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Yeztugo® (lenacapavir) Injection Site Reactions

This document is in response to your request for information regarding Yeztugo® (lenacapavir [LEN]) and injection site reactions (ISRs).

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Summary

Product Labeling[1]

- The most frequent adverse reactions associated with LEN injection for SUBQ use in PURPOSE 1 and PURPOSE 2 were ISRs.
- In PURPOSE 1, 69% of participants receiving LEN experienced ISRs, compared to 35% receiving placebo injections. Most participants who received LEN had mild (Grade 1, 50%) or moderate (Grade 2, 19%) severity ISRs.
- In PURPOSE 2, 83% of participants who received LEN experienced ISRs, compared to 69% receiving placebo injections. Most participants had mild (Grade 1, 66%) or moderate (Grade 2, 17%) severity ISRs.
- Injection site nodule was reported in 64% (PURPOSE 1) and 63% (PURPOSE 2) of participants who received LEN and resolved more slowly than other ISRs.

Clinical Data[2,3]

- In PURPOSE 1 and PURPOSE 2, the majority of ISRs were mild or moderate, with no serious ISRs. The incidence rates of ISRs decreased with subsequent injections.
- The most common ISRs were nodules, pain, swelling, and erythema.
- Injection site pain mitigation efforts included the use of ice or a cold compress before and after the injection.

Product Labeling[1]

Injection-Associated Adverse Reactions

Local ISRs

The most frequent adverse reactions associated with LEN SUBQ injection use in PURPOSE 1 and PURPOSE 2 were ISRs. The most common ISRs (all Grades) in at least 2% of participants who received LEN in either PURPOSE 1 or PURPOSE 2 are presented in Table 1.

Table 1. ISRs (All Grades) Reported in ≥2%[a] of Participants Receiving LEN in PURPOSE 1 or PURPOSE 2

Injection Site Reactions	PURPOSE 1		PURPOSE 2	
	LEN (N=2140)	FTC/TAF or FTC/TDF[b] (N=3205)	LEN (N=2183)	FTC/TDF[b] (N=1088)
Nodule	64%	17%	63%	39%
Pain	31%	24%	56%	53%
Induration	4%	<1%	16%	10%
Swelling	4%	5%	7%	10%
Pruritis	2%	1%	3%	3%
Erythema	1%	1%	17%	19%
Bruising	<1%	<1%	3%	4%
Warmth	<1%	<1%	2%	2%

[a] Frequencies are based on all injection site reactions attributed to study drug (or to the procedure) by the investigator.
[b] Participants received placebo SUBQ injections (polyethylene glycol 400).

PURPOSE 1

In PURPOSE 1, 69% of participants receiving LEN experienced ISRs, compared to 35% of participants receiving placebo injections (FTC/TAF or FTC/TDF). Most participants who received LEN had mild (Grade 1, 50%) or moderate (Grade 2, 19%) severity ISRs. Grade 3 ISRs were reported in 4 (0.2%) participants, and included ulcer and nodule. LEN was discontinued due to ISRs in 4 (0.2%) participants. None of the ISRs were serious. The incidence of ISRs decreased with subsequent injections.

Nodules

Injection site nodule was reported in 64% of participants who received LEN and resolved more slowly than other ISRs. The median duration of nodule associated with the first injections of LEN was 350 days (IQR: 182–470). The median of the maximum observed nodule diameter from each participant was 3 cm (IQR: 2–3.5). Qualitative descriptions of the visibility of injection site nodules were not routinely reported, but, where reported, the majority of injection site nodules were palpable but not visible.

Other ISRs

The other ISRs reported in more than 2% of participants who received LEN were pain (31%), swelling (4%), induration (4%), and pruritus (2%). The median duration of induration,

which resolved more slowly than most ISRs, was 173 days (IQR: 22–267). The median duration of ISRs, excluding nodules and indurations, was 9 days (IQR: 4–30).

