GILEAD | Medical Information

Yeztugo® (lenacapavir) PURPOSE 1 Study

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and the PURPOSE 1 study.

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The use of FTC/TAF for prevention of HIV in cisgender women is investigational and has not been approved by any regulatory authority. The full indication, important safety information, and boxed warning(s) are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/yeztugo/yeztugo_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Summary

Clinical Data: PURPOSE 1 Study[1]

PURPOSE 1 is a phase 3 ongoing, double-blind, randomized study evaluating the efficacy and safety of twice-yearly, SUBQ LEN (n=2138) and once-daily oral FTC/TAF (n=2137) or FTC/TDF (active control; n=1070) for HIV-1 PrEP in 5345 cisgender women and adolescent girls (16–25 years old) across South Africa and Uganda.

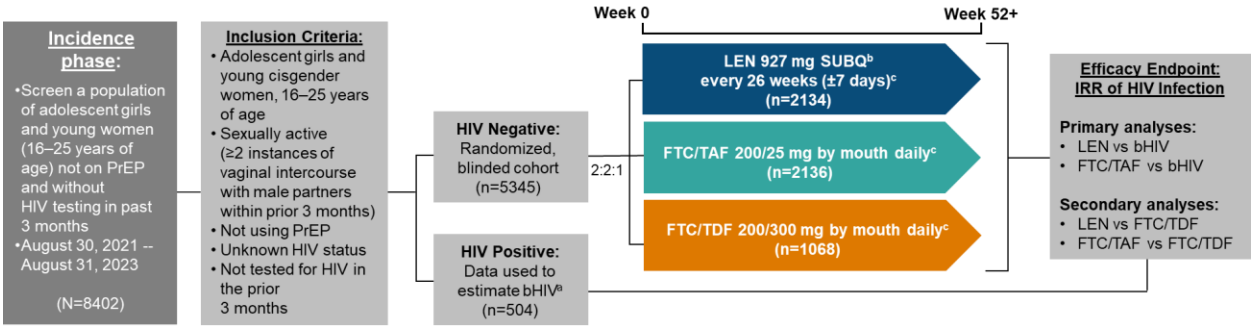
- A total of 55 incident HIV cases occurred; no participants in the LEN group acquired HIV (1939 PY; incidence rate: 0 per 100 PY; 95% CI: 0–0.91); 39 HIV cases occurred in the FTC/TAF group (1932 PY; incidence rate: 2.02 per 100 PY; 95% CI: 1.44–2.76); and 16 occurred in the FTC/TDF group (949 PY; incidence rate: 1.69 per 100 PY; 95% CI: 0.96–2.74). The background HIV incidence in the screened population was 2.41 per 100 PY (95% CI: 1.82–3.19).
- LEN significantly reduced the incidence rate of HIV by 100% compared with bHIV (IRR, 0; 95% CI: 0–0.04; *P*<0.001) and FTC/TDF (IRR, 0; 95% CI: 0–0.1; *P*<0.001).
- The incidence rate of HIV in the FTC/TAF group was not significantly different from bHIV (IRR, 0.84; 95% CI: 0.55–1.28; *P*=0.21), and there was no evidence of a meaningful difference in HIV incidence from FTC/TDF (IRR, 1.2; 95% CI: 0.67–2.14).
- LEN, FTC/TAF, and FTC/TDF were all generally well tolerated, with few discontinuations due to study drug-related AEs. The overall incidences of non-ISR AEs, including Grade ≥3 and serious AEs, were generally similar across treatment groups. Nausea and vomiting occurred at higher rates in the FTC/TAF and FTC/TDF groups than in the LEN group.
- ISRs were the most common AE in all groups and occurred at a higher rate with LEN than with placebo injections. ISRs were primarily Grade ≤2 and decreased in frequency over time. Discontinuations due to ISRs were rare, with 4 discontinuations in the LEN group and none in the groups that received placebo injections.

Clinical Data: PURPOSE 1 Study

Study Design and Demographics

PURPOSE 1 (NCT04994509) is an ongoing, phase 3, double-blind, randomized, active-controlled study evaluating the efficacy and safety of twice-yearly, SUBQ LEN and once-daily oral FTC/TAF for HIV-1 PrEP in cisgender women and adolescent girls across South Africa and Uganda. Additionally, a third group was assigned once-daily oral FTC/TDF, which served as the active control. Eligible women and adolescent girls were tested for HIV at screening, and those who tested negative were randomly assigned in a 2:2:1 ratio to receive LEN 927 mg SUBQ every 26 weeks, FTC/TAF 200/25 mg orally daily, or FTC/TDF 200/300 mg orally daily (Figure 1). Those who tested positive for HIV at screening were referred for care at a local center and their samples underwent additional testing to determine the recency of HIV; these data were used to estimate the bHIV that would be expected without PrEP. Participants who discontinued blinded study drug were given the option to take open-label FTC/TDF. Testing for HIV in the randomized cohort was conducted at Weeks 4, 8, and 13 and every 13 weeks thereafter.

