GILEAD | Medical Information

Yeztugo® (lenacapavir) Weight Changes

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

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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

Clinical Data on LEN and Weight Changes

The PURPOSE 1 study evaluated the efficacy and safety of LEN in cisgender women and adolescent girls for HIV-1 PrEP compared to FTC/TAF and FTC/TDF.[1] Among the LEN group, 1 participant experienced a decrease in weight, while 8 participants experienced an abnormal loss of weight.[2]

The PURPOSE 2 study evaluated the efficacy and safety of LEN in cisgender gay, bisexual, and other men, TGW, TGM, and GNB individuals for HIV-1 PrEP compared to FTC/TDF.[3] Across the LEN arm, 2 participants experienced an abnormal loss of weight.[5]

Clinical Data on LEN and Weight Change

PURPOSE 1

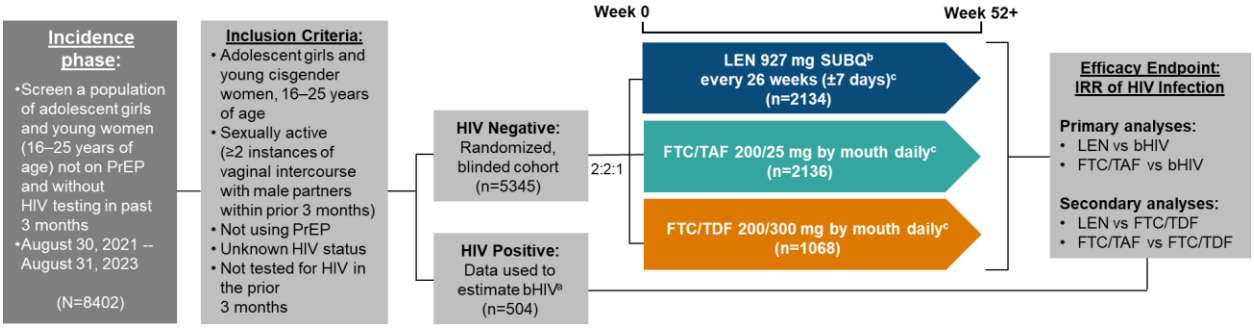
Study Design and Demographics

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.[1] Additionally, a third group was assigned once-daily oral FTC/TDF, which served as the active control (Figure 1). Participants who discontinued blinded study drug were given the option to take open-label FTC/TDF. Randomized participants had body weight ≥35 kg and eGFR ≥60 mL/min. The mean baseline screening weight of the 5368 participants randomized was 67.2 kg (SD 17.50); however, only 5345 participants received

≥1 dose of study drug. Baseline (at randomization) characteristics among the three groups were similar (Table 1).

The primary endpoint measured the rate of new HIV acquisitions among participants assigned to different study arms. The primary efficacy analysis assessed the IRR by comparing HIV incidence rates in those receiving LEN or FTC/TAF against the background HIV incidence. The secondary endpoint evaluated the IRR by comparing HIV rates in the LEN and FTC/TAF groups with those in the FTC/TDF group (Figure 1).

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.

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 and Disease Characteristics[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)
Previous use of PrEP, n (%)		143 (6.7)	121 (5.7)	71 (6.6)
Country, n (%)	South Africa	1809 (84.6)	1790 (83.8)	909 (85)
	Uganda	329 (15.4)	347 (16.2)	161 (15)

Results

In the LEN group, 1 (<0.1%) participant experienced a Grade 3 (severe) decrease in weight.[2] There were no Grade 3, or higher, decreases in weight in either the FTC/TAF or FTC/TDF groups. Overall, 10 participants experienced a Grade 3 abnormal loss of weight: 7 (0.3%) in the LEN group, 1 (<0.1%) in the FTC/TAF group, and 2 (0.2%) in the FTC/TDF group. There was 1 (<0.1%) participant in the LEN group that experienced a Grade 4 (life-threatening) abnormal loss of weight.

