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# Yeztugo® (lenacapavir) Renal Safety Profile

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and renal safety data.

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**The use of FTC/TAF for prevention of HIV-1 in individuals at risk of HIV-1 from receptive vaginal sex 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


### Product Labeling

No dosage adjustment of LEN is recommended in individuals with mild, moderate or severe renal impairment (estimated CrCl ≥15 mL/min). LEN has not been studied in individuals with ESRD (estimated CrCl <15 mL/min).[1]

### PURPOSE 1

PURPOSE 1 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 or FTC/TDF for HIV-1 PrEP in cisgender women and adolescent girls across South Africa and Uganda.[2]

Grade 3 decrease in creatinine renal clearance, and renal and urinary disorders were reported in ≤0.2% of participants in each treatment arm in PURPOSE 1. Additionally, 1 (<0.1%) participant in the FTC/TAF group had a Grade 3 abnormal creatinine renal clearance, 1 (<0.1%) participant in the FTC/TDF group experienced treatment-emergent proteinuria, and 1 (<0.1%) participant in the LEN group experienced a decrease in creatinine renal clearance leading to premature study drug discontinuation. There were no reported cases of Fanconi syndrome across study arms.[3] No sub-analysis of renal outcomes has been reported.

### PURPOSE 2

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 cisgender gay, bisexual, and other men, TGW, TGM, and GNB individuals aged ≥16 years.[4]

Grade 3 decrease in creatinine renal clearance, and renal and urinary disorders were reported in ≤0.2% of participants in each treatment arm in PURPOSE 2. There were no

reports of discontinuation due to renal AEs in the LEN study group. Two participants discontinued FTC/TDF due to a decrease in CrCl, and one participant discontinued FTC/TDF due to nephropathy.[4,5] There were no reported cases of Fanconi syndrome across both study arms.[5] No sub-analysis of renal outcomes has been reported.

# Product Labeling[1]

No dosage adjustment of LEN is recommended in individuals with mild, moderate or severe renal impairment (estimated CrCl ≥15 mL/min). LEN has not been studied in individuals with ESRD (estimated CrCl <15 mL/min).

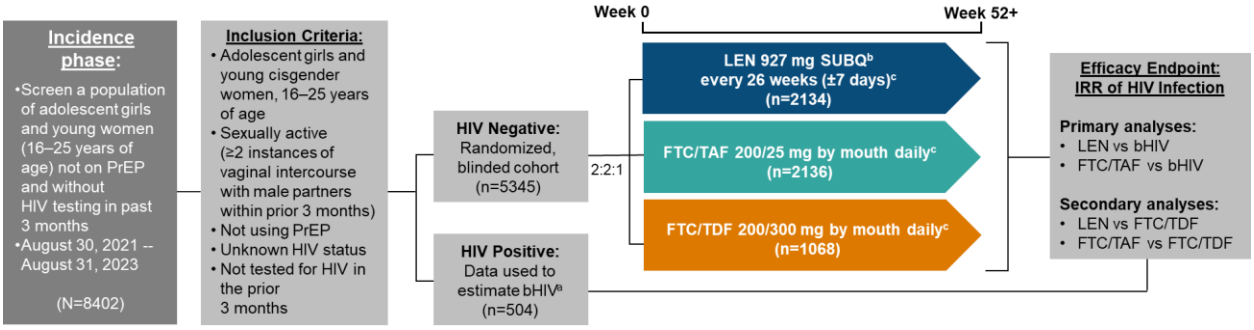
# Clinical Data

## 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 (Figure 1). Randomized participants had body weight ≥35 kg and eGFR ≥60 mL/min.[2]

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




[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 groups were similar (Table 1).[2]

**Table 1. PURPOSE 1: Select Baseline Demographics**[2]

| 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) |
| 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) |

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.[2]

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.[2]

## Renal Safety Results

Details regarding renal-related AEs and laboratory abnormalities observed in the PURPOSE 1 study are summarized in Table 2 and Table 3 below. There were no reported cases of Fanconi syndrome across study arms.[3] No sub-analysis of renal outcomes has been reported.