Figure 1. PURPOSE 1: Study Design[1]



[a] The bHIV was determined based on a cross-sectional incidence estimate derived from rates of recent HIV in 8094 screened participants; these participants were not followed longitudinally.
[b] All participants randomly assigned to receive LEN received an initial loading dose of LEN, which consisted of 600 mg (two 300-mg tablets) administered on Days 1 and 2.
[c] Participants in the LEN SUBQ group also received placebo FTC/TAF or placebo FTC/TDF (2:1), and participants in the FTC/TAF and FTC/TDF groups also received placebo LEN oral loading doses and placebo LEN SUBQ.

A total of 5345 participants were randomly assigned and received ≥1 dose of study drug. Baseline (at randomization) characteristics among the three treatment groups were similar. Overall retention in the study was high and similar across treatment groups, with 4855/5020 participants (96.7%) completing 26 weeks of follow-up, 2439/2612 participants (93.4%) completing 52 weeks, and 39/43 participants (91%) completing 104 weeks.

An independent committee determined that the planned interim efficacy analysis (when 50% of participants had completed ≥52 weeks of follow-up; data cutoff for clinical data, May 28, 2024, and data cutoff for laboratory data, May 29, 2024) met the prespecified criteria for stopping the randomized, blinded portion of the trial. Starting July 8, 2024, all participants were offered open-label LEN.

Table 1. PURPOSE 1: Baseline Demographics[1]

Key Demographics and Characteristics		LEN (n=2138)	FTC/TAF (n=2137)	FTC/TDF (n=1070)
Age	Median (range), years	21 (16–25)	21 (16–26)	21 (16–25)
	16 or 17 years of age, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race, n (%)		2135 (99.9)	2136 (>99.9)	1068 (99.8)
Living with primary partner, n/N (%)		148/2136 (6.9)	132/2134 (6.2)	73/1069 (6.8)
Previous use of PrEP, n (%)		143 (6.7)	121 (5.7)	71 (6.6)
Previously tested for HIV, n (%)		1713 (80.1)	1731 (81)	860 (80.4)
Time since last HIV test, median (IQR), months		6.8 (4.7–11.5)	6.6 (4.8–11)	6.5 (4.6–11)
Sexually transmitted infections, n (%)	*Chlamydia trachomatis*	520 (24.3)	562 (26.3)	263 (24.6)
	Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
	Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
	Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Country, n (%)	South Africa	1809 (84.6)	1790 (83.8)	909 (85)
	Uganda	329 (15.4)	347 (16.2)	161 (15)

Primary and secondary efficacy analyses results[1]

A total of 55 incident HIV cases occurred in the randomized cohort; no participants in the LEN group acquired HIV (1939 PY; incidence rate: 0 per 100 PY; 95% CI: 0–0.91); 39 HIV cases occurred in the FTC/TAF group (1932 PY; incidence rate: 2.02 per 100 PY; 95% CI: 1.44–2.76); and 16 occurred in the FTC/TDF group (949 PY; incidence rate: 1.69 per 100 PY; 95% CI: 0.96–2.74). The bHIV in the screened population was 2.41 per 100 PY (Figure 2).

LEN significantly reduced the incidence rate of HIV by 100% compared with both the background incidence rate (IRR, 0; 95% CI: 0–0.04; *P*<0.001) and the rate with FTC/TDF (IRR, 0; 95% CI: 0–0.1; *P*<0.001). The incidence rate of HIV in the FTC/TAF group did not significantly differ from the background HIV incidence rate (IRR, 0.84; 95% CI: 0.55–1.28; *P*=0.21), and there was no evidence of difference in the incidence of HIV with FTC/TDF (IRR, 1.2; 95% CI: 0.67–2.14).

