CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220018Orig1s000
220020Orig1s000

OTHER REVIEW(S)

This is a corrected review that does not change the overall recommendations/ conclusions of the original review dated 27 May 2025.

Clinical Inspection Summary

Date	28 May 2025
From	Elena Boley, MD, MBA Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kevin Allen, MS, Regulatory Project Manager Timothy Jancel, PharmD, MHS, Clinical Reviewer Ursula Kelly, MD, Clinical Safety Reviewer Stephanie Troy, MD, Clinical Team Leader/CDTL Division of Antivirals
NDA #	NDA 220018 and NDA 220020
Applicant	Gilead Sciences, Inc.
Drug	Lenacapavir
NME	No
Proposed Indication	Pre-exposure prophylaxis (PrEP) to prevent sexually acquired human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 35 kg
Consultation	21 Jan 2025
Summary Goal	28 May 2025
Action Goal Date	18 Jun 2025
PDUFA Date	19 Jun 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Frank, Madruga, Ahmed, and Makhoba were inspected in support of NDA 220018 and NDA 220020. The clinical investigator inspections of Drs. Ahmed and Makhoba covered Protocol GS-US-412-5624 (PURPOSE 1) and the clinical investigator inspections of Drs. Frank and Madruga covered Protocol GS-US-528-9023 (PURPOSE 2).

The inspections found that the primary efficacy and the safety issue of interest to the review division for Study GS-US-412-5624 (PURPOSE 1) and Study GS-US-528-9023 (PURPOSE 2) were verifiable. In general, these studies appear to have been conducted adequately, and the data generated by these inspected CI sites and reported by the sponsor appear acceptable to support the proposed indication. However, we recommend that the review division evaluates the following findings identified during the CI inspections in its review of the application for their potential impact on the study results:

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1. Underreporting of Adverse Events (AEs)

For Protocol PURPOSE 2, three AEs (folliculitis, upper respiratory infection, and dizziness) at the site of Dr Madruga were not reported to the FDA. Also unreported by this site was a serious adverse event of Dengue fever. For Protocol PURPOSE 1, a single AE (urinary tract infection) at the site of Dr. Makhoba was not reported. We recommend the review division consider these underreported AEs.

2. Injections administered outside of the protocol-specified treatment window

At the site of Dr. Ahmed (Protocol PURPOSE 1), nine subjects (see table in Results section for the inspection of Dr. Ahmed) received injections as many as 9 days to 176 days after the time window specified by the protocol. We recommend the review division consider these protocol deviations in their review.

II. BACKGROUND

NDA 220018 and NDA 220020 were submitted on December 19, 2024, to support the efficacy and safety of lenacapavir injection (for subcutaneous use) and lenacapavir tablets (for oral administration) for pre-exposure prophylaxis (PrEP) of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 35 kg. The two clinical studies supporting the application were the following:

Protocol GS-US-412-5624 (PURPOSE 1)

Title: "Phase 3, Double-Blinded, Multicenter, Randomized Study to Evaluate Safety and Efficacy of Twice Yearly Long-Acting Subcutaneous Lenacapavir, and Daily Oral Emtricitabine/Tenofovir Alafenamide for Pre-Exposure Prophylaxis in Adolescent Girls and Young Women at Risk of HIV Infection"

This was a Phase 3, multicenter, randomized, double-blind, active-controlled trial in cisgender adolescent girls and young women in South Africa and Uganda. The primary efficacy objective was to evaluate the efficacy of lenacapavir (LEN) and emtricitabine/tenofovir alafenamide (F/TAF) in preventing the risk of HIV-1 infection relative to the background HIV-1 incidence.

Eligible participants in the Incidence Phase were cisgender females, ≥ 16 to ≤ 25 years of age at screening, with unknown HIV-1 status at screening and no prior HIV-1 testing within the last three months and were sexually active (had ≥ two vaginal intercourse encounters within the last three months) with cisgender male individuals. Eligible participants were not to have had prior use of HIV PrEP (including emtricitabine/tenofovir disoproxil fumarate [F/TDF]) or HIV postexposure prophylaxis in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir), and they were not to have previously received an HIV vaccine or HIV broadly neutralizing antibody.

Eligible participants in the Randomized Blinded Phase included those meeting criteria for participation in the Incidence Phase but who also had a negative local rapid fourth generation

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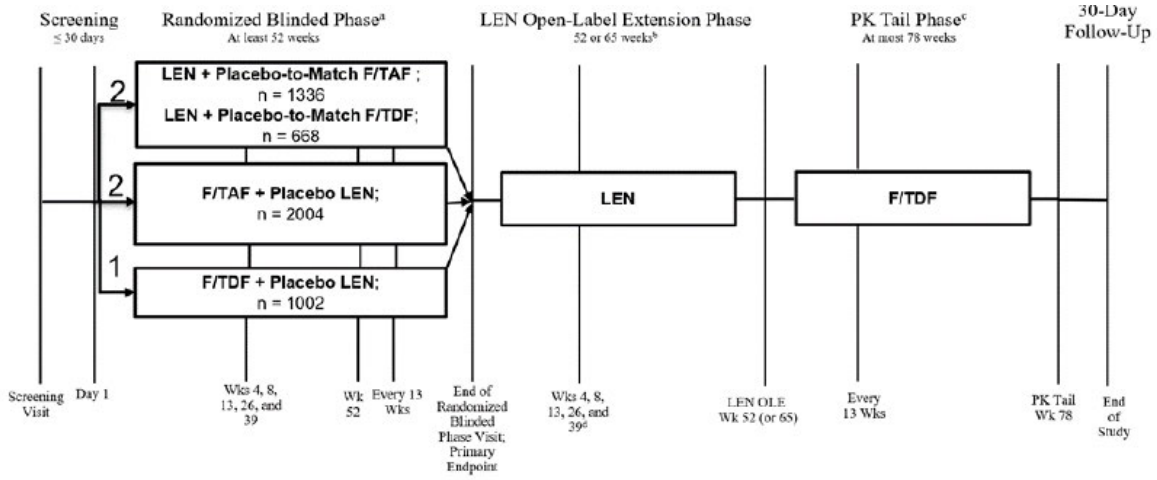
HIV-1/2 antibody (Ab)/antigen (Ag), central fourth generation HIV-1/2 Ab/Ag, and HIV-1 ribonucleic acid (RNA) quantitative nucleic acid amplification test just prior to randomization; had no acute viral hepatitis A, B, or C or evidence of chronic hepatitis B or C infection; and had an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min at screening according to the Cockcroft-Gault formula for creatinine clearance and a body weight ≥ 35 kg. Additionally, they were to have no severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, or variceal bleeding). See protocol for full eligibility criteria.

The study was comprised of four phases: an Incidence Phase (intended to provide an estimate of the concurrent background HIV incidence rate using a recency assay), a Randomized Blinded Phase [52 weeks], a LEN Open-Label Extension (OLE) Phase [52 weeks, up to 65 weeks], and a Pharmacokinetic (PK) Tail Phase [up to 78 weeks]. The primary analysis was performed using data collected after a minimum of 52 weeks of exposure to the study drug (at the end of Randomized Blinded Phase study visit). The total duration of the study for a subject completing all the phases, was 3.5 years [182 weeks].

Error! Reference source not found. is a schematic representation of the study design.

Figure 1: PURPOSE 1 Study Design



F/TAF = emtricitabine/tenofovir alafenamide (Descovy®; DVY); F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada®; TVD); LEN = lenacapavir; OL = open-label; OLE = open-label extension; PK = pharmacokinetic(s)

Source: Protocol PURPOSE 1 Clinical Study Report, p. 4.

Screening

At the Screening Visit, study staff collected consent and relevant history. Those who met initial criteria underwent extensive laboratory testing (see protocol for detailed list of tests) including the required HIV-related testing (local rapid fourth generation HIV-1 Ab/Ag testing, among others). Any participant with a positive local rapid fourth generation HIV-1 Ab/Ag test that was confirmed with central HIV testing was enrolled in the Incident Phase and was ineligible to continue screening for Part B of the study. HIV risk reduction counseling and referral for care was provided. Similar procedures were provided for any

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participant who was diagnosed with HIV-1 during Part B screening. Participants who had a negative local rapid fourth generation HIV-1 Ab/Ag test continued with Randomized Blinded Phase screening assessments including confirmation with a central HIV-1 Ab/Ag testing, a complete physical exam, medical history, and participants will be assessed for adverse events (AEs). HIV risk reduction counseling, screening for intimate partner violence and referral (as appropriate), and female and male condoms and lubricant were provided, and questionnaires about sexual behaviors and alcohol and substance use were administered.

