GILEAD | Medical Information

Yeztugo® (lenacapavir) PURPOSE 2 Study

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and the PURPOSE 2 study.

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www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi;
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Summary

Clinical Data: PURPOSE 2 Study

PURPOSE 2 is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TDF for HIV-1 PrEP in 3265 cisgender gay, bisexual, and other men, TGW, TGM, and GNB individuals in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the US who have condomless receptive anal sex with partners assigned male at birth. Study participants were randomly assigned in a 2:1 ratio to LEN or FTC/TDF, respectively.[1]

PURPOSE 2 met its key efficacy endpoints at the prespecified interim analysis, demonstrating superiority of twice-yearly SUBQ LEN over bHIV (incidence expected in the absence of PrEP) and daily oral FTC/TDF. LEN reduced HIV incidence by 96% compared with bHIV incidence (primary endpoint; IRR, 0.04; 95% CI: 0.01–0.18; $P<0.001$), and by 89% compared with daily oral FTC/TDF (secondary endpoint; IRR, 0.11; 95% CI: 0.02–0.51; $P=0.002$).[1]

- There were 2 incident cases among 2179 participants in the LEN group (incidence of 0.1 per 100 PY).
- There were 9 incident cases among 1086 individuals in the FTC/TDF group (incidence of 0.93 per 100 PY).

Overall, the frequencies of non-ISR AEs and laboratory abnormalities were similar between groups, with the exception of changes in eGFR. Most ISRs were mild to moderate in severity and were reported in 1816 participants (83.2%) who received SUBQ LEN and 756 participants (69.5%) who received SUBQ LEN placebo injections.[1]

On September 11, 2024, an external independent data monitoring committee concluded that the prespecified efficacy criteria for stopping the blinded portion of the trial had been met based on the interim results, and (per the trial protocol) the interim analysis became the primary analysis. All participants were offered the option to receive open-label SUBQ LEN on September 25, 2024.[1]

Clinical Data: PURPOSE 2 Study

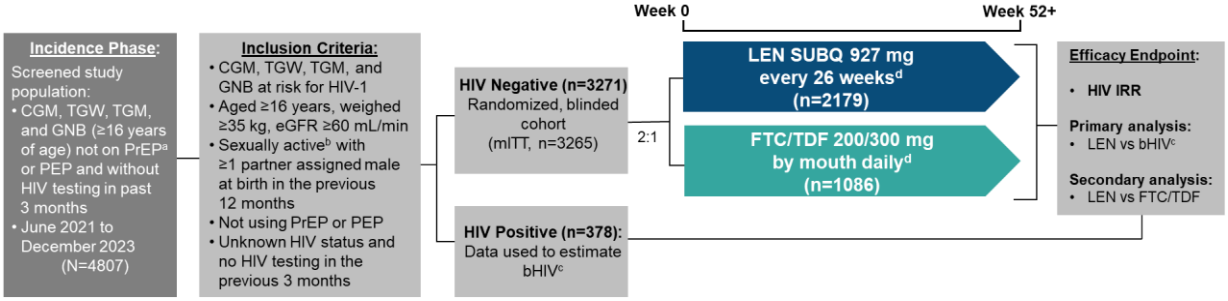
Study Design and Demographics

PURPOSE 2 (NCT04925752) is an ongoing, phase 3, double-blind, randomized study evaluating the efficacy and safety of twice-yearly SUBQ LEN and once-daily oral FTC/TDF for HIV-1 PrEP in cisgender gay, bisexual, and other men, TGW, TGM, and GNB individuals aged ≥16 years in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the US who have condomless receptive anal sex with partners assigned male at birth (N=3265). Eligible participants were tested for HIV at screening, and those who tested negative were randomly assigned in a 2:1 ratio to SUBQ LEN every 26 weeks plus daily oral FTC/TDF placebo (n=2179) or SUBQ LEN placebo every 26 weeks plus daily oral FTC/TDF (n=1086; Figure 1). Additional testing was performed with samples from participants who tested positive for HIV at screening to determine the recency of the HIV infection, and these data were used to estimate the bHIV that would be expected without PrEP.[1]