Figure 2. PURPOSE 1: Incidence of HIV[1]

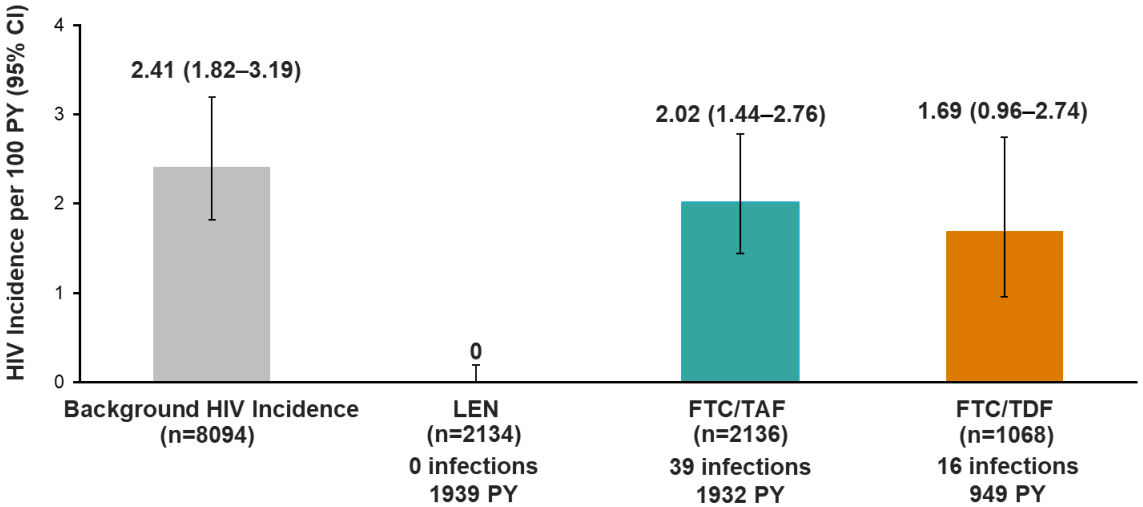
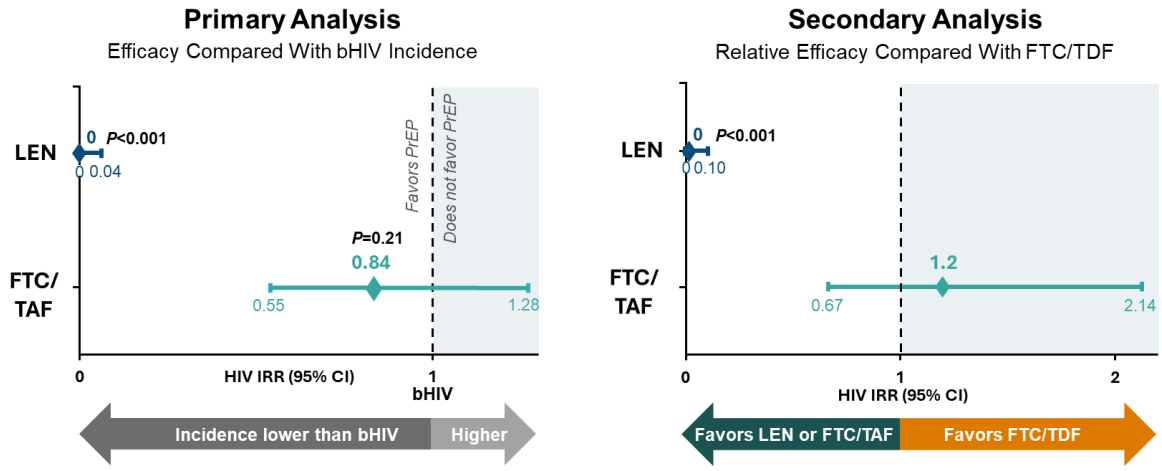


Figure 3. PURPOSE 1: Primary and Secondary Analyses[1]



Adherence results[1]

Adherence to LEN was defined as on-time injections (within 28 weeks after the last injection). Most participants received their injections (LEN and placebo LEN) on time at Weeks 26 (91.5%; 4545/4967) and 52 (92.8%; 2025/2181), and adherence to injections was similar across the groups.

Adherence to FTC/TAF and FTC/TDF was evaluated at study visits using dried blood spot analysis of TDF levels in 10% of participants, who were randomly preselected from each group. Adherence in the 10% sample of participants in the FTC/TAF and FTC/TDF groups was low and decreased over time. At Week 8, in the FTC/TAF and FTC/TDF groups, adherence was low (<2 doses/week) in 34% and 50% of participants, respectively; at Week 52, adherence was low in 84% and 93%. Among participants who acquired HIV and had data available, 34/37 participants in the FTC/TAF group and 13/14 participants in the FTC/TDF group had low or undetectable levels of TDF. In a matched case-control analysis to assess the association between adherence and efficacy in the FTC/TAF group, participants with medium (2 or 3 doses/week) or high (≥4 doses/week) adherence had lower odds of acquiring HIV than those with low adherence (odds ratio, 0.11; 95% CI: 0.01–0.49).