Randomized Blinded Phase

Day 1: Participants whose HIV tests from Randomized Blinded Phase screening were negative were administered a local rapid fourth generation HIV-1 Ag/Ab test to confirm negativity. If the test was negative and all other eligibility criteria were fulfilled, participants were randomized in a 2:2:1 (LEN: F/TAF: F/TDF) ratio to one of the following study drug groups:

- LEN study drug group:
  - Subcutaneous (SC) LEN [927 mg injection, 309 mg/mL (2 x 1.5 mL)] + placebo-to-match (PTM) F/TAF
  - SC LEN [927 mg injection, 309 mg/mL (2 x 1.5 mL)] + PTM F/TDF
- F/TAF study drug group: F/TAF [200 mg emtricitabine/25 mg tenofovir alafenamide] + placebo SC LEN
- F/TDF study drug group: F/TDF [200 mg emtricitabine/300 mg tenofovir disoproxil fumarate] + placebo SC LEN

Participants received SQ LEN or placebo SQ LEN at the study site and also a PK loading dose of oral LEN (two 300 mg tablets or 2 PTM LEN tablets). Two additional oral LEN tablets of PTM LEN tablets were provided to self-administer on Day 2. Subcutaneous LEN or placebo SQ LEN was administered every 26 weeks. Additionally, starting on Day 1, participants also received oral F/TAF (200/25 mg), PTMF/TAF, F/TDF (200/300 mg), or PTM F/TDF to self-administer daily starting on Day 1.

Study visits occurred on Weeks 4, 8, 13, and then every 13 weeks until randomized participants had completed at least 52 weeks in the Randomized Blinded Phase. At each of these visits, HIV lab testing, plasma PK, and pregnancy testing as well as a various types of counseling were provided. Participants were assessed for AEs, concomitant medications, and intimate partner violence; participants completed questionnaires; and participants underwent safety laboratory testing, vital sign testing, as well as physical examination. Additional testing at Week 26, 52 and every 26 weeks thereafter, testing for fasting lipids, HbA1c, Hepatitis B and C, and sexually transmitted infections were performed.

After the primary analysis was completed, participants at the End of Blinded Phase Visit who remained on study drug had the option to enter the LEN OLE Phase. All participants who declined to continue on to the LEN OLE Phase instead had an end of Blinded Phase visit and either transitioned to local HIV prevention services and a 30 day follow up visit (participants randomized to F/TAF or F/TDF) or proceed to the PK Tail Coverage Phase (participants randomized to LEN). See protocol for details regarding the LEN OLE Phase and the PK Tail Coverage Phase.

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Protocol GS-US-528-9023 (PURPOSE 2)

Title: "A Phase 3, Double-Blind, Multicenter, Randomized Study to Evaluate the Efficacy and Safety of Subcutaneous Twice Yearly Long-Acting Lenacapavir for HIV Pre-Exposure Prophylaxis in Cisgender Men, Transgender Women, Transgender Men, and Gender Nonbinary People ≥ 16 Years of Age Who Have Sex With Male Partners and Are At Risk for HIV Infection"

This was a Phase 3, multicenter, randomized, double-blind, active-controlled study in cisgender men, transgender women, transgender men, and gender nonbinary people ≥ 16 years of age who have sex with male partners and are at risk for human immunodeficiency virus (HIV) infection. The primary efficacy objective of the overall study was to evaluate the efficacy of lenacapavir (LEN) in preventing the risk of HIV infection relative to the background HIV incidence rate. Oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) served as the internal active control. For the Incidence Phase of this study, the primary objective was to estimate the HIV background incidence rate. For the Randomized Blinded Phase of this study, the primary objective was to evaluate the efficacy of LEN for HIV pre-exposure prophylaxis (PrEP) in cisgender men, transgender women, transgender men, and gender nonbinary people ≥ 16 years of age who have sex with partners assigned male at birth and are at risk for HIV infection.

Eligible participants in the Incidence Phase were cisgender men, transgender women, transgender men and gender nonbinary people who reported having receptive anal sex with partners assigned male at birth and were at risk for HIV infection. They were to be ≥ 16 years of age at screening, with HIV-1 status unknown at screening and no prior HIV-1 testing within the last three months. They were to be sexually active with ≥ one partner assigned male at birth (condomless anal sex) in the last 12 months and have had condomless anal sex with ≥ two partners in the prior 12 weeks, have a documented history of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks, or provide self-reported use of stimulants with sex in the last 12 weeks. They were to have no prior use of long-acting systemic PrEP (including cabotegravir or islatravir trials) and no prior vaccine trial participation.

Eligible subjects in the Randomized Blinded Phase included those meeting criteria for participation in the Incidence Phase and who had a negative local rapid fourth generation HIV-1 Ab/Ag test confirmed with central HIV-1 testing, an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min at screening according to the Cockcroft-Gault formula for creatinine clearance, and body weight ≥ 35 kg. Additionally, they were not to have acute viral hepatitis A, B or C or evidence of chronic hepatitis B or C infections, have suspected or known other active, serious infections (e.g., active tuberculosis), a history of osteoporosis or bone fragility fractures, or unexplained Grade 3 or Grade 4 proteinuria or glycosuria at screening. See protocol for full eligibility criteria.

This study overall was similar to PURPOSE 1 in that it had the same four phases. The study design was similar, except that after screening, on Day 1, participants were randomized in a 2:1 fashion to one of the following two treatment groups:

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- LEN study drug group: Subcutaneous (SC) LEN [927 mg] + placebo-to-match (PTM) F/TDF
- F/TDF study drug group: F/TDF [200 mg emtricitabine/300 mg tenofovir disoproxil fumarate] + placebo SC LEN

A Pharmacokinetic (PK) loading dose of oral LEN 600 mg (2 x 300 mg tablets) or PTM oral LEN tablets (2 tablets) was also provided to the participants to self-administer on Day 1. Two additional oral LEN tablets of PTM LEN tablets were provided to self-administer on Day 2. SQ LEN or placebo SC LEN was administered every 26 weeks. Additionally, starting on Day 1, participants also received oral F/TDF (200/300 mg) or PTM F/TDF to self-administer daily.

The remainder of the study design was similar to PURPOSE 1, the primary efficacy analysis occurred at the end of the Randomized Blinded Phase, and eligible participants had the option to continue on to the LEN Open-Label Extension Phase and the PK Tail Phase (during which participants received F/TDF [200 mg emtricitabine/300 mg tenofovir disoproxil fumarate]).

Important efficacy and safety endpoints for PURPOSE 1 and PURPOSE 2 include the following:

The primary efficacy endpoints for PURPOSE 1 and PURPOSE 2:

- Incidence Phase: The background HIV incidence reported per 100 person-years computed based on the recency assay
- Randomized Blinded Phase: The HIV incidence based on the Full Analysis Set and reported per 100 person-years of exposure to study drug

Safety issue of interest:

- Injection site reactions and whether proper injection technique (subcutaneous) was used

Details relevant to Study PURPOSE 1

Study PURPOSE 1 is being conducted at 28 sites in South Africa and Uganda. The first subject's visit occurred on August 30, 2021, and the last subject's visit for the interim complete study report (dated November 1, 2024) occurred on May 8, 2024. Of the 5338 subjects who were randomized and dosed and had no HIV-1 diagnosis on or prior to the first dose (2134 subjects were in the lenacapavir group, 2136 were in the F/TAF group, and 1068 subjects were in the F/TDF group), 4957 subjects (93%) completed the Randomized Blinded Phase. The original protocol was dated January 13, 2021. There were three protocol amendments, and the final amendment was dated October 17, 2023.

Details relevant to Study PURPOSE 2

Study PURPOSE 2 is being conducted at 96 sites in 7 countries (Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the United States). The first subject was screened on June 28, 2021, and the last subject's visit for the interim complete study report (dated November 21, 2024) occurred on August 5, 2024. Of the 3265 subjects who were randomized and dosed with

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no HIV-1 diagnosis on or prior to the first dose (2179 subjects were in the lenacapavir group and 1086 were in the F/TDF group), 2901 subjects (89%) completed the Randomized Blinded Phase. The original protocol was dated March 1, 2021. There were three protocol amendments, and the final amendment was dated March 25, 2024.

III. RESULTS (by site):

1. Ian Frank, MD
Site #366
Protocol: GS-US-528-9023 (PURPOSE 2)
3535 Market Street, 4th Floor
Philadelphia, PA 19104
PDUFA Inspection Dates: February 26 to March 4, 2025

At this site for Protocol PURPOSE 2, 44 subjects were screened, 17 subjects were enrolled and randomized, and eight completed the Randomized Blinded Phase of the study. Of the nine subjects who did not complete the randomized blinded phase of the study, one subject (subject # (b) (6) in the subcutaneous lenacapavir [SC LEN] group) withdrew consent, five subjects (subjects # (b) (6) all in the emtricitabine/tenofovir disoproxil fumarate [F/TDF] group) were lost to follow up, one subject (subject # (b) (6) in the F/TDF group) discontinued for personal reasons, and two subjects (subjects # (b) (6) in the F/TDF group and # (b) (6) in the SC LEN group) were transferred to other sites.

The inspection evaluated the study records for all 17 of the randomized subjects for Protocol PURPOSE 2. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and specified safety issues; adverse event (AE) reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; financial disclosures, and other regulatory documentation.

During the inspection, for the 17 randomized subjects, paper printouts of the electronic primary efficacy endpoint data – human immunodeficiency virus (HIV) test results during the Incidence Phase and the Randomized Blinded Phase (the local and central rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag) test, the HIV 1/2 differentiation assay, the HIV-1 and HIV-2 ribonucleic acid (RNA) qualitative nucleic acid amplification tests, and the HIV-1 RNA quantitative nucleic acid amplification test) – were reviewed. These data were verified against the data line listings provided by the sponsor. No discrepancies were noted.

Adverse events were also reviewed, and specific attention was paid to the occurrence of injection site reactions and whether proper injection technique (subcutaneous) was used. There was no underreporting of adverse events.