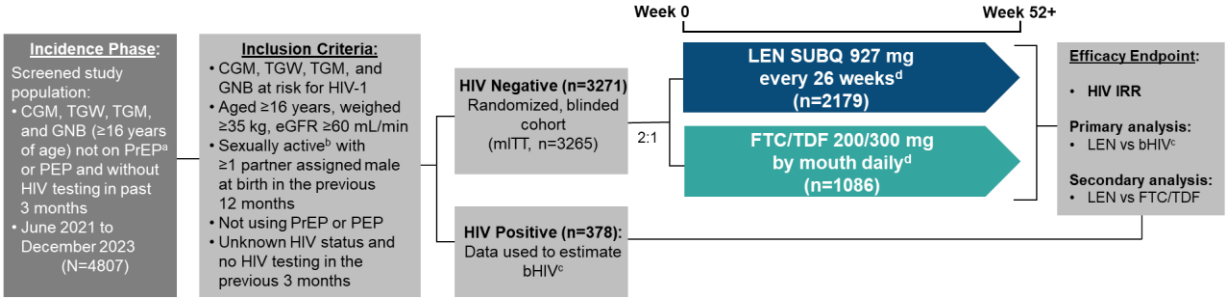
PURPOSE 2

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 or once-daily oral FTC/TDF for HIV-1 PrEP in 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 (N=3265).[3] The mean baseline screening weight of the 3291 participants randomized was 75.2 kg (Range: 39.1 - 210.8); however, only 3265 participants received ≥1 dose of study drug.

The primary endpoint measured the rate of new HIV acquisitions among participants assigned to different study arms. The primary efficacy analysis assessed the IRR by comparing HIV incidence rates in those receiving LEN against the background HIV incidence. The secondary endpoint evaluated the IRR by comparing HIV rates in the LEN group with those in the FTC/TDF group (Figure 2).

Figure 2. PURPOSE 2: Study Design[3,4]



[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.

An independent committee determined that the planned interim efficacy analysis (when 50% of the 3000 participants (target enrollment), or 1500 participants, had completed ≥52 weeks of follow-up or had permanently withdrawn from the randomized, blinded trial (52 weeks after random assignment of the 1500th participant); data cutoff for clinical data, September 11, 2024) met the prespecified criteria for stopping the randomized, blinded portion of the trial.[3] Starting September 25, 2024, all participants were offered open-label LEN.

Table 2. PURPOSE 2: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics		LEN (n=2183)	FTC/TDF (n=1088)
Age	Median (range), years	28 (17–74)	29 (17–73)
	16 or ≤25 years of age, n (%)	752 (34.4)	344 (31.6)
Race or ethnic group, n/N (%)	Asian	269/2175 (12.4)	144/1086 (13.3)
	Black	811/2175 (37.3)	420/1086 (38.7)
	Indigenous or Indigenous ancestry	341/2175 (15.7)	156/1086 (38.7)
	White	722/2175 (33.2)	344/1086 (31.7)
	Other and other multiracial	32/2175 (1.5)	22/1086 (2.0)
	Hispanic or Latine	1378/2182 (63.2)	675/1088 (62.0)
Previous use of PrEP, n (%)		515 (23.6)	249 (22.9)
Country, n (%)	Argentina	161 (7.4)	64 (5.9)
	Brazil	769 (35.2)	396 (36.4)
	Mexico	8 (0.4)	4 (0.4)
	Peru	309 (14.2)	138 (12.7)
	South Africa	1809 (84.6)	909 (85)
	Thailand	329 (15.4)	161 (15)
	United States	440 (20.2)	235 (21.6)

Results

Overall, there were 5 participants who experienced a Grade 3 abnormal loss of weight: 2 (<0.1%) in the LEN group and 3 (0.3%) in the FTC/TDF group.[5]

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, 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.
3. 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.
4. 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?term=purpose-2&draw=2&rank=1. Accessed: 30 May 2025. Last Updated: 20 December. 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.

Abbreviations

FTC=emtricitabine
GNB=gender non-binary
IRR=incidence rate ratio
LEN=lenacapavir
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
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:

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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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