Persistence results[2]

Persistence to LEN was defined as on-time injections (within 28 weeks after the last injection) at Week 26 and Week 52. Persistence was evaluated in 10% of participants, who were randomly preselected from each group and limited to those who had ≥1 year of study follow up at time of interim analysis. Most participants demonstrated high persistence to LEN and placebo LEN, with 79.5% on LEN (n=112), 81.8% on FTC/TAF with placebo LEN (n=99), and 75.9% on FTC/TDF with placebo LEN (n=54) with on-time injections at Week 26 and Week 52.

Persistence to daily oral FTC/TAF or FTC/TDF was assessed by TFV-DP concentration in DBS at Weeks 13, 26, 39, and 52. Compared with LEN injections, persistence to daily oral FTC/TAF or FTC/TDF was significantly lower, with 5.2% of participants (n=153) having DBS TFV-DP concentrations consistent with ≥4 doses/week through Week 52 (P<0.0001).

Safety results[1]

LEN, FTC/TAF, and FTC/TDF were generally well tolerated, with fewer gastrointestinal AEs in the LEN group than either the FTC/TAF or FTC/TDF groups (Table 2). LEN ISRs were relatively common, and most were Grade 1 or 2. Six deaths occurred, all in the FTC/TAF group; none of these were considered by the investigator to be related to study drug.[1]

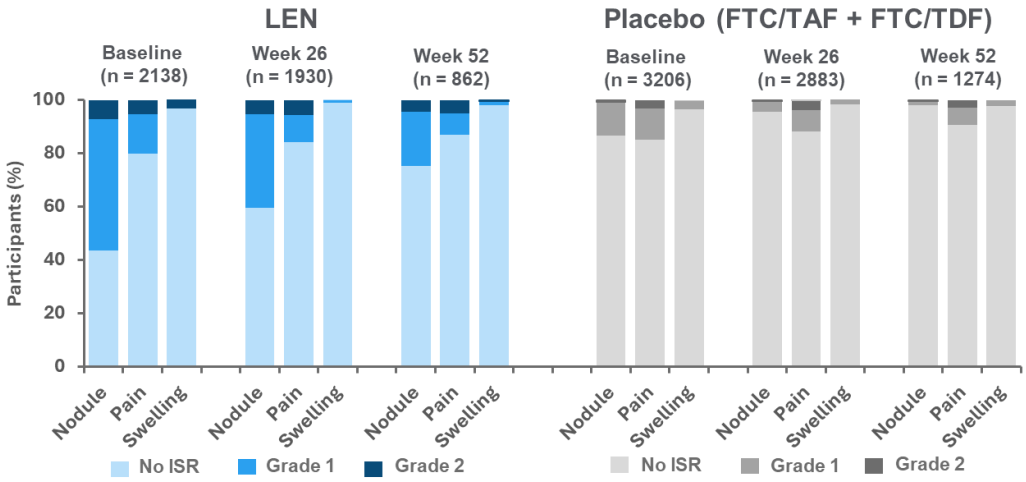
The most common AEs were ISRs. A total of 25,329 injections were administered, with 10,154 administered to 2138 participants in the LEN group and 15,175 administered to 3206 participants receiving placebo injection in the FTC/TAF and FTC/TDF groups. SUBQ nodules, injection site pain, and swelling were the most common ISRs; these events occurred in 63.8%, 31.2%, and 4.4% of participants, respectively, who received LEN injections and in 16.6%, 23.7%, and 5.4% of participants, respectively, who received placebo injections.[3] No Grade 4 ISRs occurred, and the frequency of ISRs decreased over time (Figure 3). Four ISRs (0.2%) that led to premature discontinuation occurred in the LEN group; all were reported as SUBQ nodules, including 1 that was also reported as injection site pain. No participants who receive a placebo injection discontinued due to ISR. No keloid scars were reported in any treatment group.[1]

Table 2. PURPOSE 1: Safety Summary[1]