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2. Jose Valdez Ramalho Madruga, MD
Site #1000
Protocol: GS-US-528-9023 (PURPOSE 2)
Rua Santa Cruz 81
Vila Mariana
Sao Paulo, SP
04121-000
Brazil
PDUFA Inspection Dates: March 24-28, 2025

At this site for Protocol PURPOSE 2, 318 subjects were screened, 217 subjects were enrolled and randomized, 216 were dosed with the study drug (subject # (b) (6) in the SC LEN group was never dosed), and – according to the enrollment log – 198 subjects completed the Randomized Blinded Phase of the study. Of the 18 subjects who did not complete the randomized blinded phase of the study, 11 subjects withdrew consent, five subjects were discontinued due to non-compliance with the study drug, one subject was lost to follow-up, and one subject died. The table below provides details about the 18 subjects who did not complete the Randomized Blinded Phase of the study.

Reason for discontinuation from study	Study drug group	Subject ID (randomization #)
Withdrawal of consent	SC LEN	(b) (6)
	F/TDF	
Non-compliance with study drug	SC LEN	
	F/TDF	
Lost to follow-up	SC LEN	
Death	SC LEN	

The inspection evaluated the study records for all 216 of randomized and dosed subjects for Protocol PURPOSE 2. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) oversight; subject eligibility criteria; source records, including medical records; primary efficacy endpoint data and specified safety issues; AE reporting; protocol deviations; drug accountability logs; financial disclosures, monitor logs and sponsor reports; and other regulatory documentation. Informed consent forms were reviewed for 34 subjects.

During the inspection, for the 216 randomized and dosed subjects, paper printouts of the electronic primary efficacy endpoint data – HIV test results during the Incidence Phase and the Randomized Blinded Phase (the local and central rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag) test, the HIV 1/2 differentiation assay, the HIV-1 and HIV-2 RNA qualitative nucleic acid amplification tests, and the HIV-1 RNA quantitative nucleic acid

amplification test) – were reviewed. These data were verified against the line listings generated by this reviewer from the data submitted to the NDA. No discrepancies were noted.

Adverse events were reviewed for the 216 randomized and dosed subjects, and specific attention was paid to the occurrence of injection site reactions and whether proper injection technique (subcutaneous) was used. All injections were reported as being performed subcutaneously with "nearly all subjects experiencing some injection site reactions (pain, erythema, and/or nodules)." The inspection found that three adverse events were not reported: folliculitis in subject # (b) (6) in the SC LEN group and upper respiratory infection and dizziness in subject # (b) (6) in the F/TDF group. Additionally, subject # (b) (6) in the F/TDF group was hospitalized with a Dengue Fever (Grade 3), but the subject did not report this to the site until after the data cut-off date.

Reviewer's comment: The three unreported AEs, folliculitis experienced by subject # (b) (6) in the SC LEN group (not included in the proposed label) and upper respiratory infection and dizziness experienced by subject # (b) (6) in the F/TDF group. We refer these three unreported AEs to the review division for consideration. We also refer the unreported SAE of dengue fever in subject # (b) (6) in the F/TDF group – which was not reported by the subject to the site until after the data cut-off date – to the review division.

3. Khatija Ahmed, MBChB, FCPath
Site # 11413
Protocol: GS-US-412-5624 (PURPOSE 1)
2088 Block H Soshanguve Gauteng
0152
South Africa
PDUFA Inspection Dates: May 5-9, 2025

At the time of the summary, the inspection report for Dr. Ahmed was not available. Therefore, the information below was conveyed via email by the field investigator after the inspection. An addendum to this summary will be provided should the final inspection report reveal any significant new information.

At this site for Protocol PURPOSE 1, 502 subjects were screened, 352 subjects were enrolled and randomized, and 286 (including 26 subjects in the PK Tail Coverage Phase) are currently active in the study. Of the 46 subjects who were discontinued from the study, 30 subjects were lost to follow up and 16 withdrew consent for personal reasons.

The inspection evaluated the study records for 102 of the randomized subjects for Protocol PURPOSE 1. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and specified safety data; AE reporting; protocol deviations; concomitant medications; medical monitor communications; and other regulatory documentation. The primary efficacy endpoint data was reviewed for all 102 of these subjects, while review of the other study data was limited to 30 of the randomized subjects.

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During the inspection, for these 102 randomized subjects, paper printouts of the electronic primary efficacy endpoint data – HIV test results during the Incidence Phase and the Randomized Blinded Phase (the local and central rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag) test, the HIV 1/2 differentiation assay, the HIV-1 and HIV-2 RNA qualitative nucleic acid amplification tests, and the HIV-1 RNA quantitative nucleic acid amplification test) – were reviewed. These data were verified against the data line listings provided by the sponsor and/or the line listings generated by this reviewer from the data submitted by the sponsor to the NDA. No discrepancies were noted.

Adverse events were also reviewed, and specific attention was paid to the occurrence of injection site reactions and whether proper injection technique (subcutaneous) was used. The inspection found no evidence of underreporting of adverse events or use of improper injection technique.

The inspection found that the injections for nine subjects were given outside of the protocol-specified injection window period. See table below for details regarding these subjects.

Subject ID (randomization #)	**Study drug group (per sponsor's data line listings)**	**Number of days after protocol-specified injection window that injection was given**
(b) (6)	SC LEN	9 days
	F/TAF	16 days
	SC LEN	20 days
	F/TDF	30 days
	SC LEN	176 days
	F/TDF	42 days
	F/TDF	20 days
	F/TDF	81 days
	SC LEN	60 days

Reviewer's comment: Nine subjects (in the table above) received injections as many as 9 days to 176 days after the time window specified by the protocol. We refer these protocol deviations to the review division for their consideration.

4. Philisiwe Busisiwe Makhoba, MBChB
Site # 22455
Protocol: GS-US-412-5624 (PURPOSE 1)
Philisiwe Busisiwe Makhoba
15 Parklane
Mkhamba Gardens
Ladysmith
Kwazulu-Natal
3370
South Africa
PDUFA Inspection Dates: May 12-16, 2025

At the time of the summary, the inspection report for Dr. Makhoba was not available. Therefore, the information below was conveyed via email by the field investigator after the inspection. An addendum to this summary will be provided should the final inspection report reveal any significant new information.

At this site for Protocol PURPOSE 1, 317 subjects were screened, 258 subjects were enrolled and randomized, and 228 subjects completed the study. Of the 30 subjects who were discontinued from the study, 12 were lost to follow up and 18 withdrew consent for personal reasons.

The inspection evaluated the study records for 50 of the randomized subjects for Protocol PURPOSE 1. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data and specified safety data; AE reporting; protocol deviations; and other regulatory documentation.

During the inspection, for these 50 of the randomized subjects, paper printouts of the electronic primary efficacy endpoint data – HIV test results during the Incidence Phase and the Randomized Blinded Phase (the local and central rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag) test, the HIV 1/2 differentiation assay, the HIV-1 and HIV-2 RNA qualitative nucleic acid amplification tests, and the HIV-1 RNA quantitative nucleic acid amplification test) – were reviewed. These data were verified against the data line listings provided by the sponsor and/or the line listings generated by this reviewer from the data submitted by the sponsor to the NDA. No discrepancies were noted.

Adverse events were also reviewed, and specific attention was paid to the occurrence of injection site reactions and whether proper injection technique (subcutaneous) was used. There was one unreported AE, urinary tract infection, experienced by subject # (b) (6) in the F/TAF group. There was no evidence of underreporting of protocol deviations and no observed unblinding occurrences.

Reference ID: 5598777

Reviewer's comment: A single AE of urinary tract infection, experienced by subject # (b) (6) (in the F/TAF group) was not reported. We refer this AE to the review division for consideration.

{See appended electronic signature page}

Elena Boley, M.D., M.B.A.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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Kassa Ayalew, M.D., M.P.H.
Division Director
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Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 220018 and NDA 220020
DAV/Regulatory Project Manager/Kevin Allen
DAV/Clinical Reviewer/ Timothy Jancel
DAV/Clinical Reviewer/ Ursula Kelly
DAV/Clinical Team Leader/ Stephanie Troy
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Elena Boley
OSI/GCPAB/Program Analyst/Yolanda Patague

Reference ID: 5598777

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELENA BOLEY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 19, 2025
To:	Kevin Allen Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route, Application Type/Number, Supplement Number:	YEZTUGO (lenacapavir) injection, for subcutaneous use NDA 220018 YERTUGO (lenacapavir) tablets, for oral use NDA 220020
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On December 19, 2024, Gilead Sciences, Inc. submitted for the Agency's review New Drug Applications (NDAs) 220018 for YEZTUGO (lenacapavir) injection and 220020 for YEZTUGO (lenacapavir) tablets. These original NDAs are multistage selective inhibitors of HIV-1 capsid function proposing an indication for pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on January 6, 2025, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for YEZTUGO (lenacapavir) injection, for subcutaneous use and YEZTUGO (lenacapavir) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft YEZTUGO (lenacapavir) PPI received on December 19, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 12, 2025.
- Draft YEZTUGO (lenacapavir) Prescribing Information (PI) received on December 19, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 12, 2025.
- APRETUDE (cabotegravir extended-release injectable suspension) comparator labeling dated April 11, 2025.
- Approved SUNLENCA (lenacapavir) comparator labeling dated November 25, 2024.
- TRUVADA (emtricitabine and tenofovir disoproxil fumarate) comparator labeling dated April 29, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