Key inclusion criteria in the randomized phase of the study included the following: negative results on point-of-care fourth-generation Ag/Ab test and central laboratory fourth-generation Ag/Ab test (if positive, was confirmed by an HIV-1/2 Ab differentiation assay), qualitative HIV-1 RNA test (lower limit of quantification, 20 c/mL), eGFR ≥60 mL/min, and body weight ≥35 kg at screening. Individuals were excluded if they had prior use of HIV PrEP (including FTC/TDF or FTC/TAF) or HIV PEP in the past 3 months, or any prior use of long-acting injectable HIV PrEP.[1,2]

The primary efficacy endpoint was the incidence of HIV among randomized participants.[1]

Figure 1. PURPOSE 2: Study Design[1,2]



[a] Included oral PrEP use within the last 12 weeks or any prior use of long-acting injectable forms of PrEP.
[b] Condomless receptive anal sex with ≥1 partner in the previous 12 months and met ≥1 of the following criteria: condomless receptive anal sex with ≥2 partners in the previous 12 weeks; history of syphilis, rectal gonorrhea, or rectal chlamydia in the previous 24 weeks; self-reported use of stimulants with sex in the previous 12 weeks.
[c] The bHIV was the incidence of HIV expected without PrEP that would be anticipated in a placebo group. A total of 45 participants (11.9%) were classified as recently acquiring HIV.
[d] All participants received an oral initiation dose of LEN (600 mg) or matching oral placebo on Days 1 and 2. Participants randomly assigned to the SUBQ LEN group received oral placebo FTC/TDF, and participants in the FTC/TDF group received SUBQ LEN placebo.

A total of 3271 participants were randomly assigned and received ≥1 dose of study drug; 6 participants were diagnosed with HIV on Day 1 and were excluded from the efficacy analysis (mITT, n=3265). Baseline demographics were balanced between randomized groups (Table 1).[1]

Table 1. PURPOSE 2: Select Baseline Demographics and Disease Characteristics[1]

Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
Age	Median (range), years	28 (17–74)	29 (17–73)
	16 to ≤25 years, n (%)	752 (34.4)	344 (31.6)
Country, n (%)	Brazil	769 (35.2)	396 (36.4)
	United States	440 (20.2)	235 (21.6)
	Peru	309 (14.2)	138 (12.7)
	Thailand	250 (11.5)	139 (12.8)
	South Africa	246 (11.3)	112 (10.3)
	Argentina	161 (7.4)	64 (5.9)
	Mexico	8 (0.4)	4 (0.4)
Race or ethnicity, n/N (%)	Hispanic or Latine	1378/2182 (63.2)	675/1088 (62)
	Black[a]	811/2175 (37.3)	420/1086 (38.7)
	White	722/2175 (33.2)	344/1086 (31.7)
	Indigenous or Indigenous ancestry[b]	341/2175 (15.7)	156/1086 (14.4)
	Asian	269/2175 (12.4)	144/1086 (13.3)
	Other and other multiracial[c]	32/2175 (1.5)	22/1086 (2)
Gender identity, n (%)	Cisgender man	1697 (77.7)	846 (77.8)
	Transgender woman	315 (14.4)	161 (14.8)
	Gender nonbinary[d]	136 (6.2)	63 (5.8)
	Transgender man	29 (1.3)	14 (1.3)
	Other[e]	6 (0.3)	4 (0.4)
Sexually transmitted infections,[f] n (%)	*Chlamydia trachomatis*	253 (11.6)	126 (11.6)
	Neisseria gonorrhea	193 (8.8)	115 (10.6)
	Syphilis	84 (3.8)	43 (4)
No history of HIV test, n (%)		597 (27.3)	306 (28.1)
Any history of PrEP use, n (%)		515 (23.6)	249 (22.9)
Self-reported use of stimulants with sex in last 12 weeks, n (%)		491 (22.5)	271 (24.9)