AE, n (%)		LEN (n=2138)	FTC/TAF (n=2137)	FTC/TDF (n=1070)
Any AE (excluding ISRs)		1631 (76.3)	1665 (77.9)	830 (77.6)
Grade ≥3 AE		88 (4.1)	95 (4.4)	50 (4.7)
Serious AE		59 (2.8)	85 (4)	35 (3.3)
AEs that led to discontinuation of study drug[a]		5 (0.2)	2 (<0.1)	0
Common AEs (≥5% of participants in any group; excluding ISRs)	Headache	285 (13.3)	352 (16.5)	155 (14.5)
	Urinary tract infection	307 (14.4)	305 (14.3)	163 (15.2)
	Genitourinary tract chlamydia infection	300 (14)	317 (14.8)	129 (12.1)
	Upper respiratory tract infection	271 (12.7)	274 (12.8)	121 (11.3)
	Nausea	144 (6.7)	234 (10.9)	142 (13.3)
	Vomiting	125 (5.8)	235 (11)	107 (10)
	Vaginal discharge	166 (7.8)	191 (8.9)	87 (8.1)
	Vulvovaginal candidiasis	146 (6.8)	172 (8)	67 (6.3)
	Genitourinary tract gonococcal infection	141 (6.6)	157 (7.3)	66 (6.2)
	Diarrhea	133 (6.2)	161 (7.5)	67 (6.3)
	Dizziness	120 (5.6)	141 (6.6)	79 (7.4)
Laboratory abnormalities[b]	Any	1929 (90.7)	1904 (90.1)	959 (91)
	Grade 3	92 (4.3)	81 (3.8)	50 (4.7)
	Grade 4	20 (0.9)	22 (1)	11 (1)
ISRs[c]	Any related to LEN, placebo LEN, or trial procedures	1470 (68.8)	755 (35.3)	363 (33.9)
	Led to discontinuation of study drug	4 (0.2)	0	0
	Grade 3[d]	4 (0.2)	2 (<0.1)	2 (0.2)

[a] AEs that led to discontinuation of LEN were nausea (n=1), decreased CrCl (n=1), increased liver enzyme levels (n=1), spontaneous abortion (n=1), and suicide attempt with major depression (n=1); in the FTC/TAF group, AEs that led to discontinuation were suicide attempt, depressive symptoms, and drug overdose (n=1, all in the same participant) and angioedema (n=1).
[b] Percentages shown are based on the number of participants who had ≥1 postbaseline laboratory result (LEN, n=2126; FTC/TAF, n=2113; FTC/TDF, n=1054).
[c] Reactions to trial-related injections only; percentages shown are based on the number of participants who received ≥1 placebo or LEN injection (LEN, n=2138; FTC/TAF, n=2136; FTC/TDF, n=1070).
[d] Grade 3 ISRs consisted of injection site ulcer (LEN, n=3; FTC/TAF, n=2; FTC/TDF, n=1), nodule (LEN, n=1), and pain (FTC/TDF, n=1).

Figure 4. PURPOSE 1: Occurrence or Absence of Common Grade ≤2 ISRs Over Time[4]



Pregnancies occurred in 487 participants (for a total of 510 pregnancies; LEN, n=193; FTC/TAF, n=219; FTC/TDF, n=98). A total of 277 pregnancies were completed at the time of the interim analysis; 121 (23.7% of all pregnancies) resulted in births, 66 (12.9%) resulted in spontaneous abortions, and 90 (17.6%) resulted in induced abortions. One congenital abnormality of polydactyly, which was not considered related to study drug, was observed in a participant in the LEN group who had a strong family history of the condition. Among pregnant participants, HIV occurred in no participants in the LEN group, in 4 participants in the FTC/TAF group, and in 1 participant in the FTC/TDF group.[1]

References

1. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. *N Engl J Med.* 2024;391(13):1179-1192.
2. Bekker LG, Kiwanuka N, Selepe P, et al. Annual Persistence in Use of Twice-Yearly Lenacapavir Versus Daily Oral PrEP in the PURPOSE 1 Phase 3 Trial [Presentation]. Paper presented at: HIV Drug Therapy Glasgow; November 10-13, 2024; Glasgow, UK.
3. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women [Supplementary Appendix]. *N Engl J Med.* 2024:1-69.
4. Bekker LG, Das M, Abdool Karim Q, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women [Protocol]. *N Engl J Med.* 2024:1-672.

Abbreviations

AE=adverse event
bHIV=background HIV incidence
DBS=dried blood spot
FTC=emtricitabine
IRR=incidence rate ratio
ISR=injection site reaction
LEN=lenacapavir
PrEP=pre-exposure prophylaxis
PY=person-years
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV-DP=tenofovir-diphosphate

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Yeztugo, Descovy, 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/descovy/descovy_pi; www.gilead.com/-/media/files/pdfs/medicines/hiv/truvada/truvada_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or 🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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