Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	220018 and 220020
Priority or standard	Priority
Submit date(s)	12/19/2024
Received date(s)	12/19/2024
PDUFA goal date	6/19/2025
Division/office	Division of Antivirals (DAV)
Review completion date	6/16/2025
Established/proper name	lenacapavir
(Proposed) proprietary name	YEZTUGO
Pharmacologic class	Human immunodeficiency virus type 1 (HIV-1) capsid inhibitor
Other product name(s)	GS-6207 (lenacapavir)
Applicant	Gilead Sciences, Inc.
Dosage form(s)/formulation(s)	Injection and tablet
Dosing regimen	YEZTUGO initiation dosing (927 mg subcutaneous injection [2 x 1.5 mL] and 600 mg orally [2 x 300 mg]) on Day 1, followed by 600 mg orally (2 x 300 mg) on Day 2. Following initiation dosing, YEZTUGO (927 mg subcutaneous injections [2 x 1.5 mL]) is continued once every 6 months. During continuation dosing, if scheduled injections are delayed by more than 2 weeks, YEZTUGO tablets may be taken on an interim basis (for up to 6 months if needed), until injections resume.
Applicant-proposed indication(s)/ population(s)	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.
SNOMED CT code for proposed indication disease term(s)[1]	86406008 |Human immunodeficiency virus infection (disorder)|
Regulatory action	Approval
Approved dosage (if applicable)	See dosing regimen above.
Approved indication(s)/ population(s) (if applicable)	YEZTUGO is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition. Individuals must have a negative HIV-1 test prior to initiating YEZTUGO.
SNOMED CT code for approved indication disease term(s)[1]	40780007: Human immunodeficiency virus 1 infection (disorder)

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms.

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Glossary

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
AGYW	adolescent girls and young women
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
bHIV	background HIV-1
BID	twice daily
BLA	biologics license application
BMI	body mass index
CAB	Cabotegravir
CFR	Code of Federal Regulations
CGM	cisgender men
CI	confidence interval
CL	clearance
CL_{cr}	creatinine clearance
Cl/F	apparent clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COBI	cobicistat
CSR	clinical study report
C_{trough}	trough concentration
DAIDS	Division of AIDS
DBS	dried blood spots
DCO	data cutoff
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPMH	Division of Pediatric and Maternal Health
EC_{50}	half maximal effective concentration
ECHO	Evidence for Contraceptive Options and HIV Outcomes
EFV	efavirenz
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
FRR	false recency rate
FTC	emtricitabine

FTC-DP	emtricitabine-diphosphate
F/TAF	emtricitabine/tenofovir alafenamide
F/TDF	emtricitabine/tenofovir disoproxil fumarate
F/TFV	emtricitabine/tenofovir
FTC-TP	emtricitabine-triphosphate
GCP	good clinical practice
GNB	gender nonbinary
H_{01}	first alpha-controlled null hypothesis sequentially tested (H_{02} is the second, …)
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTE	heavily treatment-experienced
IA	interim analysis
ICH	International Council for Harmonization
IND	investigational new drug
IP	investigational product
iPSP	Initial Pediatric Study Plan
IQ4	inhibitory quotient 4-fold higher than the protein-adjusted 95% effective concentration determined in vitro
IQR	interquartile range
ISR	injection site reaction
IV	intravenous
Lag-EIA	limiting antigen avidity enzyme immunoassay
LEN	Lenacapavir
MDR	Multi-drug resistant
MDRI	mean duration of recent infections
MedDRA	Medical Dictionary for Regulatory Activities
NAAT	nucleic acid amplification test
NDA	new drug application
NPRS	numeric pain rating scale
ODn	normalized optical density
OL	open-label
OLE	open-label extension
OND	Office of New Drugs
PBPK	physiologically based pharmacokinetics
PI	Prescribing Information
PK	pharmacokinetics
PMC	postmarketing commitment
PO	by mouth
PopPK	population pharmacokinetics
PrEP	pre-exposure prophylaxis
PT	preferred term
PY	person-years
Q1	first quartile (value below which 25% of the data points in a dataset fall)
Q3	third quartile (value below which 75% of the data points in a dataset fall)
QD	once daily

RAS	resistance-associated substitution
RBP	Randomized Blinded Phase
RIF	rifampin
RIFAB	rifabutin
RITA	recent infection testing algorithm
RNA	ribonucleic acid
rSE	relative standard error
SAE	serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SC	subcutaneous
SD	standard deviation
SOC	system organ class
STI	sexually transmitted infection
TEAE	treatment-emergent adverse event
TGM	transgender men
TGW	transgender women
T	cutoff for the time period
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Prescribing Information

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

New drug applications (NDAs) for injectable (NDA 220018) and oral (NDA 220020) formulations of lenacapavir (LEN; GS-6207, YEZTUGO) were submitted by Gilead Sciences, Inc., seeking the approval of LEN as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition.

LEN is a previously approved HIV-1 capsid inhibitor. On December 22, 2022, SUNLENCA (NDAs 215974 [oral] and 215973 [injection]) was approved in combination with other antiretroviral(s) for the treatment of multi-drug resistant (MDR) HIV-1 in heavily treatment-experienced (HTE) people living with HIV.

The multidisciplinary review team (clinical, virology, clinical pharmacology, pharmacometrics, pharmacology/toxicology, statistics, chemistry and manufacturing, and regulatory) did not identify any issues that preclude approval for NDAs 220018 and 220020. The signatory authority for this application concurs with those recommendations and agrees that the benefit-risk assessment supports approval.

LEN is a first-in-class HIV-1 capsid inhibitor with Breakthrough Therapy Designation for PrEP of HIV-1 infection in adults and adolescents. The dosing schedule consists of required initiation dosing (subcutaneous [SC] injections and oral tablets) followed by maintenance dosing every 6 months (SC injections). LEN injections are only administered by a healthcare provider. In addition to dosing initiation, oral tablets can be utilized as a short-term alternative to maintain the regimen when unforeseen circumstances prevent adherence to the prescribed dosing schedule. If a scheduled LEN injection is to be missed by more than 2 weeks, and 26 to 28 weeks have elapsed since the last LEN injection, 300-mg tablets orally once every 7 days may be used on an interim basis (for up to 6 months, if needed) until LEN injections resume.

In support of NDAs 220018 and 220020, the Applicant submitted data from two adequate and well-controlled Phase 3 clinical trials that provided substantial evidence of efficacy for the proposed indication. Trial GS-US-412-5624 (PURPOSE 1) was conducted in adolescent girls and young women (≥16 to ≤25 years of age) who have sex with male partners assigned male at birth. Trial GS-US-528-9023 (PURPOSE 2) was conducted in cisgender men, transgender women, transgender men, and gender nonbinary people (≥16 years of age) who have sex with male partners assigned male at birth.

Both trials demonstrated that LEN was superior to TRUVADA (emtricitabine/tenofovir disoproxil fumarate [F/TDF]) for HIV-1 PrEP, with a 100% and 89% reduction in the risk of incident HIV-1 infection compared to F/TDF in PURPOSE 1 and PURPOSE 2, respectively. The superiority over F/TDF was considered the primary basis to support substantial evidence of effectiveness. Notably, adherence to F/TDF based on TFV-DP dried blood spots (DBS)

concentrations fell markedly within 26 weeks, particularly in PURPOSE 1(Figure 30 and Figure 31), suggesting that nonadherence to oral therapy may contribute to these efficacy results. In both trials, LEN also demonstrated superiority in the risk of incident HIV-1 infection over background HIV-1 incidence, that was estimated during the Incidence Phase of each trial using the recent infection testing algorithm (RITA) and recency assay results from samples, collected from the screened population, that were positive for HIV-1 infection (See Section 6.3.1).

The safety evaluation for LEN was adequate and the demonstrated safety profile of LEN for PrEP to reduce the risk of sexually acquired HIV-1 infection is acceptable for the indicated dose and population. The safety profile of YEZTUGO was consistent with the safety profile observed with SUNLENCA and no new or unexpected safety findings were noted. Local injection site reactions (ISRs) were common, with injection site nodules reported by most PURPOSE 1 and PURPOSE 2 trial participants.

The long-acting properties of injectable SC LEN have potential advantages and disadvantages. High adherence to oral HIV-1 PrEP is crucial for its effectiveness in preventing HIV-1 infection (see Sections 14.2.2, 14.2.3, and 18). The long-acting properties of injectable LEN eliminate the need for adherence to oral daily medications because injectable LEN is administered by a healthcare provider every 6 months. However, because residual concentrations of injectable LEN remain for prolonged periods (12 months or longer after the last SC dose), selection of individuals who agree to the required injection dosing schedule every 6 months is important. Nonadherence to injections dosed every 6 months or missed injections (without oral LEN bridging) can lead to HIV-1 acquisition and potentially the development of resistance to LEN.

Overall, despite these concerns, the benefit-risk assessment is favorable for LEN. Additional risk-mitigation strategies with regards to adherence and HIV-1testing are prominently displayed in Sections 2 and 5 of labeling. Based on the available data, and similar to other drugs approved for HIV-1 PrEP, the review team determined that testing for HIV-1 infection is needed prior to initiating treatment with YEZTUGO, with each subsequent injection of YEZTUGO, and additionally as clinically appropriate, using sensitive assays approved or cleared by FDA for the diagnosis of acute or primary HIV-1 infection.

For detailed information supporting the basis for the benefit-risk assessment, please refer to the details in this integrated assessment document.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

As described above (Section 1.1), data were provided from the two adequate and well-controlled Phase 3 efficacy and safety trials, PURPOSE 1 and PURPOSE 2. PURPOSE 1 demonstrated the efficacy of LEN to reduce the risk of sexually acquired HIV-1 in adolescent girls and young women who have sex with male partners. PURPOSE 2 demonstrated the efficacy of LEN to reduce the risk of sexually acquired HIV-1 in cisgender men, transgender women, transgender men, and gender nonbinary people (≥16 years of age) who have sex with male partners.

It is important to highlight that PURPOSE 1 and PURPOSE 2 employed innovative counterfactual trial designs. A comprehensive description of the trial designs of PURPOSE 1 and PURPOSE 2 is provided in Sections 6.2 and 15. Efficacy in both trials was estimated by comparing HIV-1 incidence among participants receiving LEN with participants receiving an internal active control (F/TDF) as well as with the counterfactual control of background HIV-1 (bHIV) incidence, which was calculated using a RITA from participants who tested positive on a recency assay for HIV-1 in the screened population (Incidence Phase). For the Incidence Phase, the primary endpoint was the diagnosis of recent HIV-1 infection reported per 100 person-years (PY). Participants who tested HIV-1 negative and met eligibility criteria proceeded to the Randomized Blinded Phase.

In PURPOSE 1, participants were randomized in a 2:2:1 ratio to receive either LEN, emtricitabine/tenofovir alafenamide (F/TAF), or F/TDF, respectively. In PURPOSE 2, participants were randomized in a 2:1 ratio to receive either LEN or F/TDF. In PURPOSE 1 and PURPOSE 2, F/TDF served as the internal active control. For the Randomized Blinded Phase in both trials, the primary endpoint was diagnosis of HIV-infection, reported per 100 PY in the LEN and F/TDF groups while at risk of HIV-1 infection.

PURPOSE 1 and PURPOSE 2 had prespecified interim stopping criteria, which required the demonstration of superiority of LEN compared to the bHIV incidence and superiority of LEN compared to F/TDF. For each trial, a data monitoring committee (DMC) reviewed the planned interim analysis of efficacy and futility data after 50% of the planned sample size completed at least 52 weeks of follow-up or prematurely discontinued from the trial. The prespecified efficacy hypotheses were tested using a gated sequential testing approach. The DMC recommended the early termination of the Randomized Blinded Phase in each trial because the prespecified efficacy evaluation criteria were met in both trials. Therefore, the 52-week interim results from PURPOSE 1 and PURPOSE 2 served as the primary analysis for both trials following the DMC's recommendation.

In PURPOSE 1, no participant in the LEN group had incident HIV-1 infection (0.000 infections per 100 PY; 95% confidence interval (CI): 0.000 to 0.190) at the time of the interim analysis, with the efficacy of LEN superior to both the bHIV incidence (rate ratio: 0.000; 95% CI: 0.000 to 0.042; P<0.0001) and F/TDF (rate ratio: 0.000; 95% CI: 0.000 to 0.101; P<0.0001).

In PURPOSE 2, two participants in the LEN group had incident HIV-1 infection (0.103 infections per 100 PY; 95% CI: 0.012 to 0.373) at the time of the interim analysis, with the efficacy of LEN superior to both the bHIV incidence (rate ratio: 0.043; 95% CI: 0.010 to 0.182; P<0.0001) and F/TDF (rate ratio: 0.111; 95% CI: 0.024 to 0.513; P =0.00245).

The review team recommends that evidence of efficacy should be based on the finding that LEN demonstrated superiority over F/TDF (internal active control) in PURPOSE 1 and PURPOSE 2. The review team does not consider LEN versus bHIV as the primary evidence of efficacy. Please refer to Section 6.3.1 for more details.

Overall, the highly persuasive results from PURPOSE 1 and PURPOSE 2 support the approval of LEN to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• HIV-1 infection affects more than 39 million people globally (U.S. HHS 2025a) and an estimated 1.2 million adults and adolescents in the United States (U.S. HHS 2025b). • There is no cure for HIV-1 infection. Once infection is established, it is a life-long condition that requires chronic therapy with antiretroviral drug regimens to manage. If left untreated, it can lead to acquired immunodeficiency syndrome (AIDS), which is associated with significant morbidity and mortality, and increased risk of transmission to others, a major public health concern.	HIV-1 is a serious and life-threatening disease that affects a large population. Reducing the risk of HIV-1 acquisition through pre-exposure prophylaxis (PrEP) could have a large impact on public health.
Current PrEP options	• TRUVADA (emtricitabine/tenofovir disoproxil fumarate, or F/TDF) is approved for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 sexual acquisition in adults and adolescents weighing ≥35 kg. This indication includes both men and women at risk. – The dosing regimen for F/TDF for PrEP is one tablet by mouth once daily. – The TDF component of F/TDF has been associated with bone loss and renal toxicity, including proximal renal tubulopathy, which occurs in less than 1% of individuals using F/TDF for treatment or prevention. • DESCOVY (emtricitabine/tenofovir alafenamide, or F/TAF) is approved for PrEP to reduce the risk of HIV-1 sexual acquisition in adults and adults and adolescents weighing ≥35 kg. This indication excludes individuals at risk from receptive vaginal sex. – The dosing regimen for F/TAF for PrEP is one tablet by mouth once daily.	New drug products that are as effective as the currently approved PrEP options are needed, especially drug products that are not dependent on oral daily adherance or have less frequent injection dosing visits.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– While TAF does impact renal function and bone mineral density parameters, it may be to a lesser degree than TDF. • APRETUDE (cabotegravir [CAB] extended release injectable suspension) is approved for PrEP to reduce the risk of HIV-1 sexual acquisition in adults and adolescents weighing ≥35 kg. This indication includes both men and women at risk. – The dosing regimen for injectable CAB for PrEP consists of initiation injections followed by continuation injections every 2 months. • According to the Centers for Disease Control and Prevention (CDC), currently available HIV-1 PrEP options, including oral and injectable options, reduce the risk of aquiring HIV-1 from sex by about 99% when taken as prescribed (CDC 2025). Efficacy is strongly correlated with adherence. • In 2022, approximately 36% of the U.S. population eligible for HIV-1 PrEP were prescribed it (CDC 2023).	
Benefit	• LEN is an oral and injectable capsid inhibitor with long-acting properties. The dosing schedule consists of required initiation dosing (subcutaneous [SC] injections and oral tablets) followed by maintenance dosing every 6 months (SC injections). LEN injections are only administered by a healthcare provider. • The efficacy of LEN for PrEP was estabilised in two randomized, double-blind, active controlled trials, GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2). • PURPOSE 1 included adolescent girls and young women (16 to 25 years of age) who were sexually active with male partners and at risk of HIV-1 infection. Participants were randomized in a 2:2:1 ratio to receive SC LEN every 6 months, daily oral F/TAF, or daily oral F/TDF (internal active control); all participants also received the alternate SC or oral placebo. A total of 5,345 participants were randomized and received study drugs. There were no HIV-1 infections in the LEN group (0.00 infections per 100 PY, 95% CI: 0.00,0.19) and 16 HIV-1 infections in the F/TDF group (1.685 infections per 100 PY, 95% CI: 0.963, 2.737). The HIV-1 incidence in the LEN was group was significantly lower than in the F/TDF group (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.0001) and significantly lower	The submitted clinical data provide substantial evidence of LEN effectiveness to reduce the risk of sexually acquired HIV-1 infection among adolescent girls and young women, cisgender men, transgender women, and gender non-binary individuals who are at risk of HIV-1 acquisition. The data indicate that LEN is superior to approved F/TDF, which is the primary basis of approval. LEN also significantly reduced the rate of incident HIV-1 infections compared to the estimated bHIV incidence rate, which is considered supportive data only given the concerns with the reliability of the estimate. LEN provides an option for HIV-1 PrEP that does not require daily oral administration and is not dependent on high daily adherance for efficacy. In addition, LEN also provides less frequent dosing compared to the only approved injectable HIV-1 PrEP option (every 6 months versus every 2 months, respectively). The submitted efficacy and safety data for LEN can be extrapolated to support a PrEP indication in adolescents

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	than the estimated background HIV-1 (bHIV) incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.0001). • PURPOSE 2 included cisgender men, transgender women, transgender men, and gender-nonbinary participants (≥16 years of age) who have sex with male partners and at risk of HIV-1 infection. Participants were randomized in a 2:1 ratio to receive SC LEN every 6 months or daily oral F/TDF (internal active control); all participants also received the alternate SC or oral placebo. A total of 3,271 participants were randomized and received study drugs. There were 2 HIV-1 infections in the LEN group (0.10 infections per 100 PY, 95% CI: 0.01, 0.37). The HIV-1 incidence in the LEN group was significantly lower than in the F/TDF group (incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; P =0.00245) and significantly lower than the estimated bHIV incidence (incidence rate ratio, 0.04; 95% CI, 0.01 to 0.18; P<0.0001). • In both trials, efficacy of LEN for HIV-1 PrEP was consistent across various subgroups defined by age, race, region, or other baseline factors, although some of these comparisons were limited by subgroup sample size. • The protocol-defined primary endpoint used a novel efficacy approach comparing the HIV-1 incidence rate in the LEN group to the bHIV incidence rate estimated during the Incidence Phase using a recency assay with the recent infection testing algorithm (RITA). The reliability of this method to accurately estimate the bHIV incidence rate was a key review issue. Review of the data demonstrated that the populations for estimating the bHIV incidence rate and the observed HIV-1 incidence in the LEN group were different, and the derived parameters used in the algorithm may not be applicable to PURPOSE 1 and PURPOSE 2. However, as noted above, LEN demonstrated superiority in reducing the risk of incident HIV-1 infections over F/TDF as well as over the bHIV rate. • The safety and efficacy of LEN for HIV-1 PrEP in adolescents ≥35 kg are supported by the safety and PK data of LEN in adults and adolescents (≥16 years of age) from PURPOSE 1 and PURPOSE 2. Population PK modeling provided an acceptable description of LEN PK in adult and adolescent participants	weighing ≥35 kg. This extrapolation is justified by similar routes of HIV-1 transmission in adults and adolescents and comparable observed and simulated PK between adolescents and adults; therefore, adolescents weighing ≥35 kg are expected to have similar LEN PK compared to adults. The submitted safety and PK data support the use of LEN for HIV-1 PrEP during pregnancy. LEN provides an option for HIV-1 PrEP in pregnant women that does not require high daily adherance for efficacy or injection visits every 2 months. The use of HIV-1 PrEP during pregnancy is recommended for those who have an increased likelihood of HIV-1 acquisition. By reducing the risk of maternal HIV-1 acquisition, PrEP can indirectly help prevent vertical transmission.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	where simulated trough concentration predictions in adolescents were reasonably aligned with observed adult participants. • The safety and efficacy of LEN for HIV-1 PrEP in pregnant individuals are supported by the safety and PK of LEN in pregnant participants from PURPOSE 1. Population PK analysis was conducted and found no statistically significant differences in LEN PK by pregnancy trimester, or with the periods before pregnancy or postpartum, or with data from nonpregnant women.	
Risk and risk management	<u>Safety and Tolerability</u> • The safety database for LEN for HIV-1 PrEP was considered adequate. The most common adverse drug reactions (reported in ≥2% of LEN participants in either PURPOSE 1 or PURPOSE 2) were injection site reactions, headache, nausea, dizziness, vomiting, and diarrhea. Injection site nodules were the most common injection site reaction and were reported in most participants who received SC LEN. • Improper administration is associated with potentially serious injection site reactions (necrosis and ulcer) and is labeled under Section 5 WARNINGS AND PRECAUTIONS. *HIV-1 Resistance Development and/or Delayed HIV-1 Diagnosis in Participants who Become HIV-1 Infected While on LEN* • Accurately quantifying any possible delay in HIV-1 diagnosis within PURPOSE 1 and PURPOSE 2 was challenging, primarily due to the implementation of a comprehensive HIV testing algorithm. The available data suggest that LEN may have increased the time required to diagnose HIV-1 infections. • The RNA assay was the most sensitive for detecting infections, while the local point-of-care Ag/Ab rapid test was the least sensitive. • Potential LEN resistance substitutions were seen in 5 of the 8 prevalent HIV-1 infections (undiagnosed infection at baseline) and 3 of the 5 incident HIV-1 infections in LEN recipients (infections include those reported after the primary analysis). LEN resistance patterns in PURPOSE 1 and PURPOSE 2 aligned with other LEN development programs.	Overall, the safety data are adequate to assess the safety of LEN for the proposed indication, dosage regimen, duration, and populations. The overall safety profile of LEN from PURPOSE 1 and PURPOSE 2 is acceptable and generally similar to SUNLENCA. An adequate description of common adverse drug reactions and possible serious injection site reactions (necrosis and ulcer) associated with improper administration of SC LEN are conveyed through labeling. Any undiagnosed HIV-1 infection or delay in HIV-1 diagnosis among individuals using LEN for PrEP could lead to prolonged exposure to LEN monotherapy and the development of resistance.To minimize delay in HIV-1 diagnosis, HIV-1 testing should be conducted using tests approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection prior to initiating LEN for HIV-1 PrEP, prior to each LEN SC injection, and additionally as clinically appropriate. This recommendation is conveyed through product labeling, including through a boxed warning. The USPI will recommend administration of SC LEN into the abdomen (primary site) and thigh (alternative site), while maintaining a minimum distance of 4 inches between injection sites. This recommendation ensures that SC LEN is administered into anatomic sites for which