**Table 2. Renal-Related Adverse Events in PURPOSE 1**[3]

| Renal-Related Adverse Events | LEN (n=2138) | FTC/TAF (n=2137) | FTC/TDF (n=1070) |
|---|---|---|---|
| **Grade 3 or Higher Treatment-Emergent Adverse Events** | | | |
| Creatinine renal clearance decrease, Grade 3 | 1 (<0.1%) | 1 (<0.1%) | 2 (0.2%) |
| Creatinine renal clearance abnormal, Grade 3 | 0 | 1 (<0.1%) | 0 |
| Renal and urinary disorders, Grade 3 | 1 (<0.1%) | 1 (<0.1%) | 2 (0.2%) |
| **Treatment-Emergent Serious Adverse Events** | | | |
| Proteinuria | 0 | 0 | 1 (<0.1%) |
| **Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation** | | | |
| Creatinine renal clearance decrease | 1 (<0.1%) | 0 | 0 |

**Table 3. Renal-Related Grade 3 and 4 TE Laboratory Abnormalities in PURPOSE 1**[3]

| Renal-Related Lab Abnormalities | LEN (n=2125) | FTC/TAF (n=2113) | FTC/TDF (n=1054) |
|---|---|---|---|
| **Creatinine increased** | | | |
| Grade 3 | 12 (0.6%) | 10 (0.5%) | 9 (0.9%) |
| Grade 4 | 1 (<0.1%) | 0 | 1 (<0.1%) |
| **Creatinine clearance decreased** | | | |
| Grade 3 | 41 (1.9%) | 35 (1.7%) | 22 (2.1%) |
| Grade 4 | 0 | 1 (<0.1%) | 1 (<0.1%) |

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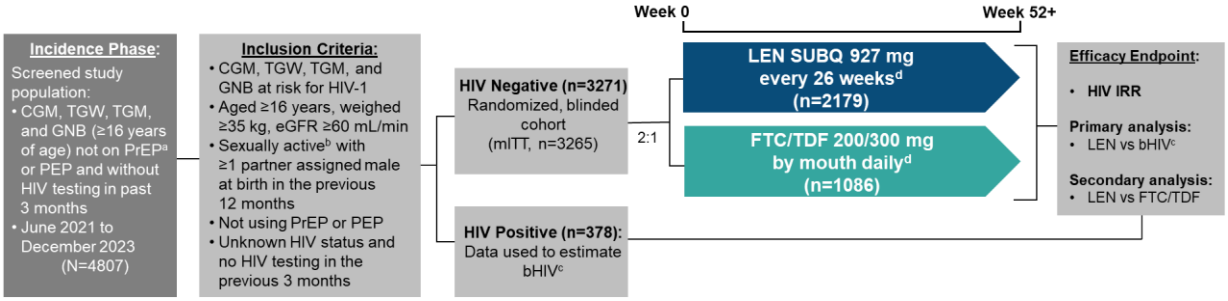
# PURPOSE 2 Study

## 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 (Figure 2).[4]

**Figure 2. PURPOSE 2: Study Design**[4,6]




[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 4).[4]

**Table 4. PURPOSE 2: Select Baseline Demographics**[4]

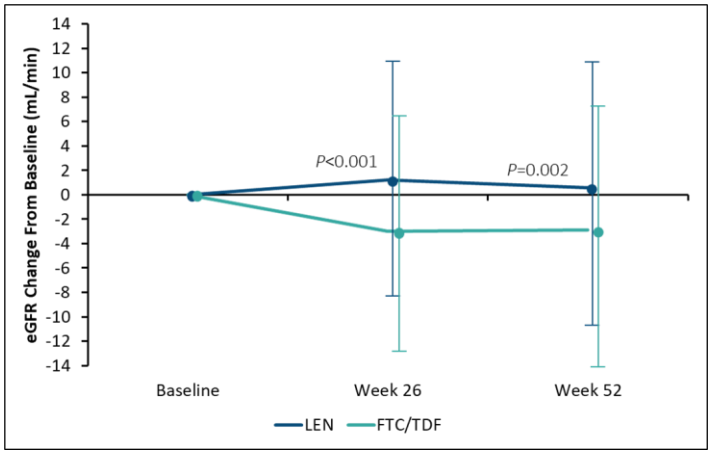
| Key Demographics and Characteristics | | LEN (n=2183) | FTC/TDF (n=1088) |
|---|---|---|---|
| Age | Median (range), years | 28 (17–74) | 29 (17–73) |
| | 16 to ≤25 years, n (%) | 752 (34.4) | 344 (31.6) |
| Race or ethnicity, n/N (%) | Hispanic or Latine | 1378/2182 (63.2) | 675/1088 (62) |
| | Black[a] | 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) |
| 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).