[a] Included all participants who identified as Black/of Black ancestry: Black, Back/White, Black/Pardo (a specific racial category in Brazil), Black/Brown (Brazil), Black/Colored (a specific racial category in South Africa), Black/American Indian or Alaskan Native, Black/Asian, and Black/Native Hawaiian or Pacific Islander.
[b] Included all participants who identified as American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Asian/Native Hawaiian or Pacific Islander, White/Native Hawaiian or Pacific Islander, and White/American Indian or Alaskan Native.
[c] Included all participants who identified as Asian/White, Colored (South Africa), Pardo (Brazil), White/Brown (Brazil), multiracial any other, and not multiracial other.
[d] Included 122 participants (89.7%) in the LEN group and 53 participants (84.1%) in the FTC/TDF group assigned male at birth.
[e] Included individuals who identified as Travesti (LEN, n=3; FTC/TDF, n=3) or as an "Other" gender (LEN, n=3; FTC/TDF, n=1).
[f] *Chlamydia trachomatis* and *Neisseria gonorrhea* were diagnosed based on testing pharyngeal, rectal, and urethral (urine) samples by central and local laboratories. Syphilis was diagnosed by testing blood and was performed locally by local testing protocols.

Results of Primary and Secondary Efficacy Analyses[1]

In total, 3220 participants had ≥1 post-randomization HIV-1 test, resulting in 2905 PY of follow-up for calculations of incident HIV. The overall study retention rate was high and similar between treatment groups: 94.4% (2834/3001) at Week 26, 93.3% (1191/1277) at Week 52, and 91.3% (63/69) at Week 104.

The prespecified interim analysis was conducted when 50% of participants had completed ≥52 weeks of follow-up. Adherence was high, and injections were administered on time (ie, within 28 weeks of prior injection) in 91% of participants (2606/2864) at Week 26 and in

92.8% of participants (1016/1095) at Week 52. In the FTC/TDF group, TFV-DP concentrations in dried blood stains consistent with high adherence (≥4 pills per week) was seen in 82% at Week 8, 67% at Week 26, and in 62% at Week 52.

The bHIV in the screened population was 2.37 per 100 PY (95% CI: 1.65–3.42; Figure 2). In the LEN group, there were 2 incident HIV cases (0.1 per 100 PY; 95% CI: 0.01–0.37) 13 and 26 weeks after the first dose. Both participants had LEN concentrations above the IQ4 (15.5 ng/mL) at the time of diagnosis; no delayed diagnosis was revealed by retrospective HIV-1 RNA viral load testing, and both participants developed the N74D capsid resistance mutation. There were 9 incident HIV cases (0.93 per 100 PY; 95% CI: 0.43–1.77) in the FTC/TDF group; these participants had low/no adherence (determined through measurements of TFV-DP levels in dried blood stains) or had documented discontinuation of FTC/TDF >10 days prior to diagnosis, and 1 participant was found to have an M184V resistance mutation.

PURPOSE 2 met its key efficacy endpoints, demonstrating superiority of twice-yearly SUBQ LEN over bHIV and daily oral FTC/TDF. LEN reduced HIV incidence by 96% compared with bHIV incidence (primary endpoint; IRR, 0.04; 95% CI: 0.01–0.18; *P*<0.001), and by 89% compared with daily oral FTC/TDF (secondary endpoint; IRR, 0.11; 95% CI: 0.02–0.51; *P*=0.002; Figure 3).