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Appropriate Injection Sites • The Applicant proposed that SC LEN injections be administered at the following anatomical sites: abdomen, thigh, (b) (4) (b) (4) The available PK and safety data only support the administration of SC LEN into the abdomen (primary site) and thigh (alternative site), while maintaining a minimum distance of 4 inches between injection sites; this corresponds to how SC LEN was administered in PURPOSE 1 and PURPOSE 2. *Co-Administration With Strong or Moderate CYP3A Inducers* • The submitted PK and safety data support the Applicant's proposal to administer supplemental doses of LEN in addition to regularly scheduled maintenance dosing when co-administration of rifampin or rifabutin is planned in individuals already receiving LEN. In addition, it is mechanistically reasonable to extend the same dosing recommendation for planned co-administration with any strong or moderate inducer of CYP3A in individuals already receiving LEN.	there is sufficient evidence to support safety and adequate exposures. The USPI will provide recommendations for supplemental dosing with coadministration of strong or moderate CYP3A inducers in individuals already receiving LEN. This will allow individuals in need of PrEP to stay on LEN even when they require concomitant administration of medications that are strong or moderate CYP3A inducers.

Abbreviations: Ag/Ab, antigen/antibody; HIV, human immunodeficiency virus; LEN, lenacapavir; PK, pharmacokinetic; PY, patient-year; SC, subcutaneous; USPI, United States Prescribing Information.

2.2. Conclusions Regarding Benefit-Risk

HIV-1 infection remains a major public health concern in the United States and abroad. While there are now many drugs available to treat HIV-1 infection safely and effectively, there is no cure. Reducing the risk of HIV-1 infection through PrEP is a key component of efforts to end the HIV epidemic. Currently approved options for HIV-1 PrEP either require once daily oral administration or an injection administered by a healthcare provider every 2 months. For the once daily oral HIV-1 PrEP options, effectiveness is closely tied to medication adherence. There is an interest among people at risk of HIV-1 acquisition and the medical community to provide additional options for HIV-1 PrEP, with particular interest in options that are not as dependent on daily medication adherence or that have less frequent injectable dosing. LEN is an injectable HIV-1 capsid inhibitor that is administered by SC injections every 6 months after initial dosing with oral and SC injections of LEN.

Across two large, randomized, double-blind, active-controlled, Phase 3 trials, LEN was found to be superior to the active comparator, F/TDF, and to the estimated background HIV-1 incidence rate, in reducing incident HIV-1 infections. Efficacy was demonstrated both among adolescent girls and young women at risk for HIV-1 from receptive vaginal sex with male partners and among cisgender men, transgender women, transgender men, and gender nonbinary people (≥16 years of age) at risk for sexually acquired HIV-1.

The safety evaluation of LEN was adequate, and the demonstrated safety profile of LEN is acceptable for the indicated dose and population.

Based on the totality of the data, the benefits of LEN for HIV-1 PrEP clearly outweigh the risks. The approval of LEN for HIV-1 PrEP will provide individuals with a new option for HIV-1 prevention that is administered only twice a year. It is hoped that this novel approach to PrEP delivery will increase PrEP adherence and also result in an increase in PrEP uptake in populations that have previously been reluctant to utilize PrEP due to the daily pill burden or more frequent injection dosing visits.

II. Interdisciplinary Assessment

3. Introduction

YEZTUGO (LEN) is an HIV-1 capsid inhibitor and is intended to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing ≥35 kg who are at risk for HIV-1 acquisition. LEN is not a new molecular entity; on December 22, 2022, SUNLENCA (LEN; NDAs 215974 [oral] and 215973 [injection]) was approved in combination with other antiretroviral(s) for the treatment of MDR HIV-1 in HTE people living with HIV.

Two similarly designed Phase 3 clinical trials, GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2) were conducted by the Applicant. PURPOSE 1 was conducted to assess the safety and efficacy of LEN compared to oral F/TDF among adolescent girls and young women (≥16 to ≤25 years of age) who have sex with male partners and are at risk for HIV-1 acquisition. PURPOSE 2 was conducted to assess the safety and efficacy of LEN compared to oral F/TDF among 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-1 acquisition.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Reliability of the Background HIV-1 Incidence Rate Estimated by RITA for the Primary Endpoint

3.1.2. Key Safety Review Issues

3.1.2.1. HIV-1 Resistance Development and/or Delayed HIV-1 Diagnosis in Participants Who Become HIV-1 Infected While on LEN

3.1.2.2. Appropriate LEN Injection Sites

3.1.2.3. Co-Administration With Rifampin or Rifabutin and Recommended Dosing Adjustments

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials to support the benefit-risk assessment of LEN for HIV-1 PrEP. Efficacy, safety, and PK data from the similarly designed Phase 3 clinical trials, PURPOSE 1 and PURPOSE 2, provide the primary basis of the review.

Data from the Phase 1 trials, the trials supporting the approval of LEN as a component of treatment of HIV-1 in adults with multidrug resistant infection (SUNLENCA), the Safety Update Report, and post-marketing safety reports were also reviewed to provide additional safety experience.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

1. Verbatim indication:

   YEZTUGO is indicated for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg who are at risk for HIV-1 acquisition. Individuals must have a negative HIV-1 test prior to initiating YEZTUGO.

2. SEE was established with:

   a. Adequate and well-controlled clinical investigation(s):

      i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[4]

3. Complete response, if applicable

   a. ☐ SEE was established
   b. ☐ SEE was not established

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998)

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

[4] See Footnote 2.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[a] for YEZTUGO

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
GS-US-412-5624 (PURPOSE 1) [NCT04994509]	Adolescent girls and young women (≥16 years of age) at risk of HIV-1 infection	Control type: Counterfactual estimate of bHIV incidence, with F/TDF serving as the active internal control Randomization: Randomized 2:2:1 to LEN, F/TAF, or F/TDF Blinding: Blinded Biomarkers: None Innovative design features: The use of the counterfactual control of the background incidence of HIV-1	Drug: SC Lenacapavir [YEZTUGO] Dosage: 927 mg injection, 309 mg/mL (2 × 1.5 mL) administered every 26 weeks starting on Day 1/Injection 1 and PO LEN 600 mg (2 × 300 mg tablets) administered on Day 1/Injection 1 and Day 2 Number treated: 2140 Drug: PO F/TDF [TRUVADA] Dosage: 200/300 mg, once daily Number Treated: 1070 Drug: PO F/TAF [DESCOVY] Dosage: 200/25 mg, once daily Number Treated: 2135 Duration (quantity and units): median duration at least 52 wk	<u>Primary:</u> Incidence Phase: Diagnosis of recent HIV-1 infection Randomized Blinded Phase: Diagnosis of HIV-1 infection <u>Secondary:</u> Randomized Blinded Phase: Diagnosis of HIV-1 infection, including among participants while adherent to study drug	Planned: 5010 Actual: 5368 Dosed: 5345 LEN: 2140 F/TAF: 2135 F/TDF: 1070	Centers: 28 Countries: 02

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
GS-US-528-9023 (PURPOSE 2) [NCT04925752]	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-1 infection	Control type: Counterfactual estimate of bHIV incidence, with F/TDF serving as the active internal control Randomization: Randomized 2:1 to LEN or F/TDF Blinding: Blinded Biomarkers: None Innovative design features: The use of a counterfactual control of the background incidence of HIV-1	Drug: SC Lenacapavir [YEZTUGO] Dosage: 927 mg injection, 309 mg/mL (2 × 1.5 mL) administered every 26 weeks starting on Day 1/Injection 1 and PO LEN 600 mg (2 × 300 mg tablets) administered on Day 1/Injection 1 and Day 2 Number treated: 2183 Drug: PO F/TDF [TRUVADA] Dosage: 200/300 mg, once daily Number treated: 1088 Duration (quantity and units): median duration at least 52 wk	<u>Primary:</u> Incidence Phase: Diagnosis of recent HIV-1 infection Randomized Blinded Phase: Diagnosis of HIV-1 infection <u>Secondary:</u> Randomized Blinded Phase: Diagnosis of HIV-1 infection, including among participants while adherent to study drug	Planned: 3000 Actual: 3292 Dosed: 3271 LEN: 2183 F/TDF: 1088	Centers: 96 Countries: 07

Source: Clinical Reviewer.
[a] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
Abbreviations: bHIV, background HIV-1; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; NCT, national clinical trial; PO, by mouth; SC, subcutaneous; wk, week(s).

4. Patient Experience Data

PURPOSE 1 and PURPOSE 2 included exploratory objectives that evaluated the acceptability of LEN injections every 6 months for HIV-1 PrEP in participants at risk of HIV-1. Participant assessments of PrEP impacts and administration preference, administration and dosing (pertaining to injection acceptability), numeric pain rating scale (NPRS), and self-reported adherence to oral study product were collected using questionnaires.

The Applicant did not seek labeling based on any of the collected patient experience data. Therefore, these data were not reviewed in detail but are briefly summarized in Section 16.5.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		Section 16.5
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Studies assessing the nonclinical activity of LEN in cell culture, including evaluations of the drug's mechanism of action, antiviral activity, and resistance, were reviewed as part of the NDA for SUNLENCA. Please refer to Section 18 the Integrated Review of NDA 215973/215974 for a summary of these data (FDA 2022a).

Additionally, two prophylaxis studies evaluating the ability of GS-CA1, a structural homolog of LEN (PC-200-2040), or LEN (PC-200-2053) to prevent infection in macaques challenged rectally with chimeric simian/human immunodeficiency virus (SHIV) were conducted. The results of these studies have been published (Vidal et al. 2022; Bekerman et al. 2023). These studies were useful for providing proof-of-concept and insight into potentially effective target concentrations but were not used for regulatory considerations when evaluating the efficacy of LEN for PrEP as part of this NDA.

5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology characteristics of oral and injectable lenacapavir were comprehensively evaluated and previously described (HIV-1 treatment in highly treatment-experienced people with HIV NDA 215973/215974, Integrated Review dated February 28, 2022 (FDA 2022a)). Relevant clinical pharmacology and pharmacokinetics as it pertains to oral and injectable lenacapavir for HIV-1 pre-exposure prophylaxis are described in Table 5.

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Lenacapavir is an HIV-1 capsid inhibitor
Mechanism of action	Lenacapavir is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Lenacapavir inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).
Active moieties	Lenacapavir[a]
QT prolongation	In a thorough QT/QTc study, LEN had no clinically relevant effect on the QTcF interval[a]. In a concentration-QT analysis, at supratherapeutic exposures of LEN (16-fold higher than the expected therapeutic exposure estimates, as measured by C_{max}, from the Phase 3 studies of LEN in PWBP), there was no association between observed LEN plasma concentrations and change in QTcF[b].

Characteristic	Drug Information
	General Information
Bioanalysis	Validated HPLC-MS/MS methods were used to determine lenacapavir concentrations in plasma and milk
Healthy subjects versus patients	Not applicable. Lenacapavir oral tablets and subcutaneous injection under current NDAs 220018/220020 were studied in people who would benefit from HIV-1 pre-exposure prophylaxis, not HIV-1 infected patients.
Drug exposure after 6 doses of every 26-week maintenance dosing	Parameter Mean (%CV)[b] AUC_{tau} (h•ng/mL) 257,334 (38.7) C_{max} (ng/ml) 82.4 (40.4) C_{trough} 36.9 (53.5) [b] PopPK analysis, simulated mean (%CV) exposures in PWBP.
Range of effective dose(s) or exposure	The proposed dosing regimen is identical to the one evaluated in the two Phase 3 trials, PURPOSE 1 and PURPOSE 2, and this dosing regimen was previously approved for the treatment of HIV-1 infection (SUNLENCA) [NDA 215973/215974] in heavily treatment experienced adults with multidrug resistant HIV-1. An exposure–response relationship analysis was not conducted for the two trials, as there were too few events (HIV-1 infection) in the drug-treated group.
Maximally tolerated dose or exposure	An MTD was not determined. The highest LEN exposures (C_{max}) were observed in the TQT study where lenacapavir was administered as: LEN 600 mg twice-daily orally for 7 days followed by once on Day 8.[a]
Dose proportionality	The single dose pharmacokinetics of LEN after oral administration are non-linear and less than dose proportional over the dose range of 50 to 1800 mg. The single dose PK of LEN after SC injection (309 mg/mL) are dose proportional over the dose range of 309 to 927 mg[a]
Accumulation	1.4[b]
Time to achieve steady-state	Steady state conditions were simulated after six SC doses of lenacapavir. Subcutaneous lenacapavir is dosed every 26 weeks.[b]
Bridge between to-be-marketed and clinical trial/study formulations	The final formulations of 300 mg tablets for oral administration and injection (309 mg/ml) for subcutaneous administration were used in the pivotal clinical trials
	Absorption
Bioavailability	Oral tablet 4-7%, SC injection 91%[b]
T_{max}	Oral tablet 4 hours; SC injection 77-84 days[a]
Food effect (fed/fasted) Geometric least square mean and 90% CI	The absorption of LEN is not affected by the presence of food. In healthy participants, LEN (300 mg) AUC_{inf}, C_{max}, and T_{max} were comparable following administration of a low- or high-fat meal relative to fasting (Study GS-US-200-4071)[a]
	Distribution
Volume of distribution	Steady state volume of distribution is 1657 liters[b]
Plasma protein binding	98.5% plasma protein bound[a]
Drug as substrate of transporters	Substrate of P-gp[a]

Characteristic	Drug Information
	Elimination
Mass balance results	Following a single intravenous dose of radiolabeled-lenacapavir to healthy subjects, 76% of the total radioactivity was recovered from feces and <1% from urine. Unchanged LEN was the predominant moiety in plasma (69%) and feces (33%). No single circulating metabolite accounted for >10% of plasma drug-related exposure.[a]
Clearance	Systemic clearance of lenacapavir was 3.4 L/h.[b]
Half-life	The median apparent half-life following oral administration ranged from 10-12 days; and after subcutaneous administration from 8 to 12 weeks.[a]
Metabolic pathway(s)	Lenacapavir was metabolized via oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation; primarily via CYP3A and UGT1A1[a]
Primary excretion pathways (% dose)	Urine <1%, Feces: 76% (33% as unchanged)[a]
	Intrinsic Factors and Specific Populations
Body weight	Population pharmacokinetic analysis using data from trials in adults and adolescents weighing at least 35 kg did not identify any clinically relevant differences in lenacapavir exposure due to body weight.[b]
Age	Population pharmacokinetic analysis using data from trials in adults and adolescents weighing at least 35 kg did not identify any clinically relevant differences in lenacapavir exposure due to age.[b]
Renal impairment	Lenacapavir exposures were higher (AUC_{inf} and C_{max} increased 84% and 162%, respectively) in participants with severe renal impairment (estimated creatinine clearance ≥15 and ≤29 mL/minute) compared with participants with normal renal function; however, the increase was not clinically relevant. Lenacapavir has not been studied in participants with end-stage renal disease.[a]
Hepatic impairment	In Child-Pugh Turcotte Class B hepatic impaired participants, LEN AUC_{inf} and C_{max} were 47% and 161% higher than participants with normal hepatic function, respectively. However, the increase was not clinically relevant. Lenacapavir has not been evaluated in Child-Pugh Turcotte Class C participants.[a]
	Drug Interaction Liability (Drug as Precipitant)
Inhibition/induction of metabolism	Lenacapavir is a moderate inhibitor of CYP3A. Lenacapavir is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. It is not an inducer of CYP3A4. It is not an inhibitor of UGT1A1.[a]
Inhibition/induction of transporter systems	Lenacapavir is an inhibitor of P-gp and BCRP. Lenacapavir is not an inhibitor of OATP, organic anion transporter 1 (OAT1), OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion transporter (MATE) 1, or MATE 2-K.[a]
	Immunogenicity (if Applicable)
Bioanalysis	Not applicable
Incidence	Not applicable
Clinical impact	Not applicable

Source: Reviewer-generated table.
[a] SUNLENCA USPI (Gilead Sciences 2022) or studies previously reviewed under NDA 215973/215974 (FDA 2022a).
[b] Based on population pharmacokinetic analysis of lenacapavir in healthy adults, adults with HIV-1, and adults and adolescents who would benefit from pre-exposure prophylaxis.
Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; CV, coefficient of variation; CYP, cytochrome P450; HIV, human immunodeficiency virus; HPLC-MS/MS, high performance liquid chromatography-tandem mass spectrometry; LEN, lenacapavir; MTD, maximum tolerated dose; P-gp, P-glycoprotein; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; PWBP, persons who would benefit from PrEP; QTc, corrected QT interval; QTcF, corrected QT interval (Fridericia's correction); SC, subcutaneous; T_{max}, time to maximum plasma concentration; TQT, thorough QT; UGT, uridine 5'-diphospho-glucuronosyltransferase.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The proposed dosing regimen for lenacapavir (LEN) for HIV-1 pre-exposure prophylaxis (PrEP) in adults and adolescents weighing ≥35 kg consists of the following:

Initiation

- Day 1: 927 mg SC (309 mg/mL, 2 x 1.5 mL injections) and 600 mg orally (2 x 300 mg tablets)
- Day 2: 600 mg orally (2 x 300 mg tablets)

Continuation (From the Date of the Last Injection)

- 927 mg SC (309 mg/mL, 2 x 1.5 mL) every 6 months (26 weeks) ±2 weeks

The proposed dosing regimen is identical to the one evaluated in the two Phase 3 clinical trials, PURPOSE 1 and PURPOSE 2. In addition, this dosing regimen was previously approved for the treatment of HIV-1 infection (SUNLENCA [NDA 215973/215974] in HTE adults with MDR HIV-1. For both HIV-1 treatment and PrEP, the Applicant has been using plasma concentration of 15.5 ng/mL, which is four-fold higher than the protein-adjusted 95% effective concentration determined in vitro (IQ4), to guide dose selection (i.e., the majority of individuals would achieve C_{trough} similar or higher than IQ4). Based on the PK, safety, and efficacy data of LEN for HIV-1 treatment in HTE adults, evaluating the same dose for the proposed indication of HIV-1 PrEP was considered reasonable as the selected dose is expected to provide at least similar exposures as HIV-1 treatment within a couple of days of initiation of oral dosing and maintained through the end of the SC dosing interval (every 6 months).