7 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this pagei

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/s/

MARIA T NGUYEN
05/19/2025 01:36:19 PM
DMPP-OPDP review of lenacapavir (YEZTUGO) NDAs 220018 and 220020 PPI

WENDY R LUBARSKY
05/19/2025 06:40:51 PM

BARBARA A FULLER
05/20/2025 07:31:43 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 19, 2025

To: Kevin Allen, Regulatory Project Manager
Division of Antivirals (DAV)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for YEZTUGO (lenacapavir) injection, for subcutaneous use; YEZTUGO (lenacapavir) tablets, for oral use

NDA: 220018, 220020

Background:

In response to DAV's consult request dated January 6, 2025, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for Yeztugo.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 9, 2025, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 19, 2025, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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Reference ID: 5612609

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/s/

WENDY R LUBARSKY
05/19/2025 11:24:07 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 7, 2025
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 220018 NDA 220020
Product Name, Dosage Form, and Strength:	Yeztugo (lenacapavir) Injection, 463.5 mg/1.5 mL (309 mg/mL) Tablet, 300 mg
Applicant Name:	Gilead Sciences, Inc.
FDA Received Date:	April 30, 2025
TTT ID #:	2024-12127-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

Reference ID: 5586442

1 PURPOSE OF MEMORANDUM

Gilead Sciences, Inc. submitted revised container labels and carton labeling received on April 30, 2025 for Yeztugo. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Yeztugo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Gilead Sciences, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Fanari, M. Label and Labeling Review for Yeztugo (NDA 220018 and NDA 220020). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 Mar 19. TTT ID: 2024-12127-11.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 5586442

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/s/

MELINA N FANARI
05/07/2025 09:30:13 AM

YEVGENIYA M KOGAN
05/07/2025 01:08:40 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 4/29/2025 **Date consulted:** 1/10/2025

From: Katherine Kratz, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: CDR Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Antivirals (DAV)

Drug: YEZTUGO (lenacapavir (LEN)) solution for subcutaneous injection and tablets for oral use

NDAs: 220018 and 220020

Applicant: Gilead Sciences, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: For pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg

Materials Reviewed:

- DPMH consult request dated 1/10/2025. DARRTS Reference ID: 5509715
- Applicant's submitted background package and proposed labeling for NDAs 220018 and 220020, Sequence Numbers (SNs) 0001 and 0002, dated 11/26/2024 and 12/19/2024, respectively.
- Information Requests (IRs) sent to Applicant 2/7/2025 and 4/3/2025. DARRTS Reference IDs: 5527438 and 5564218, respectively.
- Applicant responses to IRs submitted 2/21/2025, SN 0010 and 4/11/2024, SN 0019.

Reference ID: 5581148

- Applicant's 90-day Safety Update for NDAs 220018 and 220020, SNs 0015 and 0014, respectively; dated 3/19/2025.
- DPMH review of Truvada (emtricitabine/tenofovir disoproxil fumarate) NDA 021752/S-055 by Leyla Sahin MD, dated 4/27/2018. DARRTS Reference ID: 4254513

Consult Request: "Please comment on whether you agree with the labeling language included in Sections 8.1 (use in pregnancy) and 8.2 (use in lactation) of the USPI. We are particularly interested in your assessment of the following language in Section 8.1: (b) (4) [redacted]

I. INTRODUCTION AND BACKGROUND

On December 19, 2024, the Applicant, Gilead Sciences, Inc., submitted a 505(b)(1) New Drug Application (NDA) for LEN for PrEP to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg. LEN was previously approved by FDA in December 2022 under the tradename Sunlenca (NDAs 215973 and 215974) for treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 whose current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations. DAV consulted the DPMH MHT on January 10, 2025, to assist with the Pregnancy and Lactation subsections of labeling for the proposed drug.

Relevant Regulatory History

- Three drugs have been approved by FDA for PrEP. The oral drug productsrequire adherence to daily dosing, and the intramuscular injection is dosed more frequently than the proposed drug product:
  - Emtricitabine and tenofovir disoproxil fumarate (F/TDF, Truvada under NDA 021752): nucleoside analog HIV-1 reverse transcriptase inhibitors (NRTIs); approved in 2004; daily oral dosing
  - Emtricitabine and tenofovir alafenamide (F/TAF, Descovy under NDA 208215): NRTIs; approved in 2016; not indicated for PrEP in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated; daily oral dosing
  - Cabotegravir (CAB): HIV-1 integrase strand transfer inhibitor (INSTI); approved in 2021
    - Apretude (NDA 215499) monthly intramuscular (IM) injection x 2, followed by IM dosing every 3 months
    - Vocabria (NDA 212887) for short-term PrEP; daily oral dosing for at least 28 days followed by Apretude
- DPMH conducted consult reviews for Truvada and Vocabria.
- August 2021: Lenacapavir for PrEP was granted Fast Track Designation.
- December 2022: Sunlenca (LEN) for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 whose current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations was approved by FDA. DPMH was not consulted during the review cycle for Sunlenca.
- October 2024: Lenacapavir for PrEP was granted Breakthrough Therapy Designation.

Reference ID: 5581148

Drug Characteristics[1]

Drug class	HIV-1 capsid inhibitor
Mechanism of action	Inhibits HIV-1 replication by interfering with capsid-mediated nuclear uptake of HIV-1 proviral DNA, virus assembly and release, and capsid core formation
Dosage and administration	Initiation: 927 mg SC x 1 + 600 mg PO x 1 on day 1; 600mg PO x 1 on day 2 Maintenance: 927 mg SC q26 weeks +/- 2 weeks
Molecular weight	990.3 Daltons
Half-life	Subcutaneous: 8 to 12 weeks; Oral: 10 to 12 days
% protein bound	>98.5
Bioavailability	Subcutaneous: 91%; Oral: 4 -7%
Warnings and Precautions	(b) (4); Injection site reactions

II. REVIEW

PREGNANCY

PrEP and Pregnancy

DPMH has previously reviewed PrEP and pregnancy.[2] Briefly, clinical practice guidelines[3] recommend the following:

- PrEP with F/TDF should be offered to women seeking to conceive, are pregnant or are breastfeeding who have a sexual partner with HIV, especially when their partner's viral load is unknown, is detectable, or cannot be documented as undetectable.
- The extent to which PrEP use further decreases risk of HIV acquisition when the male partner has a documented recent undetectable viral load (<200 copies/ml) is unknown, but there may be a benefit when viral suppression is not durable or the woman has other partners.
- F/TAF is not approved for PrEP for women at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.
- The published data on CAB-exposed pregnancies among women without HIV are sparse.

Nonclinical Data

The Applicant reported that an embryo-fetal development study with IV LEN in rabbits and an embryo-fetal development study with oral LEN in rats were conducted, and "no noteworthy findings" were seen.[4]

In the draft labeling of subsection 8.1, Pregnancy, the Applicant proposed the following: "Lenacapavir was administered intravenously to pregnant rabbits (up to 20 mg/kg/day on

[1] NDA 220022, SN 0002, Module 1.14.1.3, Draft Labeling Text. Under review by DAV.
[2] DPMH review of Truvada (emtricitabine/tenofovir disoproxil fumarate) NDA 021752/S-055 by Leyla Sahin MD, dated 4/27/2018. DARRTS Reference ID: 4254513
[3] U.S. Public Health Service Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2021 Update – A Clinical Practice Guideline. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwi37aSTypaLAxVplYkEHblyNN0QFnoECAgQAQ&url=https%3A%2F%2Fwww.cdc.gov%2Fhiv%2Fpdf%2Frisk%2Fprep%2Fcdc-hiv-prep-guidelines-2021.pdf&usg=AOvVaw34RxxNOqb46MvTu4TUHnXH&opi=89978449
[4] NDA 220018, SN 0002, Module 2.4, Nonclinical Overview Addendum, p. 13.

gestation days (GD) 7 to 19), orally to rats (up to 300 mg/kg/day on GD 6 to 17), and subcutaneously to rats (up to 300 mg/kg on GD 6). No significant toxicological effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at exposures (AUC) approximately (b) (4) times (rats) and (b) (4) times (rabbits) the exposure in humans at the RHD [Recommended Human Dose]."

Reviewer comment:
At the time of this DPMH review, the Pharmacology/Toxicology review was ongoing. The reader is referred to the review by Dr. Deacqunita Harris regarding the data presented above.

Clinical Data

To support this NDA, the Applicant conducted two phase 3, double-blinded, multicenter, randomized trials: Study GS-US-412-5624 (PURPOSE 1) and Study GS-US-528-9023 (PURPOSE 2). PURPOSE 1 pertains to this maternal health review, as it was conducted in cisgender adolescent girls and young women ≥ 16 to ≤ 25 years of age who were assigned female gender at birth, have sex with cisgender males and were able to become pregnant. PURPOSE 2 does not pertain to this maternal health review, as it was conducted in cisgender men, gender nonbinary people, transgender men and transgender women who were assigned male gender at birth and were not able to become pregnant.

