilis	9 (5)	4 (5)

AEs were coded according to MedDRA Version 29.0. Treatment-emergent events began on or after study drug first dose date through last exposure date for the study phase, or the day prior to the initiation of study drug in the next study phase, whichever is earlier. Death includes any death that occurred during the randomized phase. Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [a]STI summary is from laboratory assessments or investigator diagnosis. For the STI analysis, there were 177 participants included in the LEN group and 85 participants included in the F/TDF group.

Figure 6. Most ISRs With LEN Were Mild



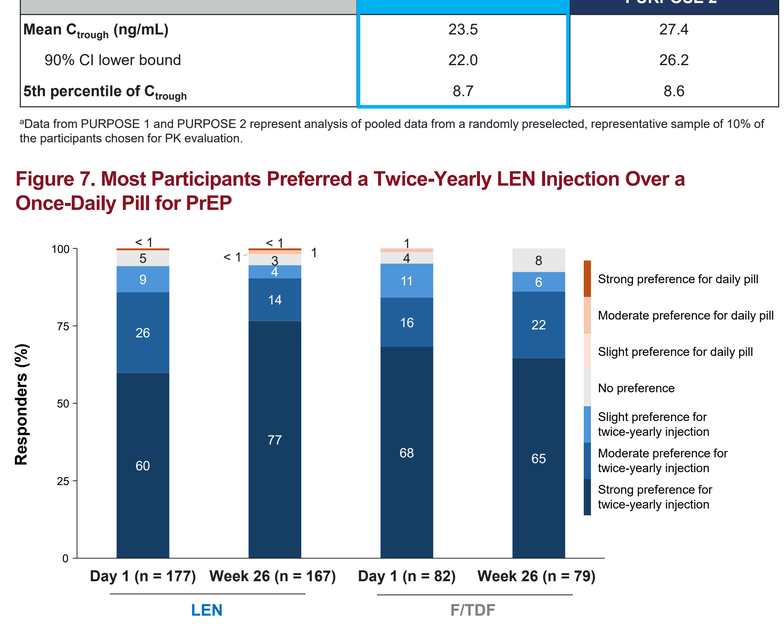
Reported ISRs were to study drug–related injection only and were coded according to the Medical Dictionary for Regulatory Activities, Version 29.0. Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. Due to rounding, percentages may not total 100. Multiple ISRs were counted only once per participant for the highest severity grade for each preferred term.

Table 4. LEN Trough Concentrations at Week 26

	PURPOSE 5	PURPOSE 1 and PURPOSE 2[a]
Mean C_{trough} (ng/mL)	23.5	27.4
90% CI lower bound	22.0	26.2
5th percentile of C_{trough}	8.7	8.6

[a]Data from PURPOSE 1 and PURPOSE 2 represent analysis of pooled data from a randomly preselected, representative sample of 10% of the participants chosen for PK evaluation.

Figure 7. Most Participants Preferred a Twice-Yearly LEN Injection Over a Once-Daily Pill for PrEP



References: **1.** Bekker LG, et al. Oral 048 presented at: HIV Drug Therapy Glasgow 2024; Nov. 10-13, 2024; Glasgow, UK. **2.** Ogbuagu O, et al. Oral PS08.5 presented at: EACS 2025; Oct.15-18, 2025; Paris, France. **3.** Kelley CF, et al. *N Engl J Med*. 2025;392:1261-76. **4.** Bekker LG, et al. *N Engl J Med*. 2024;391:1179-92. **5.** Marrazzo J, et al. *JAMA*. 2024;331:930-37. **6.** UK Health Security Agency. HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services: 2025 report (accessed Oct. 19, 2026). **7.** Public Health England. https://assets.publishing.service.gov.uk/media/602166b08fa8f51474577bf7/hpr2020_hiv19.pdf (accessed Oct.19, 2026). **8.** Whelan I, et al. *Lancet HIV*. 2023;10:e472-81. **9.** Shannon K, et al. *Lancet*. 2018;392:698-710. **10.** Santé Publique France. https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-sexuellement-transmissibles/vih-sida/documents/bulletin-national/vih-et-ist-bacteriennes-en-france.-bilan-2023 (accessed Oct. 19, 2026). **11.** Gosselin A, et al. *Sex Transm Infect*. 2020;96:227-31. **12.** Billioti de Gage S, et al. *Lancet Reg Health Eur*. 2022;22:100486. **13.** British Association for Sexual Health and HIV/British HIV Association. https://bhiva.org/wp-content/uploads/2025/07/2025-PrEP-guidelines.pdf (accessed Oct. 19, 2026). **14.** EACS. https://eacs.sanfordguide.com/eacs-part1/art/eacs-pre-exposure-prophylaxis (accessed Oct 19, 2026). **15.** Margot N, et al. Poster O-324 presented at: HIV Drug Therapy Glasgow; Oct. 5-8, 2020; Glasgow, UK.

Abbreviations: AE, adverse event; CI, confidence interval; C_{trough}, trough concentration; DBS, dried blood spot; eGFR, estimated glomerular filtration rate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; IQ4, 4 times the protein-adjusted 95% effective concentration *in vitro*[15]; IQR, interquartile range; ISR, injection site reaction; LEN, lenacapavir; NAAT, nucleic acid amplification testing; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; PY, person-years; PWBP, people who would benefit from PrEP; SC, subcutaneous; STI, sexually transmitted infection; TFV-DP, tenofovir diphosphate.

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