The safety and effectiveness of LEN with the proposed dosing regimen to reduce the risk of sexually acquired HIV-1 was assessed and demonstrated in adults and adolescents in two Phase 3 trials: GS-US-412-5264 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2). The 52-week interim results served as the primary analysis for both trials because the prespecified FDA interim stopping criteria were met. The criteria required demonstration of superiority of LEN versus the bHIV incidence with the point estimate of LEN/bHIV incidence ≤0.5 and superiority of LEN versus emtricitabine/tenofovir disoproxil fumarate (Truvada). An exposure–response relationship analysis was not conducted for the two trials, as there were too few events (HIV-1 infection) in the drug-treated group.

Oral LEN may be used on an interim basis (up to 6 months if needed, referred to as oral bridging in this review and the Applicant's submission) when a scheduled injection is anticipated to be delayed by more than 2 weeks. The proposed oral bridging with once weekly oral LEN 300 mg was previously approved under SUNLENCA for treatment of HIV-1 infection. For participants who received oral bridging with once weekly LEN in PURPOSE 1 and PURPOSE 2, adequate concentrations as measured by average $C_{trough,}$ were maintained above those concentrations achieved before initiation of oral bridging. Population PK analysis also demonstrated that

average predicted C_{trough} following oral bridging with once weekly LEN resulted in concentrations similar to or higher than C_{trough} with the proposed SC dosing regimen. These observed and simulated data indicate that once weekly oral bridging with LEN, in the event a scheduled injection is missed by more than 2 weeks, is acceptable for people receiving LEN for HIV-1 PrEP.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The evaluation of efficacy included two adequate and well-controlled trials: PURPOSE 1 in adolescent girls and young women (≥16 to ≤25 years of age) and PURPOSE 2 in cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender nonbinary (GNB) people ≥16 years of age who have sex with male partners and are at risk of HIV-1 infection.

6.2.1. PURPOSE 1

6.2.1.1. Design, PURPOSE 1

PURPOSE 1 was a Phase 3, double-blinded, multicenter, randomized trial to evaluate safety and efficacy of twice-yearly SC LEN and daily oral F/TAF for PrEP in adolescent girls and young women at risk of HIV-1 infection. The study had four phases with structured transitions: the Incidence Phase (Part A), the Randomized Blinded Phase (RBP) (Part B), the LEN Open-Label Extension (OLE) Phase, and the Pharmacokinetic (PK) Tail Phase. Multiple interim safety and one formal interim efficacy analyses were planned to be conducted prior to the primary analysis.

The background HIV-1 (bHIV) incidence rate was estimated during the Incidence Phase using the RITA and recency assay results from samples collected from the screened population that were positive for HIV-1 infection. Participants who were tested to be HIV-1 negative and met eligibility criteria proceeded to the RBP, where they were randomized in a 2:2:1 ratio to receive either LEN, F/TAF, or F/TDF, respectively. F/TDF served as the internal active control. After the completion of the RBP, participants were offered the opportunity to receive open-label (OL) LEN in the LEN OLE Phase, which allowed for further long-term efficacy and safety follow-up. Participants who discontinued study drug during the RBP entered the PK Tail Phase, which provided a known efficacious OL regimen to provide HIV-1 prevention for participants during the time when LEN concentrations decline.

6.2.1.2. Eligibility Criteria, PURPOSE 1

Inclusion Criteria for the Incidence Phase

- The ability to comprehend and provide a signed written informed consent, which must be obtained prior to initiation of study procedures. For adolescent girls, the ability to comprehend and provide a signed assent form, which must be obtained prior to initiation of study procedures. A parent/guardian may provide informed consent for adolescent girls (in accordance with local laws and regulations).

- Cisgender adolescent girls and young women (AGYW).
- Age ≥16 to ≤25 years at screening. Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first DMC review of the unblinded safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents.
- HIV-1 status unknown at initial screening and no prior HIV-1 testing within the last 3 months.
- Sexually active (has had ≥2 vaginal intercourse encounters within the last 3 months) with CGM.
- Willing and able to comply with study procedures.

Exclusion Criteria for the Incidence Phase

- Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) are not eligible. Individuals may be eligible if they participated in an HIV vaccine or bNAb study but have documentation that they did not receive active product (e.g., placebo recipients).
- Prior use of HIV PrEP (including F/TDF) or HIV PEP (postexposure prophylaxis) in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir).

Inclusion Criteria for the Randomized Blinded Phase

Participants who have a negative fourth generation HIV-1/2 antibody (Ab)/antigen (Ag) and meet the criteria from the Incidence Phase can be screened for the Randomized Blinded Phase if additional consent is obtained. Participants who meet the following criteria will be randomized in the Randomized Blinded Phase:

- Negative local rapid fourth generation HIV-1/2 Ab/Ag test, central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative nucleic acid amplification test (NAAT).
- Estimated GFR ≥60 mL/min at screening according to the Cockcroft-Gault formula for creatinine clearance (CL_{cr}).
- Body weight ≥35 kg.

Exclusion Criteria for the Randomized Blinded Phase

Participants who meet any of the following exclusion criteria are not eligible to be randomized in the Randomized Blinded Phase of this study.

- Participation in any other clinical trial (including observational and COVID-19 vaccine trials) without prior approval from the Applicant is prohibited while participating in this trial. NOTE: Receipt of routine COVID-19 vaccine is not exclusionary. Participation in the qualitative study (GS-US-528-6365) does not require Applicant approval.
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

- Acute viral hepatitis A, B, or C or evidence of chronic hepatitis B or C infection.
  - If a participant has a negative hepatitis B surface antigen, negative hepatitis B surface antibody, and positive hepatitis B core antibody, hepatitis B virus (HBV) DNA testing will be completed. If the HBV DNA result is positive, the participant is a screen failure. Participants found to be susceptible to HBV infection will be offered an HBV vaccination.
  - If the hepatitis C virus (HCV) Ab result is positive, then HCV RNA will be evaluated. Participants found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.
- Severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (e.g., ascites, encephalopathy, variceal bleeding).
- Have a suspected or known active, serious infection(s) (e.g., active tuberculosis, etc.).
- Need for continued use of any contraindicated concomitant medications.
- Have a history of osteoporosis or bone fragility fractures.
- Current alcohol or substance abuse judged by the investigator to be problematic such that it potentially interferes with participant study adherence.
- Grade 3 or Grade 4 proteinuria or glycosuria at screening that is unexplained or not clinically manageable.
- Women who are pregnant or lactating prior to administration of the first study drug dose.
- Any other clinical condition, laboratory abnormalities, or psychosocial condition or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements.

6.2.1.3. Statistical Analysis Plan, PURPOSE 1

The details of the statistical analysis plan are described in Section 15.1.

6.2.1.3.1. Objectives and Endpoints

Table 6. Primary and Secondary Objectives and Endpoints, PURPOSE 1

Objectives	Endpoints
The primary objective of this study 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 (bHIV) incidence.	
Primary Objectives	
Incidence Phase • To estimate the bHIV incidence • Randomized Blinded Phase • To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in adolescent girls and young women (AGYW) at risk of HIV-1 infection • To evaluate the efficacy of F/TAF for HIV-1 PrEP in AGYW at risk of HIV-1 infection	Incidence Phase • Diagnosis of recent HIV-1 infection Randomized Blinded Phase • Diagnosis of HIV-1 infection
Secondary Objectives	
Randomized Blinded Phase • To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the efficacy of LEN for HIV-1 PrEP in AGYW at risk of HIV-1 infection in participants adherent to LEN • To evaluate the efficacy of F/TAF for HIV-1 PrEP in AGYW at risk of HIV-1 infection in participants adherent to F/TAF • To compare the efficacy of F/TAF with F/TDF for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the safety and tolerability of LEN, F/TAF, and F/TDF for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the safety and tolerability of LEN and F/TAF for HIV-1 PrEP in AGYW ≥16 to <18 years of age who have sex with male partners and are at risk for HIV-1 infection	Randomized Blinded Phase • Diagnosis of HIV-1 infection, including among participants while adherent to study drug • Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN, F/TAF, and F/TDF for HIV-1 PrEP

Source: Study synopsis of the CSR of PURPOSE 1.

6.2.1.3.2. Sample Size and Power

A total sample size of 5,010 was considered for this study. More than 95% power would be achieved with 2,000 participants in the LEN study drug group to show at least a 20% reduction compared with the bHIV (powered for both H_{01} and H_{02}). In this sample size analysis, the following assumptions were made:

- bHIV of 3.00/100 PY

- LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 incidence compared with the nonrandomized control of bHIV
- Mean duration of recent infections (MDRI) of 173 days, with relative standard error (rSE) of 6.5%
- False recency rate (FRR) of 1.5%, with rSE of 70%
- Average follow-up of 1 year
- 2:2:1 allocation for LEN: F/TAF: F/TDF
- Alpha level of 0.025 (1-sided)

The bHIV assumption was based on recent longitudinal clinical trial data (ECHO Trial Consortium 2019). The LEN incidence corresponds to an 80% risk reduction and was consistent with the incidences observed in a large randomized controlled trial of long-acting cabotegravir for PrEP conducted in a similar study population (Delany-Moretlwe et al. 2021).

The MDRI and FRR were based on the Sedia limiting antigen avidity enzyme immunoassay (Lag-EIA) (Kassanjee et al. 2016), assuming the cutoff for the time period (T) =2 years and virologic cutoff of 75 copies/mL. Under the assumption of T =1 year, the power dropped to 94%. The power calculation was based on the formula in (Gao et al. 2021) using the test statistics for rate ratio (Gao et al. 2021).

The statistical power to compare the randomized study drug groups was not assessed.

6.2.1.3.3. Analysis Sets

Table 7. Analysis Sets, PURPOSE 1 and PURPOSE 2

Analysis Set	Definition
All Screened Set	All participants who were screened for HIV-1 in the Incidence Phase and had a nonmissing HIV-1 diagnosis based on HIV test results (defined as at least 1 nonmissing central laboratory HIV test including the HIV-1/2 Ab/Ag test, HIV-1/2 Ab differentiation assay, HIV-1/2 RNA qualitative NAAT, or HIV-1 RNA quantitative NAAT) at Incidence Phase screening. Any additional participants who took at least 1 dose of any study drug (but were missing central laboratory HIV tests at Incidence Phase screening) were included in the All Screened Set and considered as HIV-1 negative. This was the primary analysis set for estimating the bHIV incidence.
All Randomized Analysis Set	All participants who were randomized in the study
Full Analysis Set	All randomized participants who received at least 1 dose of any study drug and had not been diagnosed with HIV-1 on or prior to the first dose date (as determined by the HIV Adjudication Committee confirming an HIV-1 infection diagnosis date on or prior to the first dose date of study drug) This was the primary analysis set for efficacy analyses for participants who entered the Randomized Blinded Phase of the study.

Source: Section 3.1 of the SAP of PURPOSE 1.
Abbreviations: Ab/Ag, antibody/antigen; NAAT, nucleic acid amplification testing.

6.2.1.3.4. Multiple Alpha-Controlled Hypotheses

There were eight alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed below.

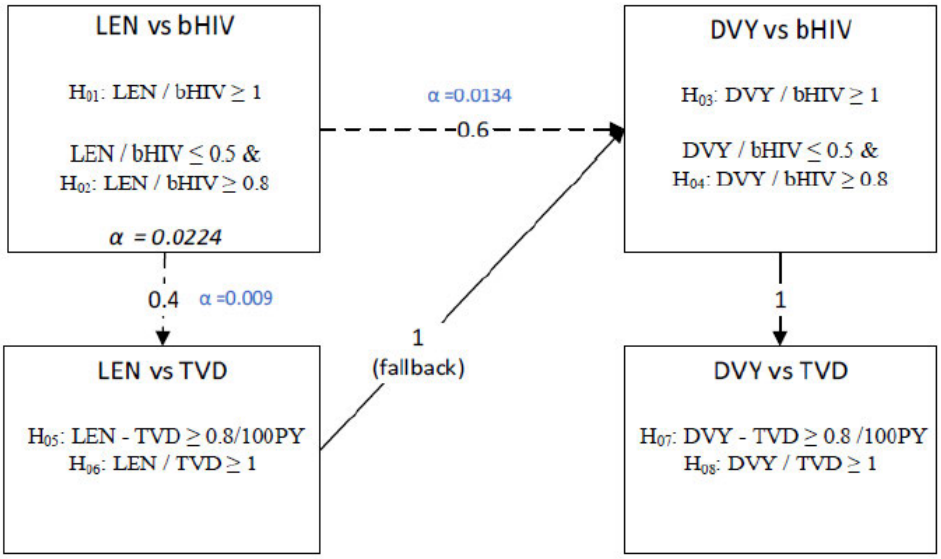
Table 8. Testing Sequence of Null Hypotheses, PURPOSE 1

Objectives	Null Hypothesis	Interpretation from Rejecting Null Hypothesis
LEN Primary Objectives	H_{01}: LEN / bHIV ≥1 H_{02}: LEN / bHIV ≥0.8	HIV-1 incidence in LEN is significantly lower than bHIV. HIV-1 incidence in LEN is significantly and at least 20% lower than bHIV and the point estimate LEN/bHIV ≤0.5.
F/TAF Primary Objectives	H_{03}: F/TAF / bHIV ≥1 H_{04}: F/TAF / bHIV ≥0.8	HIV-1 incidence in F/TAF is significantly lower than bHIV. HIV-1 incidence in F/TAF is significantly and at least 20% lower than bHIV and the point estimate of F/TAF/bHIV ≤0.5.
LEN Secondary Objectives	H_{05}: LEN – F/TDF ≥0.8/100PY H_{06}: LEN / F/TDF ≥1	HIV-1 incidence in LEN is not substantially greater than F/TDF (LEN efficacy is comparable to F/TDF). HIV-1 incidence in LEN is significantly lower than F/TDF.
F/TAF Secondary Objectives	H_{07}: F/TAF – F/TDF ≥0.8/100PY H_{08}: F/TAF / F/TDF ≥1	HIV-1 incidence in F/TAF is not substantially greater than F/TDF (F/TAF efficacy is comparable to F/TDF). HIV-1 incidence in F/TAF is significantly lower than F/TDF.

Source: Table 3-1 of the SAP of PURPOSE 1.
Abbreviations: H_0, null hypothesis; LEN, lenacapavir; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; SAP, statistical analysis plan.

If the study was not stopped at the efficacy interim analysis (IA), the planned final sequential efficacy analyses are indicated below in Figure 1.

Figure 1. Testing Procedure at the Primary Analysis, PURPOSE 1



Note: The one-sided α for the primary analysis is based on the Bonferroni method (primary alpha = 0.025 – interim alpha). Testing within each block is sequential. If H_{06} is rejected the fallback procedure will be implemented for H_{03} and the subsequent hypotheses. Transitional weights from one node to another indicates fraction of local significance level at the first node that is added to local significance level at the second node if the hypotheses in the first node are rejected.

Source: Figure 3-3 of the SAP of PURPOSE 1.
Abbreviations: bHIV, background HIV incidence; DVY, emtricitabine/tenofovir alafenamide; H_0, null hypothesis; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate; SAP, statistical analysis plan.

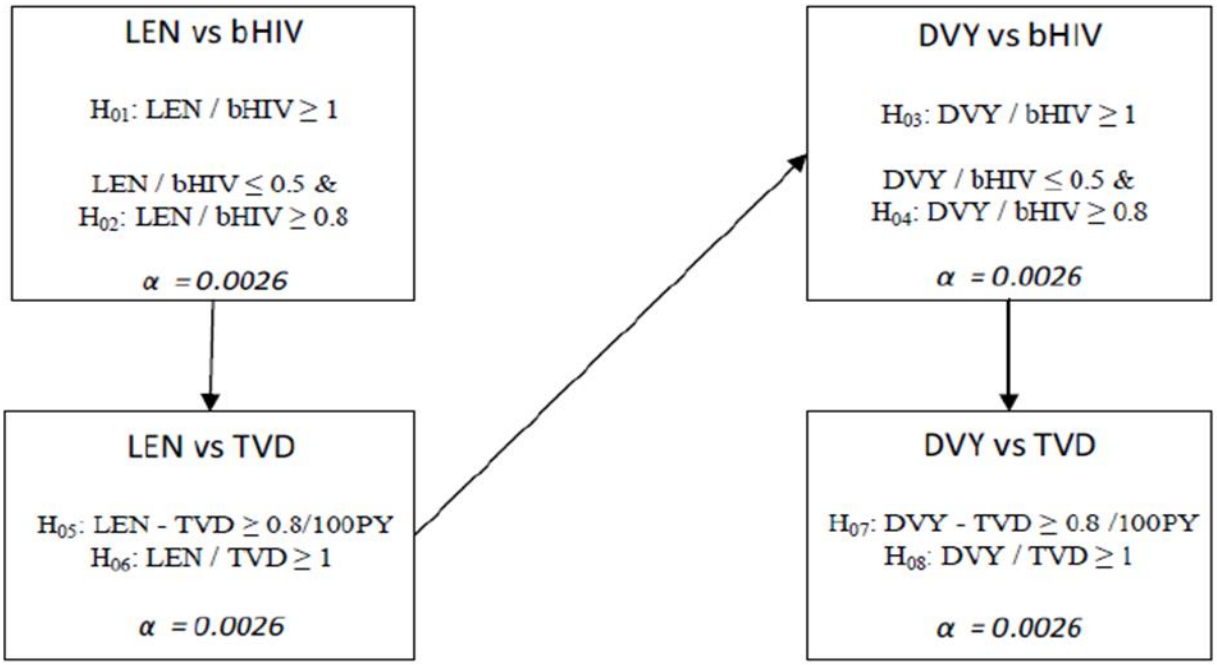
6.2.1.3.5. Interim Analyses of Efficacy Data

The DMC formally evaluated efficacy and futility data after 50% of participants enrolled completed Week 52 of the study or prematurely discontinued from the study. The DMC recommended stopping the study early after the prespecified efficacy or futility evaluation criteria were met. If the RBP could stop early due to an efficacy outcome, the interim analysis would serve as the primary analysis.

The overall testing procedure for the interim efficacy analysis used a gated sequential testing approach where the type I error level for the interim analysis was set at a one-sided alpha level of α_1=0.0026. Please see Figure 2 below for the details of the gated sequential testing.

The prespecified interim stopping criteria required the demonstration of superiority of LEN versus the bHIV incidence (H_{02}) with the point estimate of LEN/bHIV incidence ≤0.5 and superiority of LEN versus F/TDF (H_{06}), both at α_1=0.0026. Therefore, the key secondary efficacy endpoint of LEN versus F/TDF was the co-primary efficacy endpoint at the IA for efficacy and this is slightly different from the pre-specified final primary efficacy analyses. Due to the short follow-up time, we added this more stringent stopping criteria to ensure the superiority of LEN over the active control before the trial stopped. Because the stated criteria for interim stopping were met, the RBP stopped at the IA, and the interim analysis served as the primary analysis for this study.

Figure 2. Testing Procedure at the Interim Analysis, PURPOSE 1



Source: Figure 3-2 of the statistical analysis plan (SAP).
Note: For simplicity, LEN, DVY and TVD were used to denote the HIV-1 incidences for the LEN group F/TAF group and F/TDF group, respectively.
Abbreviations: bHIV, background HIV incidence; DVY, emtricitabine/tenofovir alafenamide; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; H_0, null hypothesis; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate

6.2.1.3.6. Analysis of Efficacy

For the Incidence Phase of this study, the bHIV incidence was reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to (Kassanjee et al. 2012) adjusting for participants with HIV-1 who may not have had recency assay results.

The HIV-1 incidence was reported per 100 PY in the LEN and F/TDF groups. The HIV-1 incidence rates in the LEN and F/TDF groups were estimated by the number of HIV-1 infections in the study divided by the total follow-up time in the study for each study drug group.

The primary efficacy evaluation was a comparison of the observed HIV-1 incidence rate in the LEN versus the bHIV incidence rate using rate ratio metric. The associated 95% Confidence Interval (CI) and *P* value were estimated using the delta method (Gao et al. 2021) or a likelihood-based method if there were 0 infections in the group (Shao and Gao 2024).

The difference in the HIV-1 incidence rates of LEN versus F/TDF was used to evaluate the comparability of LEN relative to F/TDF (H_{05}). In order to test this hypothesis, a 95% CI was constructed using a hybrid approach, with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI (Li et al. 2011).

It would be concluded that LEN was comparable to F/TDF if the upper bound of the 95% CI of the incidence rate difference (LEN – F/TDF) was less than 0.8 per 100 PY.

The ratio of HIV-1 incidence rates was used to evaluate the superiority of LEN versus F/TDF.