PURPOSE 1 evolved from a postmarketing commitment (PMC 3723-1) for Descovy in which the Applicant agreed to conduct a randomized, comparative trial to evaluate the safety and efficacy of Descovy (F/TAF) for PrEP in cisgender women and adolescent girls weighing at least 35 kg who are at risk of sexually acquired HIV-1 infection.[5] The PMC trial was to include a F/TDF arm. LEN was added to the planned PMC trial.[6] Given that both F/TAF and LEN were experimental arms and F/TDF was the active control arm, subjects were randomized in a 2:2:1 ratio to LEN, F/TAF and F/TDF, respectively. In the Randomized Blinded Phase (RBP) of PURPOSE 1, subjects randomized to the LEN arm received LEN 927 mg subcutaneous (SC) every 26 weeks (starting on Day 1/Injection 1 visit) and LEN 600 mg orally administered on Day 1/Injection 1 and Day 2 for and a second dose of LEN SC at 26 weeks. Subjects randomized to the F/TAF arm received Descovy 200/25 mg orally once daily. Subjects randomized to the F/TDF arm received Truvada 200/300 mg orally once daily. For inclusion in PURPOSE 1, all subjects were required to have a negative pregnancy test on study day 1.

Subjects who became pregnant during PURPOSE 1 were allowed to remain on the study drug after a discussion of potential risks and benefits and provision of additional informed consent. Subjects were not unblinded at the time that pregnancy was diagnosed. The outcome of the pregnancy was reported to the Gilead Global Patient Safety database.

Subjects who became pregnant during PURPOSE 1 and who consented to remain on study drug and breastfeed their infants were given the option to provide breast milk and infant plasma samples for PK analysis at the first two protocol-scheduled visits after delivery.

[5] Postmarketing Requirements and Commitments: Searchable Database. https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=2&StepSize=1&Paging=Yes
[6] IND 136260, SN 0096, Module 1.6.2 Type B (EOP), Pre-Phase 3 Meeting Information Package, p. 15.

Reference ID: 5581148

PURPOSE 1 was conducted in South Africa and Uganda in subjects with the following demographic characteristics, which were similar across treatment arms:

Demographic	**Across treatment arms**
Gender	Female
Race	Black (99.9%)
Ethnicity	African; Not Hispanic or Latino
Median Age (range)	21 (16-26) years
Body Mass Index (range)	25.2 (21.9, 30.4) kg/m^2

Pregnancy Outcome Data from PURPOSE 1[7,8]

There were a total of 297 confirmed pregnancies with exposure to LEN in the RBP of PURPOSE 1. Among the 297 pregnancies, there were 208 pregnancies with known outcomes, 88 ongoing pregnancies and 1 unknown outcome. Among the 208 pregnancies with known outcomes, there were 130 pregnancies that resulted in 132 deliveries (two sets of twins). These 132 deliveries consisted of 127 live births and 5 stillbirths. The remaining 78 pregnancies included 28 spontaneous abortions (SABs) and 50 terminations. The reviewer-generated table on the following page (Table 1) includes crude (i.e., unadjusted) adverse pregnancy outcome data from the PURPOSE 1 trial. This table contains data from the Applicant's initial submission and the 90-day safety update submitted on March 19, 2025. From these data, the Applicant concluded that pregnancy safety outcomes were similar in the LEN and Truvada treatment groups. The Applicant also concluded that the prevalence of adverse pregnancy outcomes related to LEN exposure were consistent with the background prevalence.

[7] NDA 220018, SN 0001, Module 5.3.5.1, Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, p. 164, p. 557-558, and p. 973.
[8] NDA 220018, SN 0015, Module 5.3.5.3 NDA Safety Update, p. 251-262.

Table 1. Reviewer-generated table of pregnancy outcomes from RBP of PURPOSE 1

Treatment Arm in RBP	LEN	F/TDF	F/TAF
Total deliveries*	132	61	122
Stillbirth (SB)	5/132 = 3.8% (95% CI 1.2, 8.6)	3/61 = 4.9% (95% CI 1.0, 13.7)	7/122 = 5.7% (95% CI 2.3, 11.5)
Preterm birth (PTB)	21/132 = 15.9% (95% CI 10.1, 23.3)	14/61 = 22.9% (95% CI 13.2, 35.5)	26/122 = 21.3% (95% CI 14.4, 29.7)
Small for gestational age (SGA)	11/132 = 8.3% (95% CI 4.2, 14.4)	10/61 = 16.4% (95% CI 8.2, 28.1)	12/122 = 9.8% (95% CI 5.2, 16.6)
Congenital anomaly (CA)	5/132 (3.8%) (95% CI 1.2, 8.6) Major congenital malformations (MCMs): VSD: 2 (1.5%) (95% CI 0.18, 5.4) Minor CAs: polydactyly: 1 (0.8%) umbilical hernia: 1 (0.8%) hemangioma: 1 (0.8%)	0 (0%)	2/122 = 1.6% (95% CI 0.2, 5.8) MCM: club foot: 1 (0.8%) Minor CA: bilateral hydrocele: 1 (0.8%)
Neonatal problem	6/132 = 4.5% (95% CI 1.7, 9.6) jaundice: 3 omphalitis/sepsis: 1 TTN: 1 respiratory distress: 1	2/61 = 3.3% (95% CI 0.4, 11.2) meconium: 1 low birth weight: 1	1/122 = 0.8% (95% CI 0.02, 4.5) jaundice: 1
Spontaneous abortion (SAB) among **completed pregnancies** in each arm	28/208 = 13.5% (95% CI 9.1, 18.9)	20/109 = 18.3% (95% CI 11.6, 26.9)	41/237 = 17.3% (95% CI 12.7, 22.7)

Definitions: PTB: estimated gestational age (EGA) of < 37 weeks; SB: fetal death occurring at ≥ 20 EGA ; SGA: <10th percentile birth weight; TTN: transient tachypnea of the newborn; CA: Not defined by the Applicant in the protocol; VSD: Ventricular Septal Defect; SAB: pregnancy loss at < 20 weeks EGA; * deliveries include live births and non-live births

Pharmacovigilance (PV) Data[9]

In addition to the 297 pregnancies from PURPOSE 1 referenced in Table 1 above, an additional 99 pregnancies with maternal exposure to LEN were reported to the Gilead global safety database. Given that the PV data are uncontrolled, fewer than reported in PURPOSE 1 and related to LEN use for multi-drug resistant HIV-1, which is a different indication than proposed in this submission, these data are not further reviewed herein.

DPMH reviewed the most recently published Antiretroviral Pregnancy Registry (APR) interim report that encompassed the time period of January 1, 1989 through July 31, 2024 for data

[9] NDA 220018, SN 0002, Module 2.5, Clinical Overview, p. 39 and Module 2.7.4, Summary of Clinical Safety, p. 74.

pertaining to LEN. There were 2 prospective cases of exposure to LEN during pregnancy and no reported birth defects.

Reviewer comment:
DPMH notes that the pregnancy outcome data from PURPOSE 1 have multiple limitations: 1) the trial was not powered for pregnancy outcomes; 2) the sample size (i.e., the number of pregnancies) was small; 3) the results were unadjusted for confounders. Nonethess, the data did not demonstrate a clear safety signal. Although the risk estimates for the adverse outcomes of SB, PTB, SGA and SAB were imprecise due to small numbers of exposed pregnancies, the rates of SB, PTB, SGA and SAB were similar across groups, as shown by overlapping confidence intervals.

The background prevalence rates for SB, PTB, SGA and SAB in the study populations are provided in a table in Appendix A of this review. The observed rates of SB and SGA in the LEN arm of PURPOSE 1 fell within the background prevalence rates in Uganda and South Africa. The observed rates of PTB and SAB in the LEN arm were slightly higher than the background prevalence rates reported in those countries; however, these observed rates for PTB and SAB were not conclusively different from the background rates given the wide confidence intervals.

In terms of congenital anomalies (CAs), overall, there were numerically more CAs in the LEN arm than the F/TDF and F/TAF arms; however, the majority of these CAs were minor and not major CAs. Specifically, the Center for Disease Control and Prevention (CDC) categorizes umbilical hernia, non-facial hemangiomas and polydactyly as minor CAs.[10] The remaining two CAs in the LEN arm were VSDs, which are major congenital malformations (MCMs).[11] Thus, there were numerically more MCMs in the LEN arm (1.5%) than in the F/TDF arm (0%) and the F/TAF arm (0.8%). Despite the higher number of MCMs in the LEN arm than in the active control arm, there were too few outcomes to inform safety and the rate of VSDs falls within the background prevalence rate. VSDs have a reported prevalence of 3.3%.[12]

In terms of the reported "neonatal problems," there were more "neonatal problems" in the LEN arm than in the F/TDF and F/TAF arms; however, the most common problem was jaundice, which is common in the neonatal period as it occurs in 60-80% of newborns.[13] The single cases of omphalitis leading to sepsis, TTN and respiratory distress in the LEN arm did not suggest a pattern of problems. Given the small numbers of these outcomes, it was not possible to attribute them to LEN.

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[10] External minor congenital anomalies.
https://archive.cdc.gov/www_cdc_gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html
Accessed 3/28/25.
[11] Birth Defects Tracking, Metropolitan Atlanta Congenital Defects Program (MACDP)
https://www.cdc.gov/birth-defects/media/files/MACDP-Code-List-Updated-Nov-2023_Rev_Website2-508c.xlsx
[12] Pihl C, Sillesen AS, Norsk JB, Vøgg ROB, Vedel C, Boyd HA, Vejlstrup N, Axelsson Raja A, Bundgaard H, Iversen KK. The Prevalence and Spontaneous Closure of Ventricular Septal Defects the First Year of Life. Neonatology. 2024;121(6):742-751. doi: 10.1159/000538810. Epub 2024 Jun 10. PMID: 38857582.
[13] Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017 Dec 2;78(12):699-704. doi: 10.12968/hmed.2017.78.12.699. PMID: 29240507.

Reference ID: 5581148

Overall, DPMH agreed with the Applicant that pregnancy safety outcomes were similar in the LEN and Truvada treatment groups. DPMH also concluded that the prevalence of adverse pregnancy outcomes related to LEN exposure were not conclusively different from the background prevalence rates.

Notably, inclusion in PURPOSE 1 required subjects to have a negative pregnancy test on study day 1. Given the long half-life of LEN SC of 8-12 weeks, subjects who became pregnant after they received LEN SC on study day 1 in PURPOSE 1 were likely exposed to LEN during all three trimesters of pregnancy. This is based on a conservative estimate of elimination using the shortest half-life of the SC dosage of 8 weeks x 5 half-lives = 40 weeks.

Maternal Outcomes

The reviewer-generated table below (Table 2) includes maternal safety data from the PURPOSE 1 trial. This table contains data from the Applicant's initial submission and the 90-day safety update submitted on March 19, 2025.

Table 2. Reviewer-generated table of maternal outcomes from RBP of PURPOSE 1

Treatment Arm in RBP	LEN	F/TDF	F/TAF
Maternal outcomes			
Death	0	0	0
Gestational hypertension	3/208 (1.4%)	2/109 (1.8%)	2/237 (0.8%)
Pre-eclampsia	1/208 (0.5%)	0	1/237 (0.4%)
Hemorrhage	3/208 (1.4%)	0	2/237 (0.8%)
Hyperemesis gravidarum	3/208 (1.4%)	0	2/237 (0.8%)

Reviewer comment:
Overall, there were very few cases of adverse maternal outcomes in the LEN arm of PURPOSE 1. Although there were more cases of pre-eclampsia, hemorrhage and hyperemesis gravidarum in the LEN arm compared to the F/TDF active-control arm, the prevalence of these outcomes was overall low. In addition, the adverse maternal outcomes in the LEN arm were lower than the background prevalence rates (see the reviewer-generated table in Appendix A).

Pharmacokinetic (PK) Pregnancy Data from PURPOSE 1[14]

The PK Tail Phase was pre-specified in the PURPOSE 1 protocol such that plasma PK samples were to be drawn on day 1, 13, and 26 and every 13 or 26 weeks until week 78. Opportunistic plasma PK sampling was done in subjects who became pregnant during PURPOSE 1, continued into the PK Tail Phase and agreed to have samples drawn. The LEN PK Analysis Set included all randomized subjects who had at least 1 non-missing LEN plasma concentration value reported by the PK laboratory.

The Applicant reported the following PK data related to pregnancy:

[14] NDA 220018, SN 0001, Module 5.3.5.1, Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, p. 12.

- Pregnancy was shown to have no clinically significant impact on LEN PK in 181 subjects. Comparable concentrations were observed prior to pregnancy and during each trimester.

- Based on the limited data available during the first 28 weeks after delivery in 20 subjects who became pregnant, postpartum LEN plasma concentrations were shown to be generally comparable with the levels observed prior to pregnancy and during pregnancy.

The reader is referred to the Clinical Pharmacology review by Dr. Jomy George.

> ***Reviewer comment:***
> *DPMH discussed the PK data reported by the Applicant with the Clinical/Pharmacology (CP) team. The CP team agreed with the Applicant's pregnancy PK data presented above.*

Review of Literature
Applicant's review:
The Applicant did not submit a literature review pertaining to pregnancy.

DPMH review:
DPMH conducted a search of published human studies in PubMed and Embase, using the search terms "lenacapavir" OR "HIV-1 capsid inhibitor" AND "pregnancy," "pregnancy outcomes," "birth defects," "malformations," "stillbirth," "spontaneous abortion." No information was found.

DPMH also searched Micromedex,[15] Reprotox,[16] TERIS,[17] and Shepard's[18] and no information was found.

LACTATION
Nonclinical Data
The Applicant did not provide new nonclinical lactation data for this NDA. Data was previously submitted to NDAs 215973 and 215974 for Sunlenca (LEN). The current labeling for Sunlenca states the following under subsection 8.2, Lactation, *Data*: "Lenacapavir was detected at low levels in the plasma of nursing rat pups in the pre/postnatal development study (post-natal day 10)."

PK Lactation Data from Drug Development Program
Optional breast milk and infant plasma samples from women who became pregnant during PURPOSE 1 and consented to remain on study drug were collected at the first two protocol-scheduled visits after delivery. Participants could subsequently opt out of breast milk and infant sample collection. The LEN PK Breast Milk Analysis Set included participants in the LEN PK Analysis Set who had at least one non-missing LEN breast milk concentration value reported by the PK laboratory. The LEN PK Infant Analysis Set included participants in the LEN PK

[15] Truven Health Analytics information, http://www.micromedexsolutions.com. Accessed 1/28/25.
[16] Reprotox Website: www.Reprotox.org. Accessed 1/28/25.
[17] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 1/28/25.
[18] Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 1/28/25.

Reference ID: 5581148

Analysis Set who had at least one non-missing LEN plasma concentration value from infants reported by the PK laboratory. The Applicant reported the following from the PK Tail Phase of the PURPOSE 1:[19]

- In lactating women, the median milk-to-plasma (M:P) ratio for LEN was 0.63 (range: 0.29-1.90) (N = 8 matched pairs).

- The median infant-to-mother plasma ratio for LEN in infants who were breastfed was 0.05 (range: 0.00-0.20) (N = 11 matched pairs).

Reviewer comment:
DPMH discussed the lactation PK data with the CP team. The CP team agreed with the lactation PK data provided by the Applicant.

DPMH noted that the M:P ratio of less than 1.0 suggests that LEN is not concentrated in breast milk. The infant-to-mother plasma ratio indicates that the amount of LEN that enters infant serum after exposure via breast milk is low.

DPMH discussed the wide ranges for the M:P ratio and of the infant-to-mother plasma ratio with the CP team. The CP team explained that the wide ranges are related to one subject who had a higher breast milk concentration than other subjects. This subject's breast milk concentration of LEN was 104 ng/mL and her plasma concentration was 54.8 ng/mL. The breastfed infant's plasma concentration of LEN was 10.7 ng/mL. Notably, this highest infant plasma concentration of LEN of 10.7 ng/mL was several fold lower than the C_{max} and C_{trough} for treated adults of 73.8 ngmL and 27 ng/mL, respectively, which DPMH found to be reassuring. The median M:P ratio for LEN without this value was 0.53 (range: 0.29-0.83) (N = 7 matched pairs).

The lowest infant plasma concentration of 0.00 ng/mL was from the only infant who had a sample drawn between 13 and 28 weeks post-delivery. The ten other infant plasma samples were drawn between 0 to <13 weeks post-delivery. When the infant with the 0.00 ng/mL plasma concentration was removed from the calculation and the ten infants with plasma concentrations drawn between 0 to <13 weeks post-delivery were included, then the infant-to-mother plasma ratio for LEN infants who were breastfed was 0.06 with a slightly narrower range of 0.01-0.2.

Pharmacovigilance Data[20]
In the Gilead global safety database, 89 cases of LEN use in lactating women were reported. There were 14 serious adverse events (SAEs) reported, including two deaths in the Applicant's initial submission. In the initial submission, the Applicant reported that the two deaths were not related to delivery circumstances or congenital anomalies and were not considered related to study drug. The Applicant also reported that the remaining 12 cases were not related to study drug, and there was no pattern of reporting that was suspicious for an adverse drug reaction in

[19] NDA 220018, SN 0001, Module 5.3.5.1, Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, p. 115
[20] NDA 220018, SN 0002, Module 2.7.4, Summary of Clinical Safety, p. 75.

Reference ID: 5581148

the infants. From these 12 cases, the Applicant concluded that there was no evidence of adverse reactions to LEN in neonates or infants via exposure through human milk.

Reviewer comment:

An IR was sent to the Applicant to obtain more information about the 14 SAEs, including two deaths, reported in lactating subjects in the initial submission. The Applicant responded to the IR as follows:

- *One infant death was due to hypothermia and/or hypoglycemia. The infant was exposed to rain. The mother had severe malaria, malnutrition and anemia during pregnancy.*
- *The second infant death was due to respiratory failure.*
- *Among the 12 other reported SAEs, 10 did not involve LEN exposure during lactation:*
  - *Two cases: The SAEs resolved prior to the mother entering the open-label extension and receiving LEN.*
  - *Three cases: The "lactation-exposure" cases were actually pregnancy-exposure cases.*
  - *Five cases: The SAEs occurred prior to the initiation of breastfeeding.*
- *Ultimately, there were two cases of LEN exposure during lactation and the reported SAEs were jaundice in the infants. As stated previously in this review, jaundice is common in the neonatal period, occurring in 60-80% of newborns; therefore, these SAEs were not likely related to LEN exposure via human milk.*

In the 90-day Safety Update, the Applicant reported another SAE involving an infant with sickle cell disease who was being breastfed by a mother who received F/TAF in the RBP and was switched to LEN in the OLE when the infant was 8 months of age. The infant experienced anemia and pneumonia at 10 months of age. The infant recovered after receiving packed red blood cells and antibiotics.