Figure 2. PURPOSE 2: Incidence of HIV-1 (mITT Population)[1]

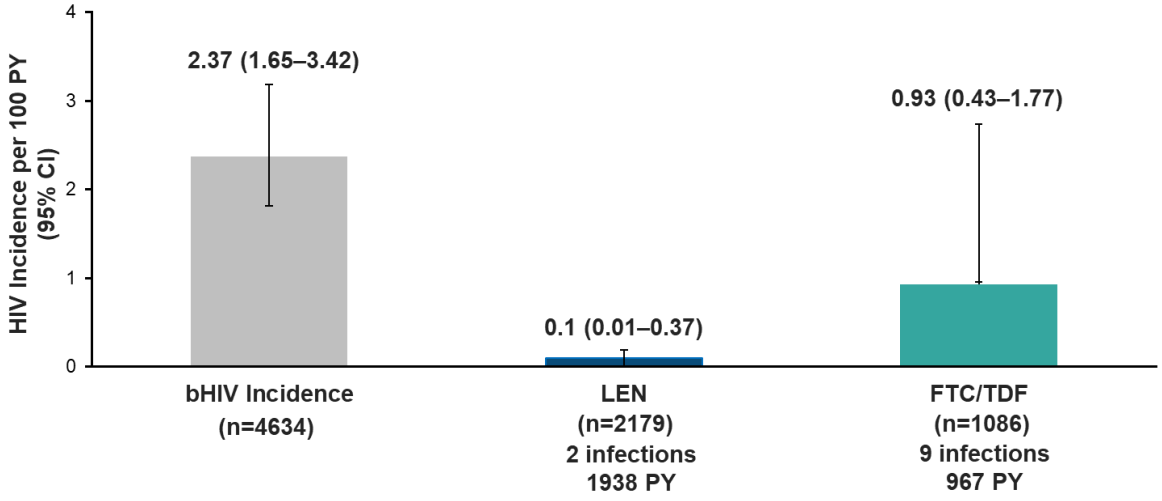
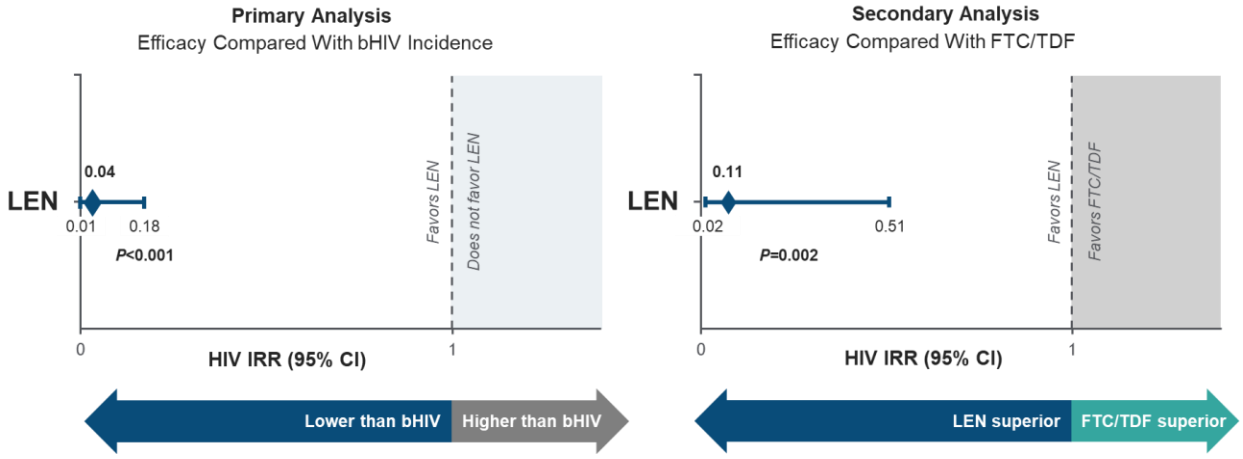


Figure 3. PURPOSE 2: Primary and Secondary Analyses (mITT Population)[1]



Safety Results[1]

Overall, the frequencies of non-ISR AEs and laboratory abnormalities were similar between groups (Table 2), except for changes in eGFR, with a median (IQR) change from baseline to Week 26 of +1.2 (-8 to +10.9) mL/min in the LEN group and -3 (-12.4 to +6.5) mL/min in the FTC/TDF group (*P*<0.001) and a median (IQR) change from baseline to Week 52 of +0.6 (-10.3 to +10.8) mL/min in the LEN group and -2.9 (-13.8 to +7.4) mL/min in the FTC/TDF group (*P*=0.002). There were 4 deaths (0.2%) in the LEN group (each, n=1: cerebrovascular accident and pulmonary thromboembolism, car collision, sudden death with an undetermined cause, and suicide) and 2 (0.2%) in the FTC/TDF group (each, n=1: intracranial hemorrhage and undetermined cause); none were deemed related to study drug by investigator.