The incidence rate ratio of the LEN group versus the F/TDF group was calculated. The associated 95% CIs and *P* values were estimated using a generalized Poisson regression model or an exact conditional Poisson regression model if there were 0 infections.

In this review, the efficacy analyses only focus on the comparison of the LEN versus F/TDF groups. The F/TAF group will not be discussed in the efficacy analyses as the data were obtained in response to a postmarketing commitment (PMC) issued under the F/TAF NDA.

6.2.1.4. Results of Analyses, PURPOSE 1

6.2.1.4.1. Participant Disposition

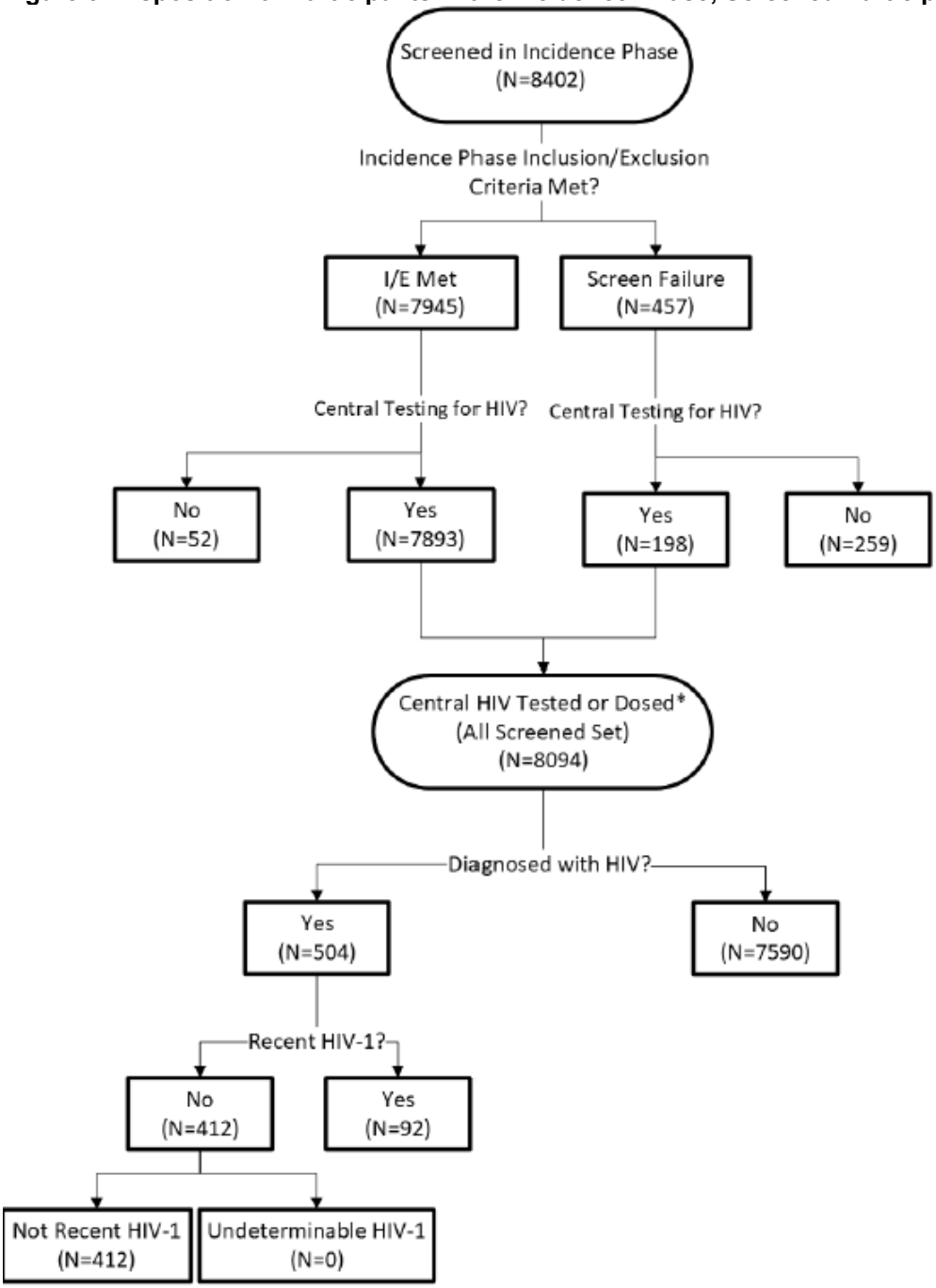
As shown in Figure 3, overall, 8,402 participants were screened in the Incidence Phase and 6,760 proceeded to RBP screening. A total of 457 participants did not meet Incidence Phase eligibility criteria, 47 were not eligible but proceeded to RBP screening, and 1,232 were eligible but did not proceed to RBP screening. Besides a positive HIV test (511 participants), the most common reasons for not proceeding to RBP screening were pregnancy or lactation (170 participants) and outside of visit window (146 participants).

Out of the 8,094 screened participants who had at least one non-missing central laboratory HIV test, 504 (6.2%) were diagnosed with HIV and 92 (18.3%) of them were identified as recent HIV-1 infection at the Incidence Phase.

In the RBP, 6,760 participants were screened and 5,368 were randomized (Figure 4). A total of 726 participants did not meet RBP eligibility criteria and were not randomized, 39 were not eligible but were randomized, and 666 were eligible but were not randomized. Of those who

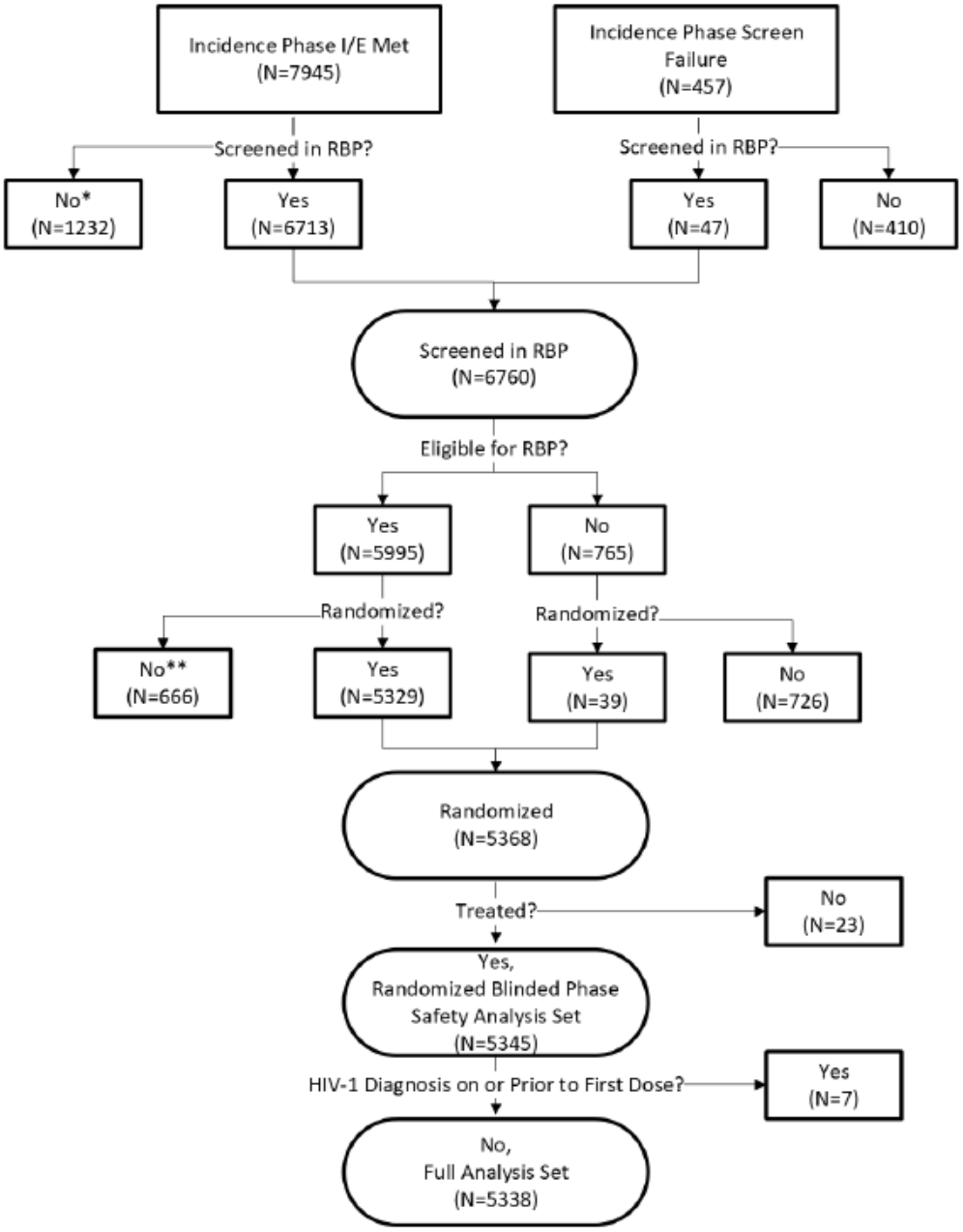
were eligible for randomization but were not randomized, the most common reasons were outside of visit window (264 participants), withdrawal of consent (127 participants), and lost to follow-up (94 participants). As shown in Table 9, of the 5,345 participants who were randomized and received study drugs, 7 participants were subsequently confirmed to have had baseline HIV-1 infections based on central testing. A total of 610 participants (11.4%) discontinued study drugs in the RBP. The most common reasons for discontinuation of study drugs were participant decision (5.8%), lost to follow-up (1.7%), and pregnancy (1.7%).

Figure 3. Disposition of Participants in the Incidence Phase, Screened Participants, PURPOSE 1



Source: Figure 4 of the CSR.
Abbreviations: HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; I/E, inclusion/exclusion criteria * Includes 3 participants with central HIV tests performed after initial screening, prior to randomization, and were randomized and dosed in the Randomized Blinded Phase.

Figure 4. Disposition of Participants in the Randomized Blinded Phase, PURPOSE 1



Source: Figure 5 of the CSR.
* Reasons not screened in RBP despite meeting Incidence Phase I/E criteria include adverse event (1), investigator's discretion (96), lost to follow-up (83), outside of visit window (146), study enrollment closed (6), withdrew consent (18), other (880), and missing (2).
** Reasons not randomized despite meeting RBP I/E criteria include investigator's discretion (37), lost to follow-up (94), outside of visit window (264), study enrollment closed (5), withdrew consent (127), screen failed Incidence Phase (4), and other (135).
Abbreviations: CSR, clinical study report; HIV-1, human immunodeficiency virus type 1; I/E, inclusion/exclusion criteria; RBP, Randomized Blinded Phase.

Table 9. Participant Disposition, PURPOSE 1

Disposition	SC LEN	F/TAF	F/TDF	Total
Randomized	2148	2147	1073	5368
Randomized and not dosed	10	10	3	23
Randomized and dosed (RBP Safety Analysis Set)	2140	2135	1070	5345
Randomized and dosed with diagnosis of HIV-1 on or prior to first dose (excluding screening HIV-1 diagnosis)	4	1	2	7
Randomized and dosed with diagnosis of no HIV-1 on or prior to Day 1 (Full Analysis Set)	2134	2136	1068	5338
Continuing study drug in RBP	1907 (89.1%)	1895 (88.8%)	933 (87.2%)	4735 (88.6%)
Did not complete the study drug in RBP	233 (10.9%)	240 (11.2%)	137 (12.8%)	610 (11.4%)
Reasons for prematurely discontinuing study drug in RBP				
Adverse event (includes injection site reactions to study SC injection)	9 (0.4%)	2 (<0.1%)	0	11 (0.2%)
Death	0	5 (0.2%)	0	5 (<0.1%)
Pregnancy	35 (1.6%)	42 (2.0%)	12 (1.1%)	89 (1.7%)
Investigator's discretion	11 (0.5%)	8 (0.4%)	12 (1.1%)	31 (0.6%)
Noncompliance with study drug	5 (0.2%)	6 (0.3%)	3 (0.3%)	14 (0.3%)
Participant never dosed with study drug	0	0	0	0
Protocol violation	6 (0.3%)	0	1 (<0.1%)	7 (0.1%)
Participant decision	125 (5.8%)	113 (5.3%)	70 (6.5%)	308 (5.8%)
Parent/guardian decision	2 (<0.1%)	0	0	2 (<0.1%)
Lost to follow-up	36 (1.7%)	32 (1.5%)	24 (2.2%)	92 (1.7%)
Study terminated by Applicant	0	0	0	0
HIV-1 infection	4 (0.2%)	32 (1.5%)	15 (1.4%)	51 (1.0%)
Clinical hold	0	0	0	0
Continuing study in RBP	1909 (89.2%)	1910 (89.5%)	937 (87.6%)	4756 (89.0%)
Did not complete the study in RBP	137 (6.4%)	148 (6.9%)	96 (9.0%)	381 (7.1%)
Reasons for prematurely discontinuing from study in RBP				
Adverse event (includes injection site reactions to study SC injection)	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)
Death	0	5 (0.2%)	0	5 (<0.1%)
Pregnancy	5 (0.2%)	5 (0.2%)	0	10 (0.2%)
Investigator's discretion	9 (0.4%)	8 (0.4%)	11 (1.0%)	28 (0.5%)
Noncompliance with study drug	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)
Protocol violation	1 (<0.1%)	0	0	1 (<0.1%)
Withdrew consent	73 (3.4%)	72 (3.4%)	46 (4.3%)	191 (3.6%)
Withdrew assent	3 (0.1%)	0	0	3 (<0.1%)
Lost to follow-up	39 (1.8%)	36 (1.7%)	26 (2.4%)	101 (1.9%)
Study terminated by Applicant	0	0	0	0
HIV-1 infection	4 (0.2%)	20 (0.9%)	12 (1.1%)	36 (0.7%)

Source: Reviewer's analysis using adsl.xpt and Table 5 of the CSR.
Denominators for percentages are the RBP Safety Analysis Set for study drug (or study) status.
Treated participants discontinued the study only once (either in RBP or Open-Label Oral PrEP Analysis); those that discontinued the study in the RBP could not be included in the Open-Label Oral PrEP Analysis.
Data through data cutoff date (May 8, 2024).
Participants' study drugs grouped by 1) randomized study drug for the Full Analysis Set, and 2) actual study drug received otherwise.
Abbreviations: F/TAF, emtricitabine/tenofovir alafenamide; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; RBP, Randomized Blinded Phase; SC, subcutaneous; F/TDF, emtricitabine/tenofovir disoproxil fumarate; CSR, clinical study report.

6.2.1.4.2. Demographics and Baseline Characteristics

In the RBP, demographics and baseline characteristics were generally comparable among study drug groups as shown in Table 10 and Table 11.

The median age was 21 years (range: 16 to 26) and median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) was 25.2 (21.9, 30.4) kg/m^2. Most participants were aged ≥18 years (97.7%), and 124 participants (2.3%) were aged between 16 and <18 years. All participants were assigned female sex at birth. Most participants were Black (99.9%), and all were not Hispanic or Latino. Most participants were never married (96.9%). Most did not live with a partner/husband or have no partner (93.4%). The median (Q1, Q3) modified VOICE risk score was 7 (5.0, 7.0).

At baseline, a high number of participants (35.1%) were diagnosed with a sexually transmitted infection (STI [chlamydia, gonorrhea, trichomonas vaginalis, or syphilis]). Of those who had an STI diagnosed at baseline, the most common was chlamydia (25.2%). In the past 3 months, the majority of participants had 1 to 2 male sex partners (59.6%), and most participants did not have any male sex partners with known HIV (84.0%). The mean (standard deviation [SD]) number of condomless vaginal sex acts in the past 3 months was 24 (84.6). The majority of the participants (96.1%) did not take drugs before or during sex (chemsex) in the past 3 months.

Table 10. Baseline Demographics and Clinical Characteristics, Randomized Blinded Phase Safety Analysis Set, PURPOSE 1

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Age (years)				
N	2140	2135	1070	5345
Mean (SD)	21 (2.2)	21 (2.1)	21 (2.1)	21 (2.1)
Median	21	21	21	21
Q1, Q3	19, 23	19, 23	19, 23	19, 23
Min, max	16, 25	16, 26	16, 25	16, 26
Age categories (years)				
16 to <18	56 (2.6%)	45 (2.1%)	23 (2.1%)	124 (2.3%)
≥18	2084 (97.4%)	2090 (97.9%)	1047 (97.9%)	5221 (97.7%)
Sex assigned at birth				
Male	0	0	0	0
Female	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Race				
Black	2137 (99.9%)	2134 (100.0%)	1068 (99.8%)	5339 (99.9%)
Multiracial–other	3 (0.1%)	1 (<0.1%)	1 (<0.1%)	5 (<0.1%)
Not multiracial–other	0	0	1 (<0.1%)	1 (<0.1%)
Ethnicity				
Not Hispanic or Latino	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Baseline weight (kg)				
N	2140	2135	1070	5345
Mean (SD)	66.8 (17.44)	68.5 (18.27)	67.6 (17.26)	67.6 (17.75)
Median	63.0	64.2	63.5	63.5
Q1, Q3	54.4, 76.0	55.0, 77.7	54.7, 76.2	54.8, 76.7
Min, max	37.1, 192.1	37.8, 174.5	38.0, 150.5	37.1, 192.1

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Baseline height (cm)				
N	2140	2135	1070	5345
Mean (SD)	158.6 (6.58)	158.8 (6.21)	158.7 (6.59)	158.7 (6.43)
Median	158.5	159.0	158.0	159.0
Q1, Q3	154.7, 163.0	155.0, 163.0	154.2, 163.0	155.0, 163.0
Min, max	110.0, 189.0	136.0, 189.0	134.0, 185.0	110.0, 189.0
Baseline body mass index (kg/m^2)				
N	2140	2135	1070	5345
Mean (SD)	26.5 (6.53)	27.1 (6.84)	26.8 (6.48)	26.8 (6.65)
Median	24.9	25.6	25.2	25.2
Q1, Q3	21.7, 30.1	22.1, 30.7	21.9, 30.4	21.9, 30.4
Min, max	15.0, 62.7	15.0, 55.7	14.8, 51.4	14.8, 62.7
Baseline waist circumference (cm)				
N	2140	2135	1070	5345
Mean (SD)	82.2 (13.66)	83.6 (14.35)	82.6 (13.37)	82.8 (13.89)
Median	79.1	80.0	80.0	80.0
Q1, Q3	72.0, 90.0	73.0, 92.0	73.0, 90.0	73.0, 90.6
Min, max	43.8, 159.0	56.0, 164.0	59.0, 150.0	43.8, 164.0
Highest education level				
Did not attend primary school	17 (0.8%)	19 (0.9%)	3 (0.3%)	39 (0.7%)
Some primary school education	169 (7.9%)	155 (7.3%)	73 (6.8%)	397 (7.4%)
Primary school complete	66 (3.1%)	68 (3.2%)	33 (3.1%)	167 (3.1%)
Some secondary school education	905 (42.3%)	926 (43.4%)	459 (42.9%)	2290 (42.9%)
Secondary school degree complete	797 (37.3%)	767 (36.0%)	392 (36.7%)	1956 (36.6%)
Some college or university degree	184 (8.6%)	197 (9.2%)	109 (10.2%)	490 (9.2%)
Missing	2	3	1	6
Needs help with completion of electronic questionnaire				
Yes	1093 (51.1%)	1119 (52.5%)	534 (50.0%)	2746 (51.4%)
No	1045 (48.9%)	1012 (47.5%)	535 (50.0%)	2592 (48.6%)
Missing	2	4	1	7
Current marital status				
Never married	2075 (97.1%)	2062 (96.7%)	1037 (97.0%)	5174 (96.9%)
Married (monogamous)	19 (0.9%)	23 (1.1%)	10 (0.9%)	52 (1.0%)
Married (polygamous)	7 (0.3%)	7 (0.3%)	7 (0.7%)	21 (0.4%)
Separated	36 (1.7%)	38 (1.8%)	14 (1.3%)	88 (1.6%)
Divorced	0	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Widowed	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Missing	2	3	1	6
Currently living with husband/partner				
Yes	148 (6.9%)	132 (6.2%)	73 (6.8%)	353 (6.6%)
No	1888 (88.3%)	1889 (88.6%)	937 (87.7%)	4714 (88.3%)
No partner	102 (4.8%)	111 (5.2%)	58 (5.4%)	271 (5.1%)
Prefer not to answer	0	0	1	1
Missing	2	3	1	6
Husband/partner provide financial and/or material support				
Yes	1310 (61.6%)	1355 (63.9%)	660 (62.1%)	3325 (62.6%)
No	713 (33.5%)	646 (30.5%)	346 (32.5%)	1705 (32.1%)
No partner	103 (4.8%)	118 (5.6%)	57 (5.4%)	278 (5.2%)
Prefer not to answer	12	13	6	31
Missing	2	3	1	6