## Renal Safety Results

There was a statistically significant difference in the median change from baseline in $eGFR_{CG}$ between the study groups at Week 26 and Week 52 (Figure 3). At Week 26, there was a median (IQR) change from baseline in $eGFR_{CG}$ of +1.2 (-8 to +10.9) mL/min in the LEN group and and -3 (-12.4 to +6.5) mL/min in the FTC/TDF group ($P$<0.001). At Week 52, there was a median (IQR) change from baseline in $eGFR_{CG}$ 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).The study authors noted the decline in median $eGFR_{CG}$ in the FTC/TDF group was consistent with the expected changes in renal function with the use of FTC/TDF.[4]

**Figure 3. Median Change from Baseline in $eGFR_{CG}$**[4]




[a]Error bars represent IQR

There were no reports of discontinuation due to renal AEs in the LEN study group. Two participants discontinued FTC/TDF due to a decrease in CrCl, and one participant discontinued FTC/TDF due to nephropathy.[4,5] There were no reported cases of Fanconi syndrome across both study arms.[5] No sub-analysis of renal outcomes has been reported.

Additional details regarding renal-related adverse events and laboratory abnormalities observed in the PURPOSE 2 study are summarized in Table 5 and Table 6 below.[5]

**Table 5. Renal-Related Adverse Events in PURPOSE 2**[5]

| Renal-Related Adverse Events | LEN (n=2183) | F/TDF (n=1088) |
|---|---|---|
| **Grade 3 or Higher Adverse Events** | | |
| Creatinine renal clearance decrease, Grade 3 | 2 (<0.1%) | 2 (0.2%) |
| Renal and urinary disorders, Grade 3 | 4 (0.2%) | 2 (0.2%) |
| **Adverse Events Leading to Premature Study Drug Discontinuation** | | |
| Creatinine renal clearance decrease | 0 | 2 (0.2%) |
| Nephropathy | 0 | 1 (<0.1%) |

**Table 6. Renal-Related Grade 3 and 4 Laboratory Abnormalities in PURPOSE 2**[5]

| Renal-Related Adverse Events | LEN (n=2153) | F/TDF (n=1071) |
|---|---|---|
| **Creatinine increased** | | |
| Grade 3 | 12 (0.6%) | 8 (0.7%) |
| Grade 4 | 0 | 2 (0.2%) |
| **Creatinine clearance decreased** | | |
| Grade 3 | 42 (2.0%) | 38 (3.5%) |
| Grade 4 | 0 | 2 (0.2%) |

# References

1. Enclosed, Gilead Sciences Inc. YEZTUGO® (lenacapavir) tablets, for oral use. YEZTUGO® (lenacapavir) injection, for subcutaneous use. U.S. Prescribing Information. Foster City, CA.

2. 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.
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. 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.
5. Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons [Supplementary Appendix]. *N Engl J Med.* 2024.
6. 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

$eGFR_{CG}$=estimated glomerular filtration rate using the Cockcroft–Gault formula
FTC=emtricitabine
GNB=gender non-binary
IQR=interquartile range
LEN=lenacapavir
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TE=treatment-emergent
TGM=transgender men
TGW=transgender women

# 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:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

# Adverse Event Reporting

Please report all adverse events to:

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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