Table 2. PURPOSE 2: Safety Summary of Non-ISR AEs and Laboratory Abnormalities[1]

Non-ISR AEs		LEN (n=2183)	FTC/TDF (n=1088)
Any-grade AE, n (%)		1607 (73.6)	803 (73.8)
Grade ≥2		1173 (53.7)	594 (54.6)
Grade ≥3		91 (4.2)	65 (6)
Serious AEs		71 (3.3)	43 (4)
AEs that led to study drug discontinuation[a]		7 (0.3)	7 (0.6)
AEs in ≥5% of participants, n (%)	Rectal chlamydia infection	289 (13.2)	128 (11.8)
	Oropharyngeal gonococcal infection	283 (13)	119 (10.9)
	Rectal gonococcal infection	233 (10.7)	99 (9.1)
	Upper respiratory tract infection	148 (6.8)	77 (7.1)
	Diarrhea	146 (6.7)	75 (6.9)
	Influenza	120 (5.5)	66 (6.1)
	Headache	119 (5.5)	76 (7)
	Latent syphilis	114 (5.2)	44 (4)
	Nausea	89 (4.1)	67 (6.2)
Laboratory abnormality,[b] n/N (%)	Any Grade ≥1	1822/2153 (84.6)	937/1071 (87.5)

[a] Decreased renal CrCl was the only non-ISR AE that led to study drug discontinuation in >1 participant in either group (FTC/TDF, n=2 [0.2%]).
[b] Included participants with ≥1 post-baseline result.

Overall, 10,094 SUBQ LEN and 5145 SUBQ LEN placebo injections were administered, and ISRs were reported in 1816 participants (83.2%) who received LEN and 756 participants (69.5%) in the FTC/TDF group who received placebo injections. Most ISRs were mild to moderate in severity, and nodules, pain, and erythema were the most common ISRs. Nodules were reported more frequently in the LEN group than in the placebo injection group (63.4% vs 39.2%, respectively), with a median (IQR) duration of 183 (89–274) days in the SUBQ LEN group and 64 (19–98) days in the placebo injection group. The median (IQR) duration of induration was 84 (8–190) days in the SUBQ LEN group and 8 (5–57) days in the placebo injection group. The incidence of pain was similar between groups (SUBQ LEN, 56.4%; placebo injection, 53.4%). There were no reports of keloid formation. Overall, the frequency and severity of ISRs decreased over time. AEs of ISRs led to study drug discontinuation in 29 participants (LEN, n=26 [1.2%]; FTC/TDF, n=3 [0.3%]).

References

1. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med.* 2024.
2. ClinicalTrials.gov. Study to Assess the Effectiveness and Safety of Lenacapavir for Human Immunodeficiency Virus (HIV) Pre-Exposure Prophylaxis (PURPOSE 2). ClinicalTrials.gov Identifier: NCT04925752. Available at: https://clinicaltrials.gov/ct2/show/NCT04925752. Accessed: 22 December. Last Updated: 21 December. 2022.

Abbreviations

Ab=antibody
AE=adverse event
Ag=antigen
bHIV=background HIV incidence
CGM=cisgender men
FTC=emtricitabine
GNB=gender non-binary
IQ4=inhibitory quotient 4
IRR=incidence rate ratio
ISR=injection site reaction
LEN=lenacapavir
mITT=modified intent-to-treat
PEP=post-exposure prophylaxis
PrEP=pre-exposure prophylaxis
PY=person-years
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV-DP=tenofovir diphosphate
TGM=transgender men
TGW=transgender women

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Yeztugo and Truvada US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Follow-Up

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