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Husband/partner have sex with other partners				
Yes	566 (27.0%)	597 (28.5%)	281 (26.8%)	1444 (27.6%)
No	547 (26.0%)	497 (23.7%)	266 (25.4%)	1310 (25.0%)
No partner	105 (5.0%)	114 (5.4%)	56 (5.3%)	275 (5.2%)
Unknown	882 (42.0%)	886 (42.3%)	444 (42.4%)	2212 (42.2%)
Prefer not to answer	38	38	22	98
Missing	2	3	1	6
Frequency of alcohol use in the past 3 months				
Never	504 (23.7%)	491 (23.1%)	240 (22.6%)	1235 (23.2%)
Monthly or less	723 (34.0%)	743 (34.9%)	362 (34.0%)	1828 (34.4%)
2 to 4 times a month	618 (29.1%)	621 (29.2%)	303 (28.5%)	1542 (29.0%)
2 to 3 times a week	164 (7.7%)	150 (7.0%)	92 (8.6%)	406 (7.6%)
4 or more times a week	117 (5.5%)	125 (5.9%)	67 (6.3%)	309 (5.8%)
Prefer not to answer	11	2	5	18
Missing	3	3	1	7
Modified VOICE Risk Score				
N	2076	2080	1037	5193
Mean (SD)	6.3 (1.31)	6.3 (1.28)	6.3 (1.29)	6.3 (1.29)
Median	7.0	7.0	7.0	7.0
Q1, Q3	5.0, 7.0	5.0, 7.0	5.0, 7.0	5.0, 7.0
Min, max	0.0, 8.0	1.0, 8.0	0.0, 8.0	0.0, 8.0
Modified VOICE Risk Score				
0	1 (<0.1%)	0	2 (0.2%)	3 (<0.1%)
1	3 (0.1%)	4 (0.2%)	1 (<0.1%)	8 (0.2%)
2	12 (0.6%)	11 (0.5%)	10 (1.0%)	33 (0.6%)
3	49 (2.4%)	48 (2.3%)	16 (1.5%)	113 (2.2%)
4	121 (5.8%)	110 (5.3%)	46 (4.4%)	277 (5.3%)
5	402 (19.4%)	381 (18.3%)	201 (19.4%)	984 (18.9%)
6	411 (19.8%)	393 (18.9%)	210 (20.3%)	1014 (19.5%)
7	737 (35.5%)	819 (39.4%)	395 (38.1%)	1951 (37.6%)
8	340 (16.4%)	314 (15.1%)	156 (15.0%)	810 (15.6%)
Missing	64	55	33	152
Modified VOICE Risk Score				
<5	186 (9.0%)	173 (8.3%)	75 (7.2%)	434 (8.4%)
≥5	1890 (91.0%)	1907 (91.7%)	962 (92.8%)	4759 (91.6%)
Missing	64	55	33	152

Source: Table 7 of the CSR.
Age (in years) was collected on the first dose date of study drug (Day 1). Participants who were 25 at screening might have been 26 by the first dose date.
"Prefer not to answer" and "missing" were excluded from the calculation of percentages.
Body mass index (kg/m2) = (Weight [kg]/Height [cm]^2) x10,000.
Components of the modified VOICE score (Balkus 2016) were collected at screening.
Frequency of alcohol use in the past 3 months was collected at screening by the sites (not electronic participant-reported outcomes).
Abbreviations: CSR, clinical study report; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

Table 11. Other Baseline HIV-Risk Characteristics, Randomized Blinded Phase Safety Analysis Set, PURPOSE 1

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Any chlamydia, gonorrhea, trichomonas vaginalis, or syphilis				
Yes	727 (34.0%)	775 (36.3%)	373 (34.9%)	1875 (35.1%)
No	1413 (66.0%)	1360 (63.7%)	697 (65.1%)	3470 (64.9%)
Chlamydia (urethral/urine)				
Detected	520 (24.3%)	562 (26.3%)	263 (24.6%)	1345 (25.2%)
Indeterminate	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)
Not detected	1618 (75.6%)	1572 (73.6%)	807 (75.4%)	3997 (74.8%)
Gonorrhea (urethral/urine)				
Detected	197 (9.2%)	178 (8.3%)	90 (8.4%)	465 (8.7%)
Indeterminate	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)
Not detected	1941 (90.7%)	1956 (91.6%)	980 (91.6%)	4877 (91.2%)
Trichomonas vaginalis (urethral/urine)				
Detected	154 (7.2%)	165 (7.7%)	82 (7.7%)	401 (7.5%)
Indeterminate	0	0	0	0
Not detected	1986 (92.8%)	1970 (92.3%)	988 (92.3%)	4944 (92.5%)
Syphilis diagnosis (investigator report)				
Yes	57 (2.7%)	63 (3.0%)	29 (2.7%)	149 (2.8%)
No	2083 (97.3%)	2072 (97.0%)	1041 (97.3%)	5196 (97.2%)
Syphilis stage				
N (total number or participants with syphilis)	57	63	29	149
Primary	0	0	0	0
Early latent	26 (45.6%)	31 (49.2%)	15 (51.7%)	72 (48.3%)
Secondary	3 (5.3%)	2 (3.2%)	1 (3.4%)	6 (4.0%)
Tertiary	0	0	0	0
Late latent	27 (47.4%)	30 (47.6%)	13 (44.8%)	70 (47.0%)
Other	1 (1.8%)	0	0	1 (0.7%)
Male sex partners in past 3 months				
N	1992	2015	998	5005
Mean (SD)	21 (84.4)	24 (97.7)	24 (100.0)	23 (93.1)
Median	2	2	2	2
Q1, Q3	1, 3	1, 3	1, 3	1, 3
Min, max	0, 999	0, 999	0, 999	0, 999
Male sex partners in past 3 months				
0	122 (6.1%)	138 (6.8%)	72 (7.2%)	332 (6.6%)
1 to 2	1171 (58.8%)	1231 (61.1%)	583 (58.4%)	2985 (59.6%)
3 to 5	340 (17.1%)	283 (14.0%)	162 (16.2%)	785 (15.7%)
6 to 9	58 (2.9%)	38 (1.9%)	23 (2.3%)	119 (2.4%)
≥10	301 (15.1%)	325 (16.1%)	158 (15.8%)	784 (15.7%)
Prefer not to answer	139	113	69	321
Missing	9	7	3	19
Male sex partners with HIV in past 3 months				
N	1853	1887	924	4664
Mean (SD)	8 (66.0)	6 (60.9)	7 (59.0)	7 (62.6)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 990	0, 999

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Male sex partners with HIV in past 3 months				
0	1544 (83.3%)	1599 (84.7%)	773 (83.7%)	3916 (84.0%)
1 to 2	212 (11.4%)	196 (10.4%)	93 (10.1%)	501 (10.7%)
3 to 5	29 (1.6%)	31 (1.6%)	10 (1.1%)	70 (1.5%)
6 to 9	6 (0.3%)	8 (0.4%)	6 (0.6%)	20 (0.4%)
≥10	62 (3.3%)	53 (2.8%)	42 (4.5%)	157 (3.4%)
Prefer not to answer	276	240	142	658
Missing	11	8	4	23
Vaginal sex acts in past 3 months				
N	1976	1964	975	4915
Mean (SD)	53 (141.3)	45 (131.9)	45 (124.7)	48 (134.4)
Median	9	8	9	9
Q1, Q3	3, 27	3, 24	3, 27	3, 25
Min, max	0, 999	0, 999	0, 999	0, 999
Vaginal sex acts in past 3 months				
0	112 (5.7%)	127 (6.5%)	46 (4.7%)	285 (5.8%)
1 to 2	236 (11.9%)	266 (13.5%)	128 (13.1%)	630 (12.8%)
3 to 5	404 (20.4%)	389 (19.8%)	201 (20.6%)	994 (20.2%)
6 to 9	244 (12.3%)	275 (14.0%)	119 (12.2%)	638 (13.0%)
≥10	980 (49.6%)	907 (46.2%)	481 (49.3%)	2368 (48.2%)
Prefer not to answer	155	164	92	411
Missing	9	7	3	19
Condomless vaginal sex acts in past 3 months				
N	1921	1911	941	4773
Mean (SD)	27 (92.1)	21 (72.2)	26 (91.7)	24 (84.6)
Median	3	3	3	3
Q1, Q3	1, 11	1, 10	1, 11	1, 10
Min, max	0, 999	0, 999	0, 999	0, 999
Condomless vaginal sex acts in past 3 months				
0	429 (22.3%)	415 (21.7%)	181 (19.2%)	1025 (21.5%)
1 to 2	397 (20.7%)	412 (21.6%)	216 (23.0%)	1025 (21.5%)
3 to 5	366 (19.1%)	377 (19.7%)	175 (18.6%)	918 (19.2%)
6 to 9	149 (7.8%)	160 (8.4%)	75 (8.0%)	384 (8.0%)
≥10	580 (30.2%)	547 (28.6%)	294 (31.2%)	1421 (29.8%)
Prefer not to answer	208	217	125	550
Missing	11	7	4	22
Anal sex acts in past 3 months				
N	2001	2002	989	4992
Mean (SD)	11 (86.0)	10 (84.1)	10 (81.0)	10 (84.3)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 999	0, 999
Anal sex acts in past 3 months				
0	1782 (89.1%)	1782 (89.0%)	873 (88.3%)	4437 (88.9%)
1 to 2	85 (4.2%)	94 (4.7%)	45 (4.6%)	224 (4.5%)
3 to 5	36 (1.8%)	45 (2.2%)	16 (1.6%)	97 (1.9%)
6 to 9	15 (0.7%)	10 (0.5%)	8 (0.8%)	33 (0.7%)
≥10	83 (4.1%)	71 (3.5%)	47 (4.8%)	201 (4.0%)
Prefer not to answer	130	126	78	334
Missing	9	7	3	19

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Condomless anal sex acts in past 3 months				
N	1986	1988	980	4954
Mean (SD)	6 (66.7)	3 (38.2)	7 (65.9)	5 (56.8)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 999	0, 999
Condomless anal sex acts in past 3 months				
0	1818 (91.5%)	1830 (92.1%)	891 (90.9%)	4539 (91.6%)
1 to 2	85 (4.3%)	83 (4.2%)	37 (3.8%)	205 (4.1%)
3 to 5	25 (1.3%)	28 (1.4%)	16 (1.6%)	69 (1.4%)
6 to 9	10 (0.5%)	10 (0.5%)	6 (0.6%)	26 (0.5%)
≥10	48 (2.4%)	37 (1.9%)	30 (3.1%)	115 (2.3%)
Prefer not to answer	145	138	87	370
Missing	9	9	3	21
Primary partner in past 3 months (and if yes, primary partner's HIV status)				
Yes	1609 (76.8%)	1609 (76.9%)	820 (77.9%)	4038 (77.1%)
HIV negative	1015 (48.5%)	1025 (49.0%)	523 (49.7%)	2563 (48.9%)
HIV positive	15 (0.7%)	13 (0.6%)	4 (0.4%)	32 (0.6%)
Do not know	568 (27.1%)	565 (27.0%)	289 (27.4%)	1422 (27.1%)
Prefer not to answer	11 (0.5%)	6 (0.3%)	4 (0.4%)	21 (0.4%)
No	485 (23.2%)	484 (23.1%)	233 (22.1%)	1202 (22.9%)
Prefer not to answer	37	35	14	86
Missing	9	7	3	19
Sex for financial and/or material support in past 3 months (and if yes, whether considered a sex worker)				
Yes	493 (23.4%)	503 (23.9%)	251 (23.8%)	1247 (23.7%)
Sex worker	161 (7.6%)	167 (7.9%)	92 (8.7%)	420 (8.0%)
Not sex worker	327 (15.5%)	329 (15.6%)	155 (14.7%)	811 (15.4%)
Prefer not to answer	5 (0.2%)	7 (0.3%)	4 (0.4%)	16 (0.3%)
No	1617 (76.6%)	1604 (76.1%)	804 (76.2%)	4025 (76.3%)
Prefer not to answer	21	21	12	54
Missing	9	7	3	19
Frequency of alcohol use in past 3 months				
Never	479 (22.7%)	461 (21.9%)	226 (21.4%)	1166 (22.1%)
Monthly or less	718 (34.1%)	771 (36.7%)	354 (33.5%)	1843 (35.0%)
2 to 4 times a month	599 (28.4%)	588 (28.0%)	309 (29.2%)	1496 (28.4%)
2 to 3 times a week	205 (9.7%)	188 (8.9%)	115 (10.9%)	508 (9.6%)
4 or more times a week	105 (5.0%)	93 (4.4%)	54 (5.1%)	252 (4.8%)
Prefer not to answer	25	27	9	61
Missing	9	7	3	19

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Six or more drinks on one occasion in past 12 weeks				
Never	708 (33.9%)	701 (33.9%)	337 (32.2%)	1746 (33.5%)
Less than monthly	638 (30.5%)	631 (30.5%)	316 (30.2%)	1585 (30.5%)
Monthly	460 (22.0%)	451 (21.8%)	226 (21.6%)	1137 (21.8%)
Weekly	244 (11.7%)	233 (11.3%)	136 (13.0%)	613 (11.8%)
Daily or almost daily	39 (1.9%)	54 (2.6%)	31 (3.0%)	124 (2.4%)
Prefer not to answer	42	58	21	121
Missing	9	7	3	19
Alcohol before or during sex in past 12 weeks				
Yes	812 (38.4%)	793 (37.6%)	431 (40.8%)	2036 (38.6%)
No	1305 (61.6%)	1315 (62.4%)	625 (59.2%)	3245 (61.4%)
Prefer not to answer	14	20	11	45
Missing	9	7	3	19
Take drugs before or during sex (chemsex) in past 12 weeks				
Yes	88 (4.1%)	74 (3.5%)	44 (4.1%)	206 (3.9%)
No	2036 (95.9%)	2047 (96.5%)	1020 (95.9%)	5103 (96.1%)
Prefer not to answer	7	7	3	17
Missing	9	7	3	19
Smoked cigarettes in the past 3 months (and if yes, number per day)				
Yes	329 (15.5%)	303 (14.3%)	177 (16.6%)	809 (15.2%)
Less than 10 cigarettes per day	279 (13.1%)	254 (12.0%)	150 (14.1%)	683 (12.9%)
Between 10 and 20 cigarettes per day	17 (0.8%)	21 (1.0%)	9 (0.8%)	47 (0.9%)
More than 20 cigarettes per day	7 (0.3%)	4 (0.2%)	2 (0.2%)	13 (0.2%)
Prefer not to answer	26 (1.2%)	24 (1.1%)	16 (1.5%)	66 (1.2%)
No	1793 (84.5%)	1820 (85.7%)	888 (83.4%)	4501 (84.8%)
Prefer not to answer	9	5	2	16
Missing	9	7	3	19
Any substance use in past 12 weeks				
Yes	626 (30.4%)	614 (29.8%)	329 (31.8%)	1569 (30.5%)
No	1432 (69.6%)	1445 (70.2%)	704 (68.2%)	3581 (69.5%)
Prefer not to answer	73	69	34	176
Missing	9	7	3	19
Cannabis use in past 12 weeks				
Yes	291 (14.1%)	309 (14.8%)	189 (18.2%)	789 (15.2%)
No	1778 (85.9%)	1775 (85.2%)	849 (81.8%)	4402 (84.8%)
Prefer not to answer	62	44	29	135
Missing	9	7	3	19
Cocaine use in past 12 weeks				
Yes	125 (6.0%)	120 (5.7%)	58 (5.5%)	303 (5.8%)
No	1974 (94.0%)	1983 (94.3%)	989 (94.5%)	4946 (94.2%)
Prefer not to answer	32	25	20	77
Missing	9	7	3	19
Amphetamine-type stimulants use in past 12 weeks				
Yes	75 (3.6%)	57 (2.7%)	35 (3.3%)	167 (3.2%)
No	2016 (96.4%)	2026 (97.3%)	1012 (96.7%)	5054 (96.8%)
Prefer not to answer	40	45	20	105
Missing	9	7	3	19

Characteristic	SC LEN (N=2140)	F/TAF (N=2135)	F/TDF (N=1070)	Total (N=5345)
Inhalants use in past 12 weeks				
Yes	73 (3.5%)	56 (2.7%)	38 (3.6%)	167 (3.2%)
No	2028 (96.5%)	2027 (97.3%)	1014 (96.4%)	5069 (96.8%)
Prefer not to answer	30	45	15	90
Missing	9	7	3	19
Sedatives or sleeping pills use in past 12 weeks				
Yes	173 (8.2%)	165 (7.9%)	72 (6.8%)	410 (7.8%)
No	1928 (91.8%)	1927 (92.1%)	983 (93.2%)	4838 (92.2%)
Prefer not to answer	30	36	12	78
Missing	9	7	3	19
Hallucinogens use in past 12 weeks				
Yes	72 (3.4%)	86 (4.1%)	26 (2.5%)	184 (3.5%)
No	2020 (96.6%)	2000 (95.9%)	1023 (97.5%)	5043 (96.5%)
Prefer not to answer	39	42	18	99
Missing	9	7	3	19
Opioids use in past 12 weeks				
Yes	66 (3.1%)	60 (2.9%)	25 (2.4%)	151 (2.9%)
No	2039 (96.9%)	2042 (97.1%)	1027 (97.6%)	5108 (97.1%)
Prefer not to answer	26	26	15	67
Missing	9	7	3	19
Prescription drugs for nonprescription purpose use in past 12 weeks				
Yes	204 (9.7%)	194 (9.3%)	107 (10.2%)	505 (9.7%)
No	1900 (90.3%)	1888 (90.7%)	938 (89.8%)	4726 (90.3%)
Prefer not to answer	27	46	22	95
Missing	9	7	3	19

Source: Table 8 of the CSR.
"Missing" and "prefer not to answer" (except within a dynamic subquestion) were excluded from the percentage calculations.
Laboratory results based on central laboratory or local laboratories for gonorrhea, chlamydia, and trichomonas vaginalis, and local laboratories only for syphilis.
Responses for condomless sex acts or sex partners with HIV were imputed as 0 (or "prefer not to answer") when responses for sex acts or sex partners were 0 (or "prefer not to answer").
Abbreviations: CSR, clinical study report; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation.

6.2.1.4.3. Primary and Key Secondary Efficacy Results

The Applicant's primary and key secondary efficacy results were confirmed by the statistical review team. The determination of efficacy was based on the planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for the LEN group compared to background followed by the LEN group compared to the F/TDF group, all at alpha level of 0.0026 when 50% of planned randomized participants completed at least 52 weeks of follow-up or prematurely discontinued from the study.

Primary Efficacy Results

Table 12 below summarizes the primary efficacy results. As shown in Figure 3, out of the 8,094 screened participants who had at least one non-missing central laboratory HIV test, 504 (6.2%) were diagnosed with HIV-1 and 92 (18.3%) of them were identified as recent HIV-1 infection at

the Incidence Phase. The bHIV incidence rate was estimated to be 2.407 infections per 100 PY with a 95% CI of (1.815, 3.191).

At the interim analysis, the total PY follow up was 1939.35 in the LEN group. There was no HIV-1 infection in the LEN group. The estimated incidence rate was 0.000 infection per 100 PY with a 95% CI of (0.000, 0.190).

The comparison of the incidence rates between the LEN group and the background was conducted using the rate ratio method based on the methods in (Gao et al. 2021) and (Shao and Gao 2024). The HIV-1 incidence in the LEN group (0.000 infections per 100 PY) was demonstrated to be significantly lower than the bHIV incidence (2.407 infections per 100 PY) (H_{01}) with a rate ratio of 0.000 (95% CI of [0.000, 0.042] and one-sided *P* value <0.0001). Furthermore, the HIV-1 incidence in the LEN group was demonstrated to be ≥20% lower than the bHIV incidence (H_{02}) with one-sided *P value* <0.0001.

Table 12. Statistical Comparisons of the HIV-1 Incidence in the LEN Group vs. the bHIV Incidence, Full Analysis Set and All Screened Set, PURPOSE1

HIV Incidence Parameter	SC LEN (N=2134)	bHIV Incidence (N=8094)
Number of diagnoses of HIV-1		
In study	0	—
On randomized study drug	0	—
On open-label oral PrEP	0	—
Off study drug PrEP	0	—
HIV-1 incidence in study		
Person-years of follow-up	1939.35	—
HIV-1 incidence per 100 person-years	0.000	2.407
95% CI	(0.000, 0.190)	(1.815, 3.191)
Rate ratio (SC LEN over bHIV incidence)	0.000	—
95% CI	(0.000, 0.042)	—
One-sided *P* value for rate ratio ≥1 (H_{01})	<0.0001	—
One-sided *P* value for rate ratio ≥0.8 (H_{02})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990).
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals/*P* values for rate ratios versus bHIV incidence are based on a Wald test (Gao et al. 2021) or a likelihood ratio test if there were 0 infections (Shao and Gao 2024).
Person-year is the sum of all participants' total number of years (1 year=365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

Key Secondary Efficacy Results

Even though this is the key secondary efficacy endpoint in the study design, it is the co-primary efficacy endpoint at the efficacy IA, i.e., LEN has to demonstrate superiority over the F/TDF in order for the study to be stopped at the IA.

Table 13 below summarizes the key secondary efficacy results. At the interim analysis, the total PY follow up was 949.38 in the F/TDF group. There were 16 HIV-1 infections in the F/TDF group. The estimated incidence rate was 1.685 infection per 100 PY with a 95% CI of (0.963, 2.737).

The test of the incidence rate difference (H_{05}) was tested according to the sequential testing procedure. The rate difference for the HIV-1 incidence (LEN versus F/TDF) was −1.685 with 95% CI of (−2.737, −0.939) and one-sided P<0.0001.

Statistical hypothesis (H_{06}) was then tested according to the sequential testing procedure. Using the rate ratio method, the estimated rate ratio for the HIV-1 incidence was 0.000 (LEN versus F/TDF) with 95% CI of (0.000, 0.101) and one-sided P<0.0001. LEN was demonstrated to be superior to F/TDF in reducing the risk of acquiring HIV-1 infection.

Table 13. Statistical Comparisons of the HIV-1 Incidences in the LEN vs. F/TDF Groups, Full Analysis Set, PURPOSE 1

HIV Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)
Number of diagnoses of HIV-1		
In study	0	16
On randomized study drug	0	14
On open-label oral PrEP	0	0
Off study drug PrEP	0	2
HIV-1 incidence in study		
Person-years of follow-up	1939.35	949.38
HIV-1 incidence per 100 person-years	0.000	1.685
95% CI	(0.000, 0.190)	(0.963, 2.737)
Rate difference (SC LEN minus F/TDF)	−1.685	—
95% CI	(−2.737, −0.939)	—
One-sided *P* value for rate difference ≥0.8/100 PY (H_{05})	<0.0001	—
Rate ratio (SC LEN over F/TDF)	0.000	—
95% CI	(0.000, 0.101)	—
One-sided *P* value for rate ratio ≥1 (H_{06})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990).
Exact CIs/*P* values for rate differences versus F/TDF are based on a hybrid approach (Li et al. 2011).
Confidence intervals/*P* values for rate ratio versus F/TDF are from a Poisson model or an exact conditional Poisson model if there were 0 infections.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1 or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person-years; SC, subcutaneous; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

6.2.1.4.4. Efficacy Analysis of Subgroups

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic factors and clinical characteristics at baseline. No participant in the LEN group had incident HIV-1 infection. The treatment effect was generally consistent across analyzed subgroups. See Section 16.1 for details.

6.2.2. PURPOSE 2

6.2.2.1. Design, PURPOSE 2

PURPOSE 2 was a Phase 3, double-blinded, multicenter, randomized study to evaluate the efficacy and safety of SC LEN for HIV-1 PrEP in CGM, TGW, TGM, and GNB participants ≥16 years of age who have sex with male partners and are at risk for HIV infection.

Similar to PURPOSE 1, this study was structured in four Phases with structured transitions; starting from the Incidence Phase (Part A), the RBP (Part B), the LEN OLE Phase, and ending with the PK Tail Phase. Multiple interim safety and one formal interim efficacy analyses were planned to be conducted prior to the primary analysis.

In the Incidence Phase, bHIV incidence rate was estimated within the population screened for eligibility using recency assay results from samples that were positive for HIV-1 infection using RITA. Participants determined to be HIV-1 negative and who met eligibility criteria proceeded to the RBP, where they were randomized in a 2:1 ratio to receive either LEN or F/TDF. After the completion of the RBP, participants were offered the opportunity to receive open-label LEN in the LEN OLE Phase, which allows for further long-term efficacy and safety follow-up. Participants who discontinued study drug during the RBP entered the PK Tail Phase, which provides a known efficacious OL regimen to provide HIV prevention for participants during the time when LEN concentrations decline.

6.2.2.2. Eligibility Criteria, PURPOSE 2

Inclusion Criteria for the Incidence Phase

- The ability to comprehend and provide a signed written informed consent, which must be obtained prior to initiation of study procedures. For adolescents, the ability to comprehend and provide a signed assent form, which must be obtained prior to initiation of study procedures. A parent/guardian may provide informed consent for adolescents (in accordance with local laws and regulations).
- CGM, TGW, TGM, and GNB who have receptive anal sex with partners assigned male at birth and are at risk for HIV infection.
- Age ≥16 years at screening. Enrollment of participants aged 16 and 17 years started following the first independent DMC safety meeting, upon notification from Gilead.
- HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months
- Sexually active with ≥1 partner assigned male at birth (condomless anal sex) in the last
- 12 months and one of the following:
  - Condomless anal sex with ≥2 partners in the last 12 weeks
  - Documented history of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks
  - Self-reported use of stimulants with sex in the last 12 weeks
- Willing and able to comply with study procedures

Exclusion Criteria for the Incidence Phase

- Prior use of HIV PrEP (including F/TDF or F/TAF) or HIV postexposure prophylaxis (PEP) in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir)
- Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) are not eligible. Individuals may be eligible if they participated in an HIV vaccine or bNAb study but have documentation that they did not receive active product (e.g., placebo recipients).

Inclusion Criteria for the Randomized Phase

Participants who have a negative fourth generation HIV-1 antibody (Ab)/antigen (Ag) test and meet the criteria from the Incidence Phase can be screened for the Randomized Phase if additional consent is obtained. Participants who meet the following criteria will be included in the Randomized Phase:

- Negative local rapid fourth generation HIV-1/2 Ab/Ag, central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT.
- Estimated glomerular filtration rate (eGFR) ≥60 mL/min at screening according to the Cockcroft-Gault formula for CL_{cr}.
- Body weight ≥35 kg
- Participants of childbearing potential who engage in frontal (vaginal) intercourse must not intend to become pregnant during the study and must agree to utilize protocol-specified method(s) of contraception.

Exclusion Criteria for the Randomized Phase

Participants who meet any of the following exclusion criteria are not eligible to be randomized in the Randomized Phase of this study.

- Participation in any other clinical trial (including observational and COVID-19 vaccine trials) without prior approval from the Applicant is prohibited while participating in this trial. An exception is made for participation in the Applicant-approved ancillary qualitative participant interview study, which is allowed and does not require medical monitor approval.
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient
- Acute viral hepatitis A, B or C or evidence of chronic hepatitis B or C infection
  - If a participant has a negative hepatitis B surface antigen, negative hepatitis B surface antibody, and positive hepatitis B core antibody, HBV DNA testing will be completed. If the HBV DNA result is positive, the participant is a screen failure. Participants found to be susceptible to HBV infection will be offered HBV vaccination.
  - If the HCV Ab result is positive, then HCV RNA will be evaluated. Participants found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.

- Severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (e.g., ascites, encephalopathy, variceal bleeding)
- Have a suspected or known active, serious infection(s) (e.g., active tuberculosis, etc.)
- Need for continued use of any contraindicated concomitant medications
- Have a history of osteoporosis or bone fragility fractures
- Current alcohol or substance abuse judged by the investigator to be problematic such that it potentially interferes with participant study adherence
- Grade 3 or Grade 4 proteinuria or glycosuria at screening that is unexplained or not clinically manageable
- Participants assigned female at birth of childbearing potential who are pregnant or lactating at screening or on Day 1. Participants must have a negative pregnancy test at screening and on Day 1
- Any other clinical or psychosocial condition or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

6.2.2.3. Statistical Analysis Plan, PURPOSE 2

The details of the statistical analysis plan are described in Section 15.2.

6.2.2.3.1. Objectives and Endpoints

Table 14. Primary and Secondary Objectives and Endpoints, PURPOSE 2

Objectives	Endpoints
Study Objectives and Endpoints: The primary objective of this study is to evaluate the efficacy of lenacapavir (LEN) in preventing the risk of HIV-1 infection relative to the background HIV-1 (bHIV) incidence.	
Primary Objectives	
Incidence Phase • To estimate the bHIV incidence Randomized Blinded Phase • To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection	Incidence Phase • Diagnosis of recent HIV-1 infection Randomized Blinded Phase • Diagnosis of HIV-1 infection

Objectives	Endpoints
Secondary Objectives	
Randomized Blinded Phase • To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada; TVD) for HIV-1 PrEP in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV 1 infection • To evaluate the efficacy of LEN for HIV-1 PrEP in participants at risk of HIV-1 infection in participants adherent to LEN. • To evaluate the safety and tolerability of LEN and F/TDF for HIV-1 PrEP in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection • To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥16 to <18 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection	Randomized Blinded Phase • Diagnosis of HIV-1 infection, including among participants while adherent to study drug • Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP

Source: Study synopsis of the CSR of PURPOSE 2.

6.2.2.3.2. Sample Size and Power

A total sample size of 3000 was considered for this study.

More than 95% power would be achieved with 2000 participants in the LEN study drug group to show at least a 20% reduction compared with the bHIV (powered for both H_{01} and H_{02}). In this sample size analysis, the following assumptions were made:

- bHIV of 3.00/100 PY
- LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 incidence compared with the nonrandomized control of bHIV
- MDRI of 173 days, with rSE of 6.5%
- FRR of 1.5%, with rSE of 70%
- Average follow-up of 1.5 years in the study
- 2:1 allocation for LEN: F/TDF
- Alpha level of 0.025 (1-sided)

The bHIV assumption was estimate based on epidemiologic data (Mera et al. 2019). The LEN incidence corresponds to an 80% risk reduction and was consistent with the incidences observed in a large randomized controlled trial of long-acting cabotegravir for PrEP conducted in a similar study population (Landovitz et al. 2021).

The MDRI and FRR were based on the Sedia Lag-EIA (Kassanjee et al. 2016), assuming T =2 years and virologic cutoff of 75 copies/mL. Under the assumption of T =1 year, the power

remains at >95%. The power calculation is based on the formula in (Gao et al. 2021) using the test statistics for rate ratio (Gao et al. 2021).

The statistical power to compare the randomized study drug groups was not assessed.

6.2.2.3.3. Analysis Sets

Please refer to Table 7 for the description of the analysis sets.

6.2.2.3.4. Multiple Alpha-Controlled Hypotheses

There were 4 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed in Table 15. If the RBP continues to the primary analysis, the null hypotheses $H01$, $H02$, $H03$ and $H04$ will be tested sequentially, with the final analysis critical value set to 0.0224 to account for the interim analysis.

Table 15. Testing Sequence of Null Hypotheses, PURPOSE 2

Objectives	Null Hypothesis	Interpretation for Rejecting Null Hypothesis
LEN primary objectives	H_{01}: LEN / bHIV ≥1	HIV-1 incidence in LEN is significantly lower than bHIV
	H_{02}: LEN / bHIV ≥0.8	HIV-1 incidence in LEN is significantly and at least 20% lower than bHIV and the point estimate LEN/bHIV ≤0.5.
LEN secondary objectives	H_{03}: LEN – F/TDF ≥0.8/100PY	in LEN is not substantially greater than F/TDF (LEN efficacy is comparable to F/TDF)
	H_{04}: LEN / F/TDF ≥1	HIV-1 incidence in LEN is significantly lower than F/TDF

Source: Table 3-1 of the SAP of PURPOSE 2.
Abbreviations: bHIV, background HIV-1 incidence; H_0, null hypothesis; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SAP, statistical analysis plan.

6.2.2.3.5. Interim Analyses of Efficacy Data

An external independent multidisciplinary DMC reviewed the progress of the study and performed interim reviews of the data (both interim efficacy and periodic safety) in order to protect participant welfare and preserve study integrity.

The DMC formally evaluated efficacy and futility data, only once, after 50% of participants enrolled have completed Week 52 of the study or prematurely discontinued from the study. The DMC recommended stopping the study early after the prespecified efficacy or futility evaluation criteria were met. Because the RBP stopped early due to an efficacy outcome, the interim analysis served as the primary analysis for this study.

The overall testing procedure for the interim efficacy analysis used a gated sequential testing approach (Table 15) where the type I error level for the interim analysis was set at a one-sided alpha level of α_1=0.0026.

The interim stopping criteria were to demonstrate both superiority of LEN versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and superiority of LEN versus F/TDF, designated H_{04}, at α_1=0.0026. Therefore, the key secondary efficacy endpoint of LEN versus F/TDF was the co-primary efficacy endpoint at the IA for efficacy, and this is slightly different from the pre-specified final primary efficacy analyses. Due to the short follow-up time, we added this more stringent stopping criteria to ensure the superiority of LEN over the active

control before the trial stopped at the IA. The interim analysis served as the primary analysis because the trial met the stated criteria and stopped early.

6.2.2.3.6. Analysis of Efficacy

For the Incidence Phase of this study, the bHIV incidence was reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to (Kassanjee et al. 2012) adjusting for participants with HIV-1 who may not have had recency assay results.

The HIV-1 incidence was reported per 100 PY in the LEN and F/TDF groups while at risk of HIV-1 infection in the study. The HIV-1 incidence rate was estimated by the number of HIV-1 infections in study divided by the total follow-up time in study for each study drug group.

The primary efficacy evaluation was a comparison of the observed HIV-1 incidence rate in the LEN group versus the bHIV incidence rate using the rate ratio metric. The associated 95% CIs and *P* values were estimated using the delta method (Gao et al. 2021).

The difference in HIV-1 incidence rates was used to evaluate the comparability of LEN relative to F/TDF (H_{03}). In order to test this hypothesis, a 95% CI was constructed using a hybrid approach, with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI (Li et al. 2011).

It would be concluded that LEN was comparable to F/TDF if the upper bound of the 95% CI of the incidence rate difference (LEN – F/TDF) was less than 0.8 per 100 PY.

The ratio of HIV-1 incidence rates was used to evaluate the superiority of LEN versus F/TDF.

The incidence rate ratio of the LEN group versus the F/TDF group was calculated. The associated 95% CIs and *P* values were estimated using a generalized Poisson regression.

6.2.2.4. Results of Analyses, PURPOSE 2

6.2.2.4.1. Participant Disposition

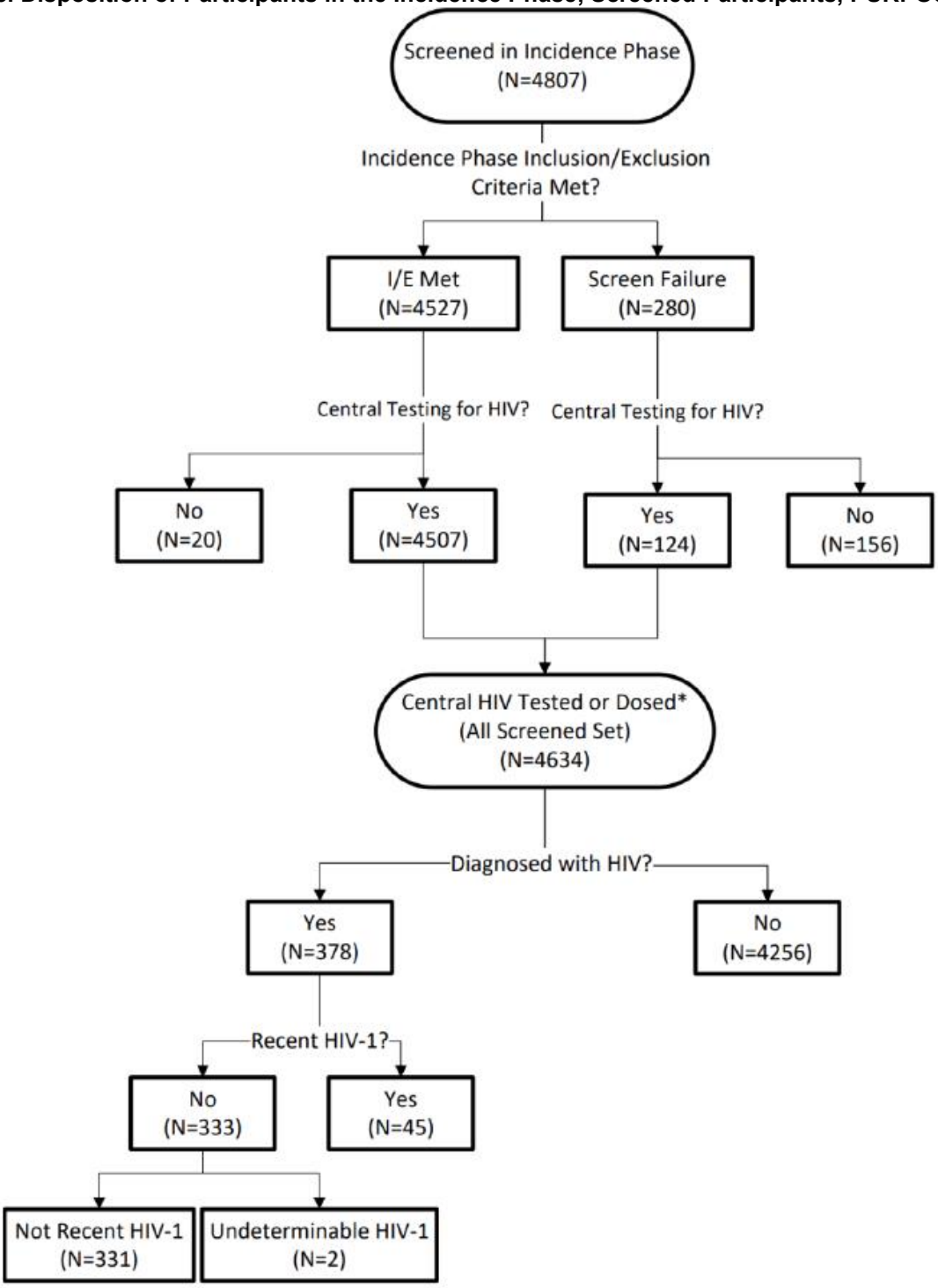
As shown in Figure 5, Overall, 4807 participants were screened in the Incidence Phase and 3868 proceeded to Randomized Blinded Phase screening. A total of 171 participants did not meet Randomized Blinded Phase eligibility criteria and were not randomized, and 10 out of these 181 participants who were not eligible were randomized. Also, there were 405 eligible participants who were not randomized, with the most common reasons cited being outside of visit window (121 participants), study enrollment closed (105 participants), and lost to follow-up (61 participants).

Out of the 4634 screened participants who had at least one non-missing central laboratory HIV test, 378 (8.2%) were diagnosed with HIV and 45 (12.0%) of them were identified as recent HIV-1 infection at the Incidence Phase.

In the randomized blinded Phase, 3868 participants were screened and 3292 were randomized (Figure 6). As shown in Table 16, of the 3271 participants who were randomized and received study drugs, 6 participants were subsequently confirmed to have had baseline HIV-1 infections based on central testing. A total of 532 participants (16.3%) discontinued study drugs in the

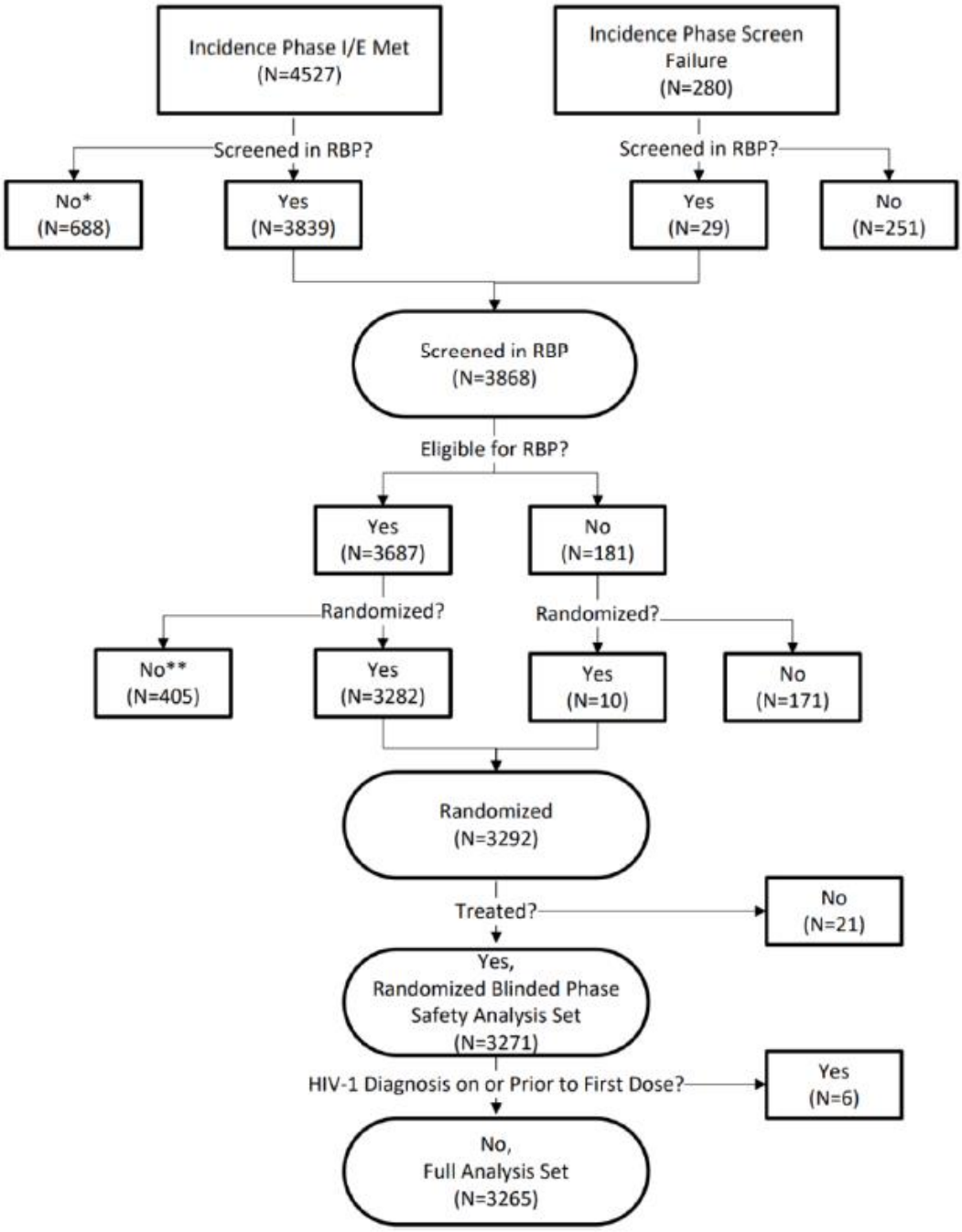
Randomized Blinded Phase. The most common reasons for discontinuation of study drugs were participant decision (9.2%), lost to follow-up (3.6%), and Adverse Events (AEs) (includes ISRs to study SC injection) (1.3%). Among the 301 study drug discontinuations that were investigator-reported as due to participant decision, 98 (LEN 85; F/TDF 13) were related to participant concerns about injection.

Figure 5. Disposition of Participants in the Incidence Phase, Screened Participants, PURPOSE 2



Source: Figure 2 of the CSR.
*Includes 3 participants with central HIV tests performed after initial screening, prior to randomization, and were randomized and dosed in Randomized Blinded Phase.
Abbreviations: CSR, clinical study report; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; I/E, inclusion/exclusion criteria.

Figure 6. Disposition of Participants in the Randomized Blinded Phase, PURPOSE 2



Source: Figure 3 of the CSR
* Reasons not screened in RBP despite meeting Incidence Phase I/E criteria include investigator's discretion (12), lost to follow-up (31), outside of visit window (36), study enrollment closed (12), withdrew consent (18), and other (579, including positive HIV test =348).
** Reasons not randomized despite meeting RBP I/E criteria include investigator's discretion (5), lost to follow-up (61), outside of visit window (121), study enrollment closed (105), withdrew consent (32), screen failed Incidence Phase (15), and other (66).
Abbreviations: CSR, clinical study report; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; I/E, inclusion/exclusion criteria; RBP, Randomized Blinded Phase

Table 16. Participant Disposition, PURPOSE 2

Disposition	SC LEN	F/TDF	Total
Randomized	2195	1097	3292
Randomized and dosed (RBP Safety Analysis Set)	2183	1088	3271
Randomized and dosed with diagnosis of HIV-1 on or prior to first dose (excluding screening HIV-1 diagnosis)	4	2	6
Randomized and dosed with diagnosis of no HIV-1 on or prior to Day 1 (Full Analysis Set)	2179	1086	3265
Continuing study drug in RBP	1819 (83.3%)	920 (84.6%)	2739 (83.7%)
Did not complete the study drug in RBP	364 (16.7%)	168 (15.4%)	532 (16.3%)
Reasons for prematurely discontinuing study drug in RBP			
Adverse event (includes injection site reactions to study SC injection)	32 (1.5%)	10 (0.9%)	42 (1.3%)
Death	4 (0.2%)	2 (0.2%)	6 (0.2%)
Pregnancy	0	0	0
Investigator's discretion	10 (0.5%)	9 (0.8%)	19 (0.6%)
Noncompliance with study drug	9 (0.4%)	6 (0.6%)	15 (0.5%)
Participant never dosed with study drug	0	0	0
Protocol violation	8 (0.4%)	3 (0.3%)	11 (0.3%)
Participant decision	220 (10.1%)	81 (7.4%)	301 (9.2%)
Parent/guardian decision	0	0	0
Lost to follow-up	74 (3.4%)	45 (4.1%)	119 (3.6%)
Study terminated by Applicant	0	0	0
HIV-1 infection	6 (0.3%)	10 (0.9%)	16 (0.5%)
Clinical hold	1 (<0.1%)	2 (0.2%)	3 (<0.1%)
Continuing study in RBP	1826 (83.6%)	926 (85.1%)	2752 (84.1%)
Did not complete the study in RBP	234 (10.7%)	130 (11.9%)	364 (11.1%)
Reasons for prematurely discontinuing from study in RBP			
Adverse event (includes injection site reactions to study SC injection)	5 (0.2%)	2 (0.2%)	7 (0.2%)
Death	4 (0.2%)	2 (0.2%)	6 (0.2%)
Pregnancy	0	0	0
Investigator's discretion	8 (0.4%)	5 (0.5%)	13 (0.4%)
Noncompliance with study drug	8 (0.4%)	5 (0.5%)	13 (0.4%)
Protocol violation	1 (<0.1%)	3 (0.3%)	4 (0.1%)
Withdrew consent	128 (5.9%)	59 (5.4%)	187 (5.7%)
Withdrew assent	1 (<0.1%)	0	1 (<0.1%)
Lost to follow-up	73 (3.3%)	47 (4.3%)	120 (3.7%)
Study terminated by Applicant	0	0	0
HIV-1 infection	6 (0.3%)	7 (0.6%)	13 (0.4%)

Source: Reviewer's analysis using adsl.xpt and Table 5 of the CSR.
Denominators for percentages are the RBP Safety Analysis Set for study drug (or study) status.
Treated participants discontinued the study only once (either in RBP or Open-Label Oral PrEP Analysis); those who discontinued the study in the RBP could not be included in the Open-Label Oral PrEP Analysis.
Data through data cutoff date (August 5, 2024).
Abbreviations: CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; RBP, Randomized Blinded Phase; SC, subcutaneous.

6.2.2.4.2. Demographics and Baseline Characteristics

In the Randomized Blinded Phase, demographics and baseline characteristics were generally similar between study drug groups as shown in Table 17 and Table 18.

As shown in Table 17, the median age was 29 years (range: 17 to 74) and median (Q1, Q3) BMI was 25.1 (22.0, 29.0) kg/m^2. Most participants were aged ≥18 years (99.9%) and 4 participants (0.1%) were aged between 16 and <18 years. The majority of the participants were male (98.0%), and 22.3% of participants were self-identified as gender diverse (476 TGW [14.6%], 199 GNB [6.1%], 43 TGM [1.3%], and 10 were under the "other" category [0.3%]). The majority of participants identified as non-White (67.3%), including 37.7% Black or of Black ancestry and 12.7% Asian participants. The majority of participants were Hispanic or Latino (62.8%).

As shown in Table 18, a high number of participants were diagnosed with an STI at baseline (chlamydia, gonorrhea, or syphilis). The most common diagnosed STIs at baseline were rectal chlamydia (8.3%), pharyngeal gonorrhea (6.4%), and rectal gonorrhea (4.9%). In the past 3 months, the number (median [Q1, Q3]) of sex partners was 5 (3, 10) for both groups, and the majority of participants did not have any sex partners with known HIV (69.9%). The mean (SD) number of condomless receptive anal sex acts in the past 3 months was 7 (29.2).

Table 17. Baseline Demographics and Clinical Characteristics, Randomized Blinded Phase Safety Analysis Set, PURPOSE 2

Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Age (years)			
N	2183	1088	3271
Mean (SD)	30 (8.7)	31 (9.5)	30 (9.0)
Median	28	29	29
Q1, Q3	24, 34	24, 36	24, 35
Min, max	17, 74	17, 73	17, 74
Age categories (years)			
16 to <18	3 (0.1%)	1 (<0.1%)	4 (0.1%)
18 to ≤25	749 (34.3%)	343 (31.5%)	1092 (33.4%)
>25 to <35	912 (41.8%)	423 (38.9%)	1335 (40.8%)
35 to <50	454 (20.8%)	267 (24.5%)	721 (22.0%)
≥50	65 (3.0%)	54 (5.0%)	119 (3.6%)
Sex assigned at birth			
Male	2140 (98.0%)	1064 (97.8%)	3204 (98.0%)
Female	43 (2.0%)	24 (2.2%)	67 (2.0%)
Gender identity			
Cisgender man (CGM)	1697 (77.7%)	846 (77.8%)	2543 (77.7%)
Transgender man (TGM)	29 (1.3%)	14 (1.3%)	43 (1.3%)
Transgender woman (TGW)	315 (14.4%)	161 (14.8%)	476 (14.6%)
Nonbinary	136 (6.2%)	63 (5.8%)	199 (6.1%)
Assigned male at birth	122 (5.6%)	53 (4.9%)	175 (5.4%)
Assigned female at birth	14 (0.6%)	10 (0.9%)	24 (0.7%)
Other	6 (0.3%)	4 (0.4%)	10 (0.3%)
Travesti	3 (0.1%)	3 (0.3%)	6 (0.2%)
Assigned male at birth	3 (0.1%)	3 (0.3%)	6 (0.2%)
Any other	3 (0.1%)	1 (<0.1%)	4 (0.1%)
Assigned male at birth	3 (0.1%)	1 (<0.1%)	4 (0.1%)

Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Sexual orientation			
Straight/heterosexual	148 (6.8%)	66 (6.1%)	214 (6.6%)
Gay	1634 (75.4%)	806 (74.7%)	2440 (75.1%)
Lesbian	2 (<0.1%)	0	2 (<0.1%)
Bisexual	322 (14.9%)	166 (15.4%)	488 (15.0%)
Other	62 (2.9%)	41 (3.8%)	103 (3.2%)
Pansexual	46 (2.1%)	26 (2.4%)	72 (2.2%)
Homosexual	3 (0.1%)	3 (0.3%)	6 (0.2%)
Queer	10 (0.5%)	12 (1.1%)	22 (0.7%)
Any other	3 (0.1%)	0	3 (<0.1%)
Prefer not to disclose	15	9	24
Race			
American Indian or Alaska Native	20 (0.9%)	13 (1.2%)	33 (1.0%)
Asian	269 (12.4%)	144 (13.3%)	413 (12.7%)
Black	584 (26.9%)	301 (27.7%)	885 (27.1%)
Native Hawaiian or Pacific Islander	3 (0.1%)	0	3 (<0.1%)
White	722 (33.2%)	344 (31.7%)	1066 (32.7%)
Hispanic or Latino	592 (27.2%)	278 (25.6%)	870 (26.7%)
Not Hispanic or Latino	130 (6.0%)	66 (6.1%)	196 (6.0%)
Black/White	185 (8.5%)	98 (9.0%)	283 (8.7%)
Black/Asian	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Black/American Indian or Alaska Native	5 (0.2%)	1 (<0.1%)	6 (0.2%)
Black/Native Hawaiian or Pacific Islander	2 (<0.1%)	0	2 (<0.1%)
Asian/White	3 (0.1%)	4 (0.4%)	7 (0.2%)
Asian/Native Hawaiian or Pacific Islander	1 (<0.1%)	0	1 (<0.1%)
White/American Indian or Alaska Native	316 (14.5%)	141 (13.0%)	457 (14.0%)
White/Native Hawaiian or Pacific Islander	1 (<0.1%)	2 (0.2%)	3 (<0.1%)
Multiracial—other	53 (2.4%)	34 (3.1%)	87 (2.7%)
Colored	5 (0.2%)	1 (<0.1%)	6 (0.2%)
Pardo	1 (<0.1%)	3 (0.3%)	4 (0.1%)
Black/Brown	12 (0.6%)	8 (0.7%)	20 (0.6%)
Black/Colored	7 (0.3%)	4 (0.4%)	11 (0.3%)
Black/Pardo	15 (0.7%)	7 (0.6%)	22 (0.7%)
White/Brown	6 (0.3%)	2 (0.2%)	8 (0.2%)
Any other	7 (0.3%)	9 (0.8%)	16 (0.5%)
Not multiracial—other	10 (0.5%)	3 (0.3%)	13 (0.4%)
Unknown	10 (0.5%)	3 (0.3%)	13 (0.4%)
Not permitted	8	2	10
Ethnicity			
Hispanic or Latino	1378 (63.2%)	675 (62.0%)	2053 (62.8%)
Not Hispanic or Latino	804 (36.8%)	413 (38.0%)	1217 (37.2%)
Not reported	1	0	1
Baseline weight (kg)			
N	2183	1088	3271
Mean (SD)	78.4 (19.82)	79.2 (19.58)	78.6 (19.74)
Median	75.3	75.2	75.2
Q1, Q3	64.5, 88.0	65.3, 90.2	64.8, 88.5
Min, max	37.8, 195.4	42.0, 178.7	37.8, 195.4

Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Baseline height (cm)			
N	2183	1088	3271
Mean (SD)	173.1 (7.61)	172.8 (7.66)	173.0 (7.63)
Median	173.0	173.0	173.0
Q1, Q3	168.0, 178.0	167.6, 178.0	168.0, 178.0
Min, max	123.0, 199.0	128.0, 200.7	123.0, 200.7
Baseline body mass index (kg/m^2)			
N	2183	1088	3271
Mean (SD)	26.1 (6.13)	26.4 (5.86)	26.2 (6.04)
Median	25.1	25.2	25.1
Q1, Q3	21.9, 28.9	22.3, 29.3	22.0, 29.0
Min, max	13.7, 89.6	15.6, 67.4	13.7, 89.6
Baseline waist circumference (cm)			
N	2182	1087	3269
Mean (SD)	88.2 (14.92)	89.0 (15.46)	88.5 (15.10)
Median	86.0	86.4	86.0
Q1, Q3	77.5, 96.0	78.0, 97.0	78.0, 96.5
Min, max	58.0, 159.0	60.0, 152.4	58.0, 159.0
Highest education level			
Did not attend primary school	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Some primary school education	11 (0.5%)	11 (1.0%)	22 (0.7%)
Primary school complete	68 (3.1%)	48 (4.4%)	116 (3.5%)
Some secondary school education	260 (11.9%)	114 (10.5%)	374 (11.4%)
Secondary school degree complete	737 (33.8%)	338 (31.1%)	1075 (32.9%)
Some college or university degree	1105 (50.6%)	574 (52.9%)	1679 (51.4%)
Missing	1	2	3
Needs help with completion of electronic questionnaire			
Yes	233 (10.7%)	127 (11.7%)	360 (11.0%)
No	1949 (89.3%)	960 (88.3%)	2909 (89.0%)
Missing	1	1	2

Source: Table 7 of the CSR.
Age (in years) was collected on the first dose date of study drug (Day 1).
"Not permitted" = local regulators or participants did not allow collection of race or ethnicity information. "Not permitted," "prefer not to disclose," or "missing" were excluded for calculation of percentage.
Body mass index (kg/m^2) = (Weight [kg]/Height [cm]^2) × 10,000.
Abbreviations: CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation.

Table 18. Baseline HIV-Risk Characteristics, Randomized Blinded Phase Safety Analysis Set, PURPOSE 2

Risk Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Urethral/urine chlamydia			
Detected	55 (2.6%)	21 (1.9%)	76 (2.4%)
Indeterminate	1 (<0.1%)	0	1 (<0.1%)
Not detected	2099 (97.4%)	1057 (98.1%)	3156 (97.6%)
Missing	28	10	38
Rectal chlamydia			
Detected	177 (8.2%)	92 (8.5%)	269 (8.3%)
Indeterminate	12 (0.6%)	7 (0.6%)	19 (0.6%)
Not detected	1982 (91.3%)	986 (90.9%)	2968 (91.2%)
Missing	12	3	15

Risk Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Pharyngeal chlamydia			
Detected	51 (2.3%)	22 (2.0%)	73 (2.2%)
Indeterminate	2 (<0.1%)	1 (<0.1%)	3 (<0.1%)
Not detected	2125 (97.6%)	1063 (97.9%)	3188 (97.7%)
Missing	5	2	7
Urethral/urine gonorrhea			
Detected	18 (0.8%)	3 (0.3%)	21 (0.6%)
Indeterminate	1 (<0.1%)	0	1 (<0.1%)
Not detected	2136 (99.1%)	1075 (99.7%)	3211 (99.3%)
Missing	28	10	38
Rectal gonorrhea			
Detected	104 (4.8%)	54 (5.0%)	158 (4.9%)
Indeterminate	12 (0.6%)	7 (0.6%)	19 (0.6%)
Not detected	2055 (94.7%)	1024 (94.4%)	3079 (94.6%)
Missing	12	3	15
Pharyngeal gonorrhea			
Detected	129 (5.9%)	81 (7.5%)	210 (6.4%)
Indeterminate	2 (<0.1%)	1 (<0.1%)	3 (<0.1%)
Not detected	2047 (94.0%)	1004 (92.4%)	3051 (93.5%)
Missing	5	2	7
Trichomonas vaginalis (urethral/urine)			
Detected	1 (1.6%)	0	1 (0.9%)
Indeterminate	0	0	0
Not detected	63 (98.4%)	44 (100.0%)	107 (99.1%)
Not tested	2119	1044	3163
Syphilis diagnosis (investigator report)			
Yes	84 (3.8%)	43 (4.0%)	127 (3.9%)
No	2099 (96.2%)	1045 (96.0%)	3144 (96.1%)
Syphilis stage			
N (total number of participants with syphilis)	84	43	127
Primary	2 (2.4%)	0	2 (1.6%)
Early latent	37 (44.0%)	17 (39.5%)	54 (42.5%)
Secondary	8 (9.5%)	4 (9.3%)	12 (9.4%)
Tertiary	0	0	0
Late latent	35 (41.7%)	20 (46.5%)	55 (43.3%)
Other	2 (2.4%)	2 (4.7%)	4 (3.1%)
Sex partners in past 3 months			
N	2043	1016	3059
Mean (SD)	14 (49.8)	16 (63.9)	15 (54.9)
Median	5	5	5
Q1, Q3	3, 10	3, 10	3, 10
Min, max	0, 900	0, 999	0, 999
Sex partners in past 3 months			
0	40 (2.0%)	24 (2.4%)	64 (2.1%)
1	120 (5.9%)	58 (5.7%)	178 (5.8%)
2	258 (12.6%)	142 (14.0%)	400 (13.1%)
3	312 (15.3%)	147 (14.5%)	459 (15.0%)
4 to 5	392 (19.2%)	190 (18.7%)	582 (19.0%)
6 to 10	436 (21.3%)	221 (21.8%)	657 (21.5%)
≥11	485 (23.7%)	234 (23.0%)	719 (23.5%)
Prefer not to answer	53	31	84
Missing	87	41	128

Risk Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Sex partners with HIV in past 3 months			
N	1019	522	1541
Mean (SD)	1 (7.5)	2 (24.4)	1 (15.4)
Median	0	0	0
Q1, Q3	0, 1	0, 1	0, 1
Min, max	0, 213	0, 545	0, 545
Sex partners with HIV in past 3 months			
0	710 (69.7%)	367 (70.3%)	1077 (69.9%)
1	194 (19.0%)	92 (17.6%)	286 (18.6%)
2	55 (5.4%)	25 (4.8%)	80 (5.2%)
3	33 (3.2%)	13 (2.5%)	46 (3.0%)
4 to 5	12 (1.2%)	12 (2.3%)	24 (1.6%)
6 to 10	10 (1.0%)	9 (1.7%)	19 (1.2%)
≥11	5 (0.5%)	4 (0.8%)	9 (0.6%)
Prefer not to answer	71	37	108
I don’t know	1006	487	1493
Missing	87	42	129
Condomless receptive anal sex acts in past 3 months			
N	2002	983	2985
Mean (SD)	7 (32.0)	6 (22.4)	7 (29.2)
Median	2	2	2
Q1, Q3	1, 5	1, 5	1, 5
Min, max	0, 800	0, 444	0, 800
Condomless receptive anal sex acts in past 3 months			
0	442 (22.1%)	214 (21.8%)	656 (22.0%)
1	303 (15.1%)	168 (17.1%)	471 (15.8%)
2	330 (16.5%)	151 (15.4%)	481 (16.1%)
3	231 (11.5%)	110 (11.2%)	341 (11.4%)
4 to 5	218 (10.9%)	123 (12.5%)	341 (11.4%)
6 to 10	262 (13.1%)	123 (12.5%)	385 (12.9%)
≥11	216 (10.8%)	94 (9.6%)	310 (10.4%)
Prefer not to answer	91	62	153
Missing	90	43	133
Taken drugs before or during sex (chemsex) in past 3 months			
Yes	549 (26.4%)	286 (27.6%)	835 (26.8%)
No	1530 (73.6%)	750 (72.4%)	2280 (73.2%)
Prefer not to answer	17	11	28
Missing	87	41	128
Frequency of alcohol use in past 3 months			
Never	179 (8.6%)	123 (11.8%)	302 (9.7%)
Monthly or less	641 (30.7%)	295 (28.4%)	936 (30.0%)
2 to 4 times a month	844 (40.5%)	406 (39.0%)	1250 (40.0%)
2 to 3 times a week	333 (16.0%)	172 (16.5%)	505 (16.2%)
4 or more times a week	88 (4.2%)	44 (4.2%)	132 (4.2%)
Prefer not to answer	11	7	18
Missing	87	41	128

Risk Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Six or more drinks on one occasion in past 12 weeks			
Never	586 (28.3%)	274 (26.4%)	860 (27.6%)
Less than monthly	647 (31.2%)	309 (29.8%)	956 (30.7%)
Monthly	456 (22.0%)	251 (24.2%)	707 (22.7%)
Weekly	346 (16.7%)	180 (17.4%)	526 (16.9%)
Daily or almost daily	39 (1.9%)	23 (2.2%)	62 (2.0%)
Prefer not to answer	22	10	32
Missing	87	41	128
Alcohol before or during sex in past 12 weeks			
Yes	1155 (55.5%)	584 (56.5%)	1739 (55.8%)
No	927 (44.5%)	450 (43.5%)	1377 (44.2%)
Prefer not to answer	14	13	27
Missing	87	41	128
Take drugs before or during sex (chemsex) in past 3 months			
Yes	549 (26.4%)	286 (27.6%)	835 (26.8%)
No	1530 (73.6%)	750 (72.4%)	2280 (73.2%)
Prefer not to answer	17	11	28
Missing	87	41	128
Smoked cigarettes in the past 3 months (and if yes, number per day)			
Yes	833 (39.9%)	432 (41.5%)	1265 (40.4%)
Less than 10 cigarettes per day	639 (30.6%)	341 (32.8%)	980 (31.3%)
Between 10 and 20 cigarettes per day	127 (6.1%)	62 (6.0%)	189 (6.0%)
More than 20 cigarettes per day	32 (1.5%)	17 (1.6%)	49 (1.6%)
Prefer not to answer	35 (1.7%)	12 (1.2%)	47 (1.5%)
No	1257 (60.1%)	609 (58.5%)	1866 (59.6%)
Prefer not to answer	6	6	12
Missing	87	41	128
Any substance use in past 12 weeks			
Yes	1153 (55.9%)	593 (57.7%)	1746 (56.5%)
No	910 (44.1%)	435 (42.3%)	1345 (43.5%)
Prefer not to answer	33	19	52
Missing	87	41	128
Cannabis use in past 12 weeks			
Yes	886 (42.8%)	448 (43.6%)	1334 (43.1%)
No	1182 (57.2%)	580 (56.4%)	1762 (56.9%)
Prefer not to answer	28	19	47
Missing	87	41	128
Cocaine use in past 12 weeks			
Yes	280 (13.6%)	158 (15.3%)	438 (14.1%)
No	1785 (86.4%)	874 (84.7%)	2659 (85.9%)
Prefer not to answer	31	15	46
Missing	87	41	128
Amphetamine-type stimulants use in past 12 weeks			
Yes	242 (11.7%)	115 (11.2%)	357 (11.5%)
No	1826 (88.3%)	914 (88.8%)	2740 (88.5%)
Prefer not to answer	28	18	46
Missing	87	41	128

Risk Characteristic	SC LEN (N=2183)	F/TDF (N=1088)	Total (N=3271)
Inhalants use in past 12 weeks			
Yes	166 (8.0%)	85 (8.2%)	251 (8.1%)
No	1917 (92.0%)	950 (91.8%)	2867 (91.9%)
Prefer not to answer	13	12	25
Missing	87	41	128
Sedatives or sleeping pills use in past 12 weeks			
Yes	168 (8.1%)	83 (8.0%)	251 (8.1%)
No	1913 (91.9%)	951 (92.0%)	2864 (91.9%)
Prefer not to answer	15	13	28
Missing	87	41	128
Hallucinogens use in past 12 weeks			
Yes	257 (12.4%)	116 (11.2%)	373 (12.0%)
No	1822 (87.6%)	919 (88.8%)	2741 (88.0%)
Prefer not to answer	17	12	29
Missing	87	41	128
Opioids use in past 12 weeks			
Yes	33 (1.6%)	14 (1.4%)	47 (1.5%)
No	2053 (98.4%)	1022 (98.6%)	3075 (98.5%)
Prefer not to answer	10	11	21
Missing	87	41	128
Prescription drugs for nonprescription purpose use in past 12 weeks			
Yes	294 (14.1%)	135 (13.0%)	429 (13.8%)
No	1788 (85.9%)	900 (87.0%)	2688 (86.2%)
Prefer not to answer	14	12	26
Missing	87	41	128

Source: Reviewer's analysis using adsl.xpt and Table 8 of the CSR.
"Missing," "not tested," "I don't know," and "prefer not to answer" (except within a dynamic subquestion) were excluded from the percentage calculation.
Laboratory results based on central laboratory or local laboratories for gonorrhea, chlamydia, and trichomonas vaginalis, and local laboratories only for syphilis.
Responses for condomless sex acts or sex partners with HIV are imputed with 0 (or "prefer not to answer") when responses for sex acts or sex partners are 0 (or "prefer not to answer").
Not Tested = Trichomonas vaginalis laboratory collection not required; protocol only recommended collection at the investigator's discretion for participants assigned female at birth. Actual collection of trichomonas vaginalis laboratories occurred occasionally for participants assigned male at birth.
Abbreviations: CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; LEN, lenacapavir; Q1, first quartile; Q3, third quartile; SC, subcutaneous; SD, standard deviation.

6.2.2.4.3. Primary and Key Secondary Efficacy Results

The Applicant's primary and key secondary efficacy results were confirmed by the statistical review team. The determination of efficacy was based on planned interim analyses (which became the final analyses) following sequential testing of HIV-1 incidence for the LEN group compared to background followed by the LEN group compared to the F/TDF group, all at alpha level of 0.0026 when 50% of planned randomized participants completed at least 52 weeks of follow-up or prematurely discontinued from the study.

Primary Efficacy Results

Table 19 below summarizes the primary efficacy results. As shown in Figure 5, out of the 4634 screened participants who had at least one non-missing central laboratory HIV test, 378 (8.2%) were diagnosed with HIV-1 and 45 (12.0%) of them were identified as recent HIV-1 infection at

the Incidence Phase. The background HIV-1 (bHIV) incidence rate was estimated to be 2.374 infections per 100 PY with a 95% CI of (1.649, 3.417).

At the interim analysis, the total PY follow up was 1938.07 in the LEN group. There were 2 HIV-1 infections in the LEN group. The estimated incidence rate was 0.103 infection per 100 PY with a 95% CI of (0.012, 0.373).

The comparison of the incidence rates between the LEN group and the background was conducted using the rate ratio method based on the methods in (Gao et al. 2021). The HIV-1 incidence in the LEN group (0.103 infections per 100 PY) was demonstrated to be significantly lower than the bHIV incidence (H_{01}) with a rate ratio of 0.043 (95% CI of [0.010, 0.182] and one-sided *P* value <0.0001). Furthermore, the HIV-1 incidence in the LEN group was demonstrated to be ≥20% lower than the bHIV incidence (H_{02}) with one-sided *P* value <0.0001.

Table 19. Statistical Comparisons of the HIV-1 Incidence in the LEN Group vs. the bHIV Incidence, Full Analysis Set and All Screened Set, PURPOSE 2

Incidence Parameter	SC LEN (N=2179)	bHIV Incidence (N=4634)
Number of diagnoses of HIV-1		
In study	2	—
On randomized study drug	2	—
On open-label oral PrEP	0	—
Off study drug PrEP	0	—
HIV-1 incidence in study		
Person-years of follow-up	1938.07	—
HIV-1 incidence per 100 person-years	0.103	2.374
95% CI	(0.012, 0.373)	(1.649, 3.417)
Rate ratio (SC LEN over bHIV incidence)	0.043	—
95% CI	(0.010, 0.182)	—
One-sided *P* value for rate ratio ≥1 (H_{01})	<0.0001	—
One-sided *P* value for rate ratio ≥0.8 (H_{02})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CI for HIV-1 incidence in the randomized study drug group is based on a method appropriate for single Poisson rates (Ulm 1990).
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals/*P* values for rate ratios versus bHIV incidence used the delta method (Gao et al. 2021).
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

Key Secondary Efficacy Results

Even though this is the key secondary efficacy endpoint in the study design, it is the co-primary efficacy endpoint at the efficacy IA, i.e., LEN has to demonstrate superiority over the F/TDF in order the study to be stopped at IA.

Table 20 below summarizes the key secondary efficacy results. At the interim analysis, the total PY follow up was 966.54 in the F/TDF group. There were 9 HIV-1 infections in the F/TDF group. The estimated incidence rate was 0.931 infection per 100 PY with a 95% CI of (0.426, 1.768).

The test of the incidence rate difference (H_{03}) was tested according to the sequential testing procedure. The rate difference for the HIV-1 incidence (LEN versus F/TDF) was −0.828 with 95% CI of (−1.669, −0.255) and one-sided P<0.0001.

Statistical hypothesis (H_{04}) was then tested according to the sequential testing procedure. Using the rate ratio method, the estimated rate ratio for the HIV-1 incidence was 0.111 (LEN versus F/TDF) with 95% CI of (0.024, 0.513) and one-sided P =0.00245 which is right below the pre-specified α_1=0.0026. Thus, LEN was demonstrated to be superior to F/TDF in reducing the risk of acquiring HIV-1 infection.

Table 20. Statistical Comparisons of the HIV-1 Incidences in the LEN vs. F/TDF Groups, Full Analysis Set, PURPOSE 2

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)
Number of diagnosis of HIV-1		
In study	2	9
On randomized study drug	2	6
On open-label oral PrEP	0	0
Off study drug PrEP	0	3
HIV-1 incidence in study		
Person-years of follow-up	1938.07	966.54
HIV-1 incidence per 100 person-years	0.103	0.931
95% CI	(0.012, 0.373)	(0.426, 1.768)
Rate difference (SC LEN minus F/TDF)	−0.828	—
95% CI	(−1.669, −0.255)	—
One-sided *P* value for rate difference ≥0.8/100 PY (H_{03})	<0.0001	—
Rate ratio (SC LEN over F/TDF)	0.111	—
95% CI	(0.024, 0.513)	—
One-sided *P* value for rate ratio ≥1 (H_{04})	0.00245	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CI for HIV-1 incidence in the randomized study drug group is based on a method appropriate for single Poisson rates (Ulm 1990).
Exact CI/*P* value for rate difference versus F/TDF are based on a hybrid approach (Li et al. 2011). Confidence interval/*P* value for rate ratio versus F/TDF are from a Poisson model.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person-years; SC, subcutaneous.

6.2.2.4.4. Efficacy Analysis of Subgroups

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic factors and clinical characteristics at baseline. The subgroups analyses by age groups, race, gender, ethnicity, country, level of education were conducted. The treatment effect was consistent across subgroups. See Section 16.2 for details.

6.3. Key Efficacy Review Issues

6.3.1. Reliability of the Background HIV-1 Incidence Rate Estimated by RITA for the Primary Endpoint

Issue

The primary efficacy evaluation for both pivotal trials was the comparison of the observed HIV-1 incidence rate in the LEN group versus the counterfactual bHIV incidence rate estimated during the Incidence Phase using a recency assay with the RITA. Comparison to the counterfactual bHIV incidence rate is a novel efficacy approach that has not previously been utilized to support a marketing application for an HIV-1 PrEP indication. In both pivotal trials, LEN demonstrated superiority in reducing the risk of incident HIV-1 infection compared to both the bHIV incidence rate and the active comparator F/TDF (the co-primary efficacy endpoint at the interim analysis and a more traditional efficacy approach for HIV-1 PrEP trials). Therefore, the efficacy of LEN is not in question. However, whether the methodology utilized to estimate the bHIV incidence rate in PURPOSE 1 and PURPOSE 2 was reliable enough to support an efficacy claim based on the primary efficacy evaluation alone is unclear.

Background

Because of the large sample size required for a fully powered active-controlled superiority or non-inferiority study, and due to concern that that the required sample size may balloon further with the increasing availability of highly effective HIV-1 PrEP options, Sponsors have been searching for alternative study designs to develop products for the HIV-1 PrEP indication. In PURPOSE 1 and PURPOSE 2, the Applicant proposed to compare the observed HIV-1 incidence in the LEN group to the bHIV incidence rate as the primary efficacy evaluation along with the key secondary efficacy endpoint of LEN compared to an active control (F/TDF). The bHIV incidence rate would be estimated from the Incidence Phase based on a RITA using an incidence estimator similar to (Kassanjee et al. 2012). The sample size calculations were based on this approach.

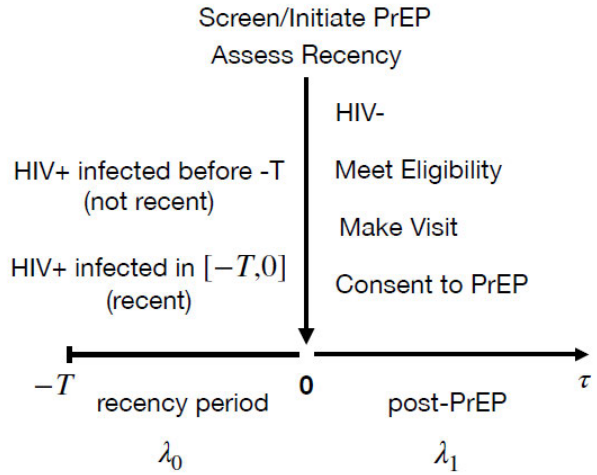
The reliability of this method to estimate the bHIV incidence rate was unknown when the trials were designed, and there are important but different concerns if this method either overestimates or underestimates the true rate. If the bHIV incidence is overestimated, then a finding of superiority in reducing the risk of incident HIV-1 infection for LEN compared to the estimated bHIV incidence rate may not be clinically meaningful. In that case, LEN could have no efficacy and still have a lower incident HIV-1 infection rate compared to an overestimated bHIV incidence rate. To address that concern, the Applicant utilized other methods to estimate the bHIV incidence rate to demonstrate consistency in the estimate. Alternatively, if this method underestimates the bHIV incidence rate, it would be challenging for even an efficacious product to demonstrate superiority over bHIV in the trials. Given that concern, the Applicant communicated in their statistical analysis plan that if the point estimate of the RITA-based counterfactual bHIV was less than 1.5/100 PY, the estimate of bHIV by this methodology would be deemed as not performing as expected, referred to as RITA malperformance. The statistical analysis plans of both trials stated that in the case of RITA malperformance, hypotheses H_{01} and

H_{02} comparing LEN to bHIV would be skipped (no gating or alpha adjustment) at the interim efficacy analysis for testing the hypotheses comparing LEN to F/TDF.

In our review, we strove to evaluate the following concerns regarding the comparison of the observed HIV-1 incidence in the LEN group during the RBP to the estimated bHIV using RITA during the Incidence Phase:

- The populations for the evaluations of the bHIV incidence rate and the observed HIV-1 incidence rate in the LEN group may be different. The bHIV incidence rate was estimated from all screened participants. In contrast, the HIV-1 incidence rate in the LEN group was estimated based on the full analysis set (FAS). Figure 7 below shows the study design. All screened participants were tested at time 0 for HIV infection status and for recency status over the period T. The bHIV incidence rate was estimated based on the information collected for these two tests. Participants who tested HIV negative, met the eligibility, and signed the consent form were randomized to the RBP and received assigned treatment. These two populations could have potential differences because the FAS may not be a random subset of the All Screened Set. This is a typical concern when using an external control for an efficacy assessment and is discussed in the FDA draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023).

Figure 7. Study Design With Recency Test at Screening



Source: Figure 3 (Gao et al. 2021).
Abbreviations: PrEP, pre-exposure prophylaxis.

- **The estimation of bHIV incidence rate may not be accurate.** In both studies, the bHIV incidence rate was reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to (Kassanjee et al. 2012) adjusting for participants with HIV-1 who may not have had recency assay results. We have concerns regarding the estimate of the bHIV incidence rate because of the following reasons:
  - For the bHIV estimation, the assay parameters (MDRI and FRR) for each HIV subtype given by (Kassanjee et al. 2016) were used. However, the parameters from different sources and by different post-infection time cutoffs, T, were not the same. The choice of the source and cutoff would affect the estimation of the bHIV incidence rate.

Additionally, we have constancy concerns regarding the applicability of the previously derived estimated parameters to current and future trials. In (Kassanjee et al. 2016), RITAs were assessed using a selected subset of 2500 plasma specimens, termed the 'Evaluation Panel'. In this panel, each of 928 patients contributed 1 to 13 specimens drawn at different times after infection, and patients were from the USA (52%), Zambia (20%), Rwanda (11%), Uganda (8%), Brazil (3%), South Africa (3%), and Kenya (3%). We are concerned about the accuracy of the estimations of MDRI and FRR for each subtype due to the relatively small sample size of the specimens. Both PURPOSE studies started in 2021 and the RBPs ended in 2024. It's questionable whether the derived parameters in (Kassanjee et al. 2016) are still applicable to the data collected in PURPOSE studies.

- Two parameters, MDRI and FRR, were used in the estimation of bHIV incidence. They were estimated based on estimated proportions of the HIV-1 subtypes, not the actual subtypes. Ideally, the estimations of MDRI and FRR should be based on the actual HIV-1 infection subtype of each participant with HIV-1 infection. However, because the subtype data were not available for PURPOSE studies, the Applicant used country, as a correlate, to estimate the percentage of each HIV-1 subtype instead. They estimated the subtype proportions for each county based on a literature review for the geographical distribution of the study sites. The final MDRI and FRR values were estimated as the weighted average of MDRIs and FRRs for the estimated subtypes in each study. Therefore, these two important parameters were estimated based on estimated proportions of the HIV-1 subtypes, not the actual subtypes.
- Notably, the report published by amfAR's Public Office (amfAR 2022), listed several limitations, such as poor sensitivity/specificity, concerns of inter-reliability of recency testing, bias of estimate in unpredictable ways, etc. As a result, the report stated that the recency assay cannot be used as a tool to derive data suitable to meet their programming goals.

In addition to evaluating the above concerns with the methodology, we reviewed alternative methods to estimate the bHIV incidence rate using the PURPOSE 1 and PURPOSE 2 data or historical data. Each of the alternative methods has multiple uncertainties and limitations. However, if these alternative bHIV incidence rate estimates were consistent with the RITA estimation of the bHIV incidence rate used for the primary efficacy analysis, this would provide some reassurance for the reliability of the estimate (with the caveat that consistency of the alternative incidence estimates does not necessarily mean the estimate is accurate as all the estimates could be biased in the same direction). Alternatively, if these alternative bHIV incidence rate estimates