Reviewer comment:

The SAEs of anemia and pneumonia in the breastfed infant were not likely related to LEN exposure through breast milk because infants with sickle cell disease are at risk for anemia and pneumonia.

Upon review of the three cases of LEN exposure through lactation, DPMH concurred with the Applicant that there is no clear evidence of adverse reactions to LEN in neonates or infants via exposure through human milk.

Review of Literature

Applicant's review:

The Applicant did not submit a literature review pertaining to lactation.

DPMH review:

DPMH conducted a search for published human studies in PubMed and Embase, using the search terms: "lenacapavir" OR "HIV-1 capsid inhibitor" AND "lactation" and "breastfeeding." No publications were found.

Reference ID: 5581148

In addition, DPMH conducted a search for "lenacapavir" AND "HIV-1 capsid inhibitor" in Micromedex, Hale's *Medications and Mothers' Milk*,[21] Reprotox, the Drugs and Lactation Database (LactMed),[22] and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.*[23] Micromedex, Reprotox and Briggs did not contain any information. The results from LactMed and Hale's are as follows:

- LactMed and Hale's both report that no information is available on the use of lenacapavir during breastfeeding or its transfer to breast milk. Because the drug is greater than 98.5% protein bound and has a large molecular weight, the amounts in milk are likely to be low. The oral bioavailability of <10% limits systemic exposure in the breastfed infant.

  Reviewer comment:
  The review of the literature did not identify any safety signals related to LEN exposure via lactation. The available information suggests that exposure to LEN via breast milk is likely to be low.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Data

The Applicant did not provide new nonclinical reproduction or fertility data for this NDA. Data was previously submitted to NDAs 215973 and 215974 for Sunlenca (LEN). In the Fertility and Early Embryonic Development (FEED) study conducted in rats for NDA 215973, no effects on male and female reproductive performance or male spermatogenesis were noted.[24] In the in vitro human lymphocyte chromosome aberration assay and bacterial reverse mutation assay, no genotoxicity was noted.[25] Sunlenca labeling does not include subsection 8.3.

Reviewer comment:
There were no nonclinical data to suggest that LEN affects male or female fertility or causes genotoxicity.

Clinical Data

PK Reproduction Data

The Applicant stated that coadministration of LEN did not result in clinically significant changes in the PK of long-acting hormonal contraceptives, including medroxyprogesterone acetate, norethindrone enanthate, and etonogestrel.[26]

[21] Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com
[22] Drugs and Lactation Database (LactMed). Accessed 1/28/25.
[23] Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.
[24] NDA 215973, SN 0001, Module 4.2.3.5.1, Fertility and Early Embryonic Development, p. 12.
[25] NDA 215973, SN 0001, Module 4.2.3.3, Genotoxicity.
[26] NDA 220018, SN 0001, Module 5.3.5.1, Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, p. 116.

Reference ID: 5581148

Reviewer comment:
DPMH discussed the PK findings with the CP team. The CP team agreed with the Applicant that LEN did not result in clinically significant changes in the PK of hormonal contraceptives.

Clinical Cases from Drug Development Program
The Applicant reported that there were "no cases of potential infertility."[27]

Review of Literature
There was no literature provided by the Applicant or found by DPMH pertaining to LEN and fertility.

Reviewer comment:
There were no clinical data to suggest that LEN affects male or female fertility.

III. DISCUSSION AND CONCLUSIONS

Pregnancy
Nonclinical data related to LEN use during pregnancy in rats and rabbits did not demonstrate LEN-associated embryofetal toxicity. Available clinical data from the randomized, controlled PURPOSE 1 trial, involving 208 pregnancies with known outcomes and 132 deliveries with LEN exposure, did not suggest an increased risk of the adverse birth outcomes of PTB, SB, SGA or SAB or adverse maternal outcomes in LEN-treated subjects compared to F/TDF- or F/TAF-treated subjects during pregnancy. In PURPOSE 1, MCMs were higher in the LEN arm than in the F/TDF and F/TAF arms, but MCMs in the LEN arm but did not exceed background prevalence rates. Overall, the data are not conclusive, as they are based on small sample sizes and are unadjusted. Although the data are not conclusive, DPMH recommends including these data in labeling in subsection 8.1 under the Risk Summary and the Data sections; see the labeling recommendations below.

DPMH recommends including a section under 8.1 titled Clinical Considerations, similar to what appears in labeling for other drug products used for PrEP. The Clinical Considerations section, with the subheading of *Disease-associated maternal and/or embryo/fetal risk,* should convey the risk associated with maternal-fetal transmission of HIV during pregnancy and the importance of PrEP to reduce the risk of HIV acquisition during pregnancy.

A pregnancy exposure registry for antiretroviral drug products called the Antiretroviral Pregnancy Registry (APR) exists. Data are already being collected for Sunlenca (LEN) through that registry, and the APR information will be included in the labeling for Yeztugo to collect safety data on exposed pregnancies; therefore, DPMH does not recommend issuing a postmarketing requirement (PMR) for a pregnancy exposure registry.

Lactation
In terms of nonclinical lactation data, the labeling of Sunlenca includes information about LEN being detected at low levels in the plasma of nursing rat pups. In terms of clinical data, limited data from the PK Tail Phase of PURPOSE 1 showed that LEN is present in human milk and

[27] NDA 220018, Module 2.7.4, Summary of Clinical Safety, p. 74.

Reference ID: 5581148

infant plasma at low levels when infants were breastfed by mothers receiving LEN from 0 to less than 13 weeks after delivery. In one infant who was breastfed by a mother who received LEN between 13 and 28 weeks after delivery, LEN was below the limit of quantitation in the infant's plasma. No toxicity was reported in breastfed infants exposed to LEN via milk. There are no data related to the effects of LEN on milk production. DPMH recommends including the information discussed in this paragraph in labeling; see the labeling recommendations below.

No new safety concerns related to LEN use during lactation were identified in this review. The PK data submitted by the Applicant are similar to those that would be obtained from a clinical lactation study. Therefore, DPMH does not recommend issuing a PMR for a clinical lactation study.

Females and Males of Reproductive Potential

There are no new nonclinical or clinical data available related to the effects of LEN on reproduction or fertility since Sunlenca was approved in 2022. In studies submitted to support the approval of Sunlenca, LEN was not shown to cause genotoxicity or impact male or female fertility or hormonal contraception; therefore, there are no reproductive data to convey to healthcare providers, and DPMH recommends omitting subsection 8.3 from labeling.

IV. LABELING RECOMMENDATIONS

DPMH recommends the text below for subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DAI on 4/22/2025. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

APPENDIX A – Reviewer-generated table of background prevalence

Birth Outcomes	Prevalence in Uganda and South Africa
Stillbirth (SB)	3[28]-3.96,[29] 2[30]-3.31%[31]
Preterm birth (PTB)	14%,[32]15%[33]
Small for gestational age (SGA)	12.7%, [34]18.6%[35]
Spontaneous abortion (SAB)	11.8%,[36]12.5%[37]
Maternal Outcomes	
Gestational hypertension	6.7%,[38] 7.0%[39]
Pre-eclampsia	5.75%,[40] 8.0%[41]
Hemorrhage	9%,[42] 10.5%[43]
Hyperemesis gravidarum	Up to 2%[44]

[28] Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, Noguchi L, Balkus JE. Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front Reprod Health. 2021;3:672446. doi: 10.3389/frph.2021.672446. Epub 2021 Nov 26. PMID: 35187529; PMCID: PMC8856667.

[29] Balkus JE, Neradilek M, Fairlie L, Makanani B, Mgodi N, Mhlanga F, et al. Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results from a systematic chart review. PLoS One 2021;16 (3):e0248423.

[30] See ref 28.

[31] See ref 39.

[32] Uganda Profile of Preterm and Low Birth Weight Prevention and Care https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwijsY_W15aLAxWLFlkFHXz9Ji8Q-tANegQIGRAN&url=https%3A%2F%2Fwww.healthynewbornnetwork.org%2Fhnn-content%2Fuploads%2FUganda-1.pdf&usg=AOvVaw0aUNjmxq_OAjomunUkXw2P&opi=89978449

[33] South African Government, Health commemorates World Prematurity Awareness Month, 22 Nov 2023 https://www.google.com/search?q=preterm+birth+rate+in+south+africa

[34] Mangiza M, Ehret DEY, Edwards EM, Rhoda N, Tooke L. Morbidity and mortality in small for gestational age very preterm infants in a middle-income country. Front Pediatr. 2022 Aug 9;10:915796. doi: 10.3389/fped.2022.915796. PMID: 36016879; PMCID: PMC9396138.

[35] Kumbowi P, Nherera, R. Prevalence and factors associated with small for gestational age among women who delivered at Hoima Regional Referral Hospital, Western Uganda: A cross-sectional study. (2023). 10.21203/rs.3.rs-2986104/v1.

[36] Kwesiga D, Wanduru P, Eriksson L, Malqvist M, Waiswa P, Blencowe H. Psychosocial effects of adverse pregnancy outcomes and their influence on reporting pregnancy loss during surveys and surveillance: narratives from Uganda. BMC Public Health. 2023 Aug 18;23(1):1581. doi: 10.1186/s12889-023-16519-5. PMID: 37596665; PMCID: PMC10439567.

[37] Lockett M, Mash RJ. Lived experiences of women with spontaneous abortion at a district hospital, South Africa. S Afr Fam Pract (2004). 2024 Apr 30;66(1):e1-e9. doi: 10.4102/safp.v66i1.5917. PMID: 38708752; PMCID: PMC11079354.

[38] Moodley J, Onyangunga OA, Maharaj NR. Hypertensive disorders in primigravid black South African women: A one-year descriptive analysis. Hypertens Pregnancy. 2016 Nov;35(4):529-535. doi: 10.1080/10641955.2016.1193190. Epub 2016 Jul 8. PMID: 27391770.

[39] Abdille, Aden & Extension, Kiu Publication. (2023). Prevalence and Factors Associated with Hypertension in Pregnancy among Pregnant Women attending Fort Portal Regional Referral Hospital in Uganda. 3. 218-227.

[40] See ref 18 (Moodley)

[41] Okong P, Byamugisha J, Mirembe F, Byaruhanga R, Bergstrom S. Audit of severe maternal morbidity in Uganda--implications for quality of obstetric care. Acta Obstet Gynecol Scand. 2006;85(7):797–804. doi: 10.1080/00016340600593331.

[42] Ononge S, Mirembe F, Wandabwa J, Campbell OM. Incidence and risk factors for postpartum hemorrhage in Uganda. Reprod Health. 2016 Apr 14;13:38. doi: 10.1186/s12978-016-0154-8. PMID: 27080710; PMCID: PMC4832492.

[43] Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol. 2008;22:999–1012. doi: 10.1016/j.bpobgyn.2008.08.004.

[44] Philip B. Hyperemesis gravidarum: literature review. WMJ. 2003;102(3):46-51. PMID: 12822290.

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KATHERINE G KRATZ
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LYNNE P YAO
05/05/2025 02:11:48 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 19, 2025
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 220018 NDA 220020
Product Name, Dosage Form, and Strength:	Yeztugo (lenacapavir) Injection, 463.5 mg/1.5 mL (309 mg/mL) Tablet, 300 mg
Product Type:	Combination Product (Drug-Device) Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Gilead Sciences, Inc. (Gilead)
FDA Received Date:	December 19, 2024
TTT ID #:	2024-12127
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

Reference ID: 5552701

1 INTRODUCTION

As part of the approval process for Yeztugo (lenacapavir) injection and tablet, the Division of Antivirals (DAV) requested that we review the proposed Yeztugo prescribing information (PI), Patient Package Insert (PPI), Instruction for Use (IFU) container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Gilead is proposing to market Yeztugo, a dual proprietary name for lenacapavir, for the treatment of pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg. Gilead currently markets lenacapavir injection and tablets under the proprietary name Sunlenca (NDA 215973 & NDA 215974) for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. The currently approved products and associated labeling are the same as those being proposed under the Yeztugo proprietary name.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review.

Table 1. Materials Considered for this Review	
Materials Considered	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We collaborated with DAV to ensure the Yeztugo PI, PPI and IFU did not contain areas of vulnerability that may lead to medication errors, however, we provide the below comment for Gilead in section 4 below.

4 RECOMMENDATIONS FOR GILEAD SCIENCES, INC. (GILEAD)

Table 1. Identified Issues and Recommendations for Gilead Sciences, Inc. (Gilead) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, the proprietary name is denoted by the placeholder “Trade name”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our February 21, 2025 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name,

Table 1. Identified Issues and Recommendations for Gilead Sciences, Inc. (Gilead) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			Yeztugo, was found conditionally acceptable. We recommend replacing the placeholder “Trade name” with the conditionally acceptable proprietary name, Yeztugo, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 1 presents relevant product information for Yeztugo received on December 19, 2024 from Gilead Sciences, Inc. (Gilead), and the US-licensed Reference Product (RP).

Table 1. Relevant Product Information for Yeztugo and the US-licensed Reference Product (RP).

Product Name	Yeztugo	Sunlenca[a] (NDA 215973 & NDA 215974)
Initial Approval Date	NA	12/22/2022
Active Ingredient	lenacapavir	
Indication	Pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg. Individuals must have a negative HIV-1 test prior to initiating	In combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 whose current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations.
Dosage Form	injection and tablet	
Strength	Injection: 463.5 mg/1.5 mL (309 mg/mL) Tablet: 300 mg	
Route of Administration	Subcutaneous and Oral	

[a] Sunlenca [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. July 2024. [cited 2025 Feb 11]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215973s006,215974s008lbl.pdf

Table 1. Relevant Product Information for Yeztugo and the US-licensed Reference Product (RP).

<table>
<tr><th>Product Name</th><th>Yeztugo</th><th>Sunlenca[a] (NDA 215973 & NDA 215974)</th></tr>
<tr><td>Dose and Frequency</td><td>Dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months maintenance dosing (subcutaneous injections). Tablets may be taken without regard to food.
<table>
<tr><td colspan="2">Initiation</td></tr>
<tr><td>Day 1</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections)
600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td colspan="2">Maintenance</td></tr>
<tr><td colspan="2">927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6-months (26 weeks) from the date of the last injection +/-2 weeks.</td></tr>
</table></td><td>Initiation dosing (injection and tablets) followed by once every 6-months maintenance injection dosing. Tablets may be taken without regard to food
<table>
<tr><td colspan="2">Initiation Option 1</td></tr>
<tr><td>Day 1</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections) 600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td colspan="2">Initiation Option 2</td></tr>
<tr><td>Day 1</td><td>600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 x 300 mg tablets)</td></tr>
<tr><td>Day 8</td><td>300 mg orally (1 x 300 mg tablet)</td></tr>
<tr><td>Day 15</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections)</td></tr>
<tr><td colspan="2">Maintenance</td></tr>
<tr><td colspan="2">927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) from the date of the last injection +/-2 weeks.</td></tr>
</table></td></tr>
</table>

Table 1. Relevant Product Information for Yeztugo and the US-licensed Reference Product (RP).		
Product Name	Yeztugo	Sunlenca[a] (NDA 215973 & NDA 215974)
How Supplied	tablets, 300 mg are beige, capsule-shaped, and film-coated with "GSI" debossed on one side and "62L" on the other side. Each bottle contains 4 tablets (NDC 61958-3401-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure. injection is packaged in a dosing kit (NDC 61958-3402-1) containing: 2 single-dose clear glass vials, each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir. The injection solution is sterile, preservative-free, clear, and yellow with no visible particles. Vials are sealed with a stopper and aluminium overseal with flip-off cap. 2 disposable syringes, 2 withdrawal needles (18-gauge, 1½ inch), and 2 injection safety needles for subcutaneous injection (22-gauge, ½ inch).	tablets, 300 mg are beige, capsule-shaped, and film-coated with "GSI" debossed on one side and "62L" on the other side packaged as follows: *Bottle* bottle contains 4 tablets (NDC 61958-3001-3). *Blister Packs* 4-Tablets™ blister pack(NDC 61958-3001-1) 5-Tablets™ blister pack (NDC 61958-3001-2) Within the blister packs, tablets are packaged in a clear blister film sealed to a foil lidding material. The blister card is fitted between two paperboard cards, and packaged with silica gel desiccant in a sealed child-resistant flexible laminated pouch. injection is packaged in one of two different injection kits containing the following: *Vial access device injection kit (NDC 61958-3002-1):* 2 single-dose clear glass vials, each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir. The injection solution is sterile, preservative-free, clear, and yellow with no

Table 1. Relevant Product Information for Yeztugo and the US-licensed Reference Product (RP).		
Product Name	Yeztugo	Sunlenca[a] (NDA 215973 & NDA 215974)
		visible particles. Vials are sealed with a stopper and aluminium overseal with flip-off cap. 2 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, ½ inch). *Withdrawal needle injection kit (NDC 61958-3005-1):* 2 single-dose clear glass vials, each containing sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir. The injection solution is sterile, preservative-free, clear, and yellow with no visible particles. Vials are sealed with a stopper and aluminium overseal with flip-off cap. 2 disposable syringes, 2 withdrawal needles (18-gauge, 1.5 inch), and 2 injection safety needles for subcutaneous injection (22-gauge, ½ inch).
Storage	Store bottle and injection in original packaging at 20°C-25°C (68°F–77°F), excursions permitted to 15°C–30°C (59°F–86°F) (see USP Controlled Room Temperature)	

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Yeztugo labels and labeling submitted by Gilead.

- Prescribing Information, Patient Package Insert and Instruction for Use received on December 19, 2024, available from \\CDSESUB1\evsprod\NDA220018\0002\m1\us\114-labeling and \\CDSESUB1\evsprod\NDA220020\0002\m1\us\114-labeling
- Container labels and Carton labeling received on December 19, 2024

B.2 Container Labels and Carton Labeling Images

Container Labels:

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MELINA N FANARI
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YEVGENIYA M KOGAN
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