PURPOSE 2

In PURPOSE 2, 83% of participants receiving LEN experienced ISRs, compared to 69% of participants receiving placebo injections (and FTC/TDF). Most participants had mild (Grade 1, 66%) or moderate (Grade 2, 17%) severity ISRs. Grade 3 ISRs were reported in 14 (0.6%) participants, and included ulcer, pain, erythema, edema, and dermatitis. LEN was discontinued due to ISRs in 26 (1.2%) participants. None of the ISRs were serious. The incidence of reported ISRs decreased with subsequent injections.

Nodules

Injection site nodule was reported in 63% of participants who received LEN and resolved more slowly than other ISRs. The median duration of nodules associated with the first injections of LEN was 297 days (IQR: 176–423). The median of the maximum observed nodule diameter for each participant was 3 cm (IQR: 2–4).

Other ISRs

The other ISRs reported in more than 2% of participants who received LEN were pain (56%), erythema (17%), induration (16%), swelling (7%), bruising (3%), pruritus (3%), and warmth (2%). The median duration of induration, which resolved more slowly than most other ISRs, was 151 days (IQR: 15–267). The median duration of ISRs, excluding nodules and indurations, was 4 days (IQR: 2–8).

Clinical Data on SUBQ LEN and ISRs

PURPOSE 1: LEN for PrEP in CGW[2]

Study Design

PURPOSE 1 (NCT04994509) is a phase 3, double-blind, randomized clinical study designed to evaluate twice-yearly LEN SUBQ (n=2138) versus daily oral FTC/TAF (n=2137), or daily oral FTC/TDF (n=1070) for prevention of HIV infection in CGW. Adolescent girls and women aged 16–25 years-old, not previously on PrEP and HIV-negative, were randomized in a 2:2:1 ratio to each cohort.

ISR

Within the LEN cohort, 1470 participants (68.8%) experienced an ISR (Table 2). The majority of ISRs were Grade 1 or 2, with no serious ISRs. Grade 3 ISRs were rare with similar rates of occurrence between the LEN, FTC/TAF and FTC/TDF cohorts, including 3 cases of ulcers and 1 case of nodule in the LEN cohort. There were 4 discontinuations due to ISRs in the LEN cohort; all were SUBQ nodules, with 1 discontinuation due to both nodule and injection-site pain. There were no discontinuations due to ISRs in the FTC/TAF and FTC/TDF cohorts.

Table 2. ISRs in PURPOSE 1

AE, n (%)	LEN (N=2138)	FTC/TAF (N=2137)	FTC/TDF (N=1070)
Participants who received at least 1 injection	**2138**	**2136**	**1070**
Serious ISRs	0 (0)	0 (0)	0 (0)
ISRs leading to premature discontinuations[a]	4 (0.2)	0 (0)	0 (0)
Participants with ISRs	**1470 (68.8)**	**755 (35.3)**	**363 (33.9)**
Grade 1	1060 (49.6)	563 (26.4)	281 (26.3)
Grade 2	406 (19)	190 (8.9)	80 (7.5)
Grade 3[b]	4 (0.2)	2 (<0.1)	2 (0.2)
Grade 4	0 (0)	0 (0)	0 (0)

ISRs that were reported were trial-related injections only; reactions to other types of injections (e.g., vaccines) were excluded

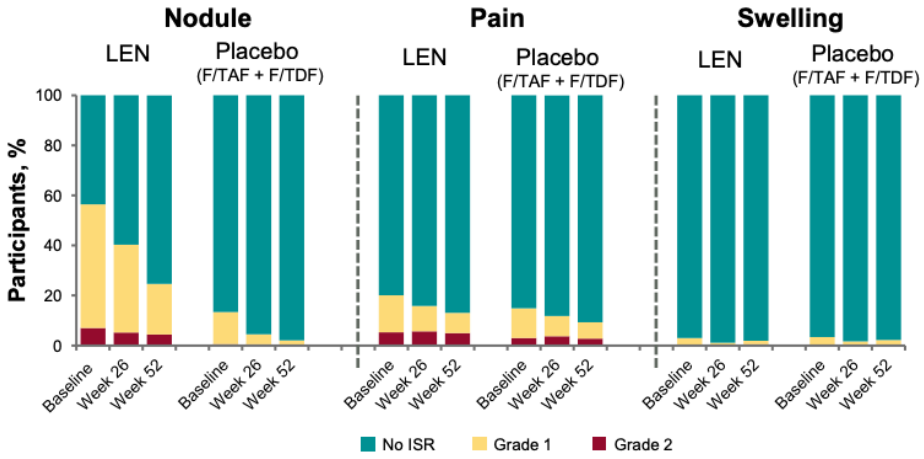
[a] All 4 ISRs leading to discontinuation were SC nodules (1 of whom discontinued due to both SUBQ nodule and injection-site pain)

[b] Grade 3 ISRs included 6 cases of injection-site ulcer (3 in the LEN group, 2 in the FTC/TAF group and 1 in the FTC/TDF group), 1 case of nodule (in the LEN group) and 1 case of pain (in the FTC/TDF group)

The frequency of ISRs decreased with subsequent injections, from baseline to Weeks 26 and 52 (Figure 1). Injection site nodule was the most common ISR, occurring most often at the beginning of therapy, followed by pain and swelling.

The median duration of nodules in PURPOSE 1 was 190 days, indicating that just over half of participants would have a palpable nodule by the time of their follow-up injection. For most participants, the nodule size significantly decreases by the 6-month mark. This aligns with the expected pharmacokinetics of the nodule formation, given that plasma drug concentrations at 6 months post-injection are not zero but are nearing the lower end of the target concentration range. This suggests that some drug depot remains at 6 months. Pharmacokinetic modeling indicates that a depot may persist for approximately 1 to 1.5 years post-injection.

Figure 1. Most Commonly Reported ISRs in PURPOSE 1: Nodule, Pain and Swelling



Subcutaneous nodules, injection site pain, and swelling were the most commonly reported injection site reactions; over the period of study they occurred in 63.8%, 31.2%, and 4.4% of participants in the LEN group, respectively, versus 16.6%, 23.7%, and 5.4% of participants given placebo injections. Grade 1 and 2 ISRs are

shown; there was a single case of grade 3 injection site nodule (associated with Week 52/third injection) and one of injection site pain (associated with Week 26/second injection) in the LEN group.

PURPOSE 2: LEN for PrEP in Men and Gender-Diverse Individuals[3]

Study Design

PURPOSE 2 (NCT04925752) is a phase 3, double-blind, randomized, controlled clinical study designed to evaluate the safety and efficacy of twice-yearly LEN SUBQ versus daily oral FTC/TDF for PrEP in cisgender men, transgender women, transgender men, and gender-nonbinary persons who were sexually active with partners assigned male at birth. Eligible participants who were HIV-negative and not on PrEP were randomized 2:1 to receive LEN SUBQ (n=2179) or daily oral FTC/TDF (n=1086).

ISR

Among the 2183 participants in the LEN cohort, 1816 (83.2%) experienced ISR, with the majority being Grade 1 (66%) and Grade 2 (16.5%; Table 3). Fourteen participants (0.6%) experienced Grade 3 ISRs, including 7 (0.3%) ulcers. No serious ISRs occurred in both cohorts. There were 26 discontinuations due to ISRs in the LEN group and 3 in the FTC/TDF group.

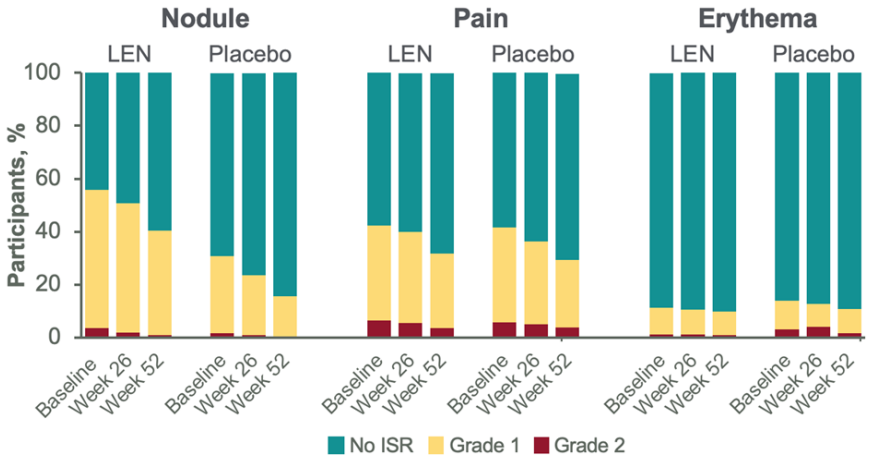
Table 3. ISRs in PURPOSE 2

AE, n (%)	LEN (N=2183)	FTC/TDF (N=1088)
Participants who received at least 1 injection	**2183**	**1088**
Serious ISRs	0 (0)	0 (0)
ISRs leading to premature discontinuations	26 (1.2)	0 (0)
Participants with ISRs	**1816 (83.2)**	**756 (69.5)**
Grade 1	1441 (66)	594 (54.6)
Grade 2	361 (16.5)	161 (14.8)
Grade 3[a]	14 (0.6)	1 (<0.1)
Grade 4	0 (0)	0 (0)

ISRs were categorized according to the Medical Dictionary for Regulatory Activities (Version 27.0).
[a] All Grade 3 ISRs included n=7 (0.3%) ulcers in the LEN group

In the PURPOSE 2 trial, the most common reported ISRs were nodules, pain and erythema, which occurred in 63.4%, 56.4% and 17.3% of participants in the LEN group, respectively (Figure 2). The frequency of these events decreased with subsequent injections, at Weeks 26 and 52.

Figure 2. Most Commonly Reported ISRs in PURPOSE 2: Nodule, Pain and Erythema



AEs coded according to Medical Dictionary for Regulatory Activities, Version 27.0. SUBQ nodules, injection-site pain, and erythema were the most commonly reported ISRs; over the period of study, they occurred in 63.4%, 56.4% and 17.3% of participants in the LEN group, respectively, vs. 39.2%, 53.4% and 19.4% of participants given placebo injections. Grade 1 and 2 ISRs are shown. Grade 3 ISRs in the LEN group: n=4 pain, n=3 erythema; FTC/TDF group: n=1 pain. LEN n: baseline, 2183; Week 26, 1859; Week 52, 744. Placebo n: baseline, 1088; Week 26, 946; Week 52, 379

LEN is injected into the SUBQ space and forms a drug depot that may be palpable under the skin but is usually not visible. As the drug elutes over time, the depot may get smaller. The nodules may resolve or reduce in size prior to the next injection.

Clinical Considerations

Injection Techniques Considerations

The provider should use their clinical judgement to make a medically appropriate decision for their patients. The following mitigation techniques are commonly used in routine clinical care and are not specific to LEN.

- Ice may be applied before and after injection and may help with post-injection soreness. Apply ice ~10 minutes before injection to both injection sites.[4]
- Topical analgesics, such as lidocaine and prilocaine cream (not patches), may be used as clinically appropriate. Apply at least 30 minutes before injection to both injection sites if not contraindicated. Cream may be wiped off with alcohol swab during injection site prep.[5]
- Oral analgesics, such as acetaminophen or NSAIDs, may be considered if not contraindicated and as clinically appropriate.[4]

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 Oral Emtricitabine/Tenofovir Alafenamide for HIV Prevention in Cisgender Women: Interim Analysis

Results from the PURPOSE 1 Study [Oral Presentation]. Paper presented at: AIDS 2024, the 25th International AIDS Conference; July 22-26, 2024; Munich, Germany, and virtually.
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. Kroger A, Bahta L, Long S, Sanchez P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: www.cdc.gov/vaccines/hcp/acip-recs/generalrecs/downloads/general-recs.pdf. Accessed: 30 May 2025. 2023.
5. Schechter NL, Zempsky WT, Cohen LL, McGrath PJ, McMurtry CM, Bright NS. Pain reduction during pediatric immunizations: evidence-based review and recommendations. *Pediatrics.* 2007;119(5):e1184-1198.

Abbreviations

AE=adverse event
CGW=cisgender women
FTC=emtricitabine
ISR=injection site reaction
LEN=lenacapavir
NSAID=non-steroidal anti-inflammatory drugs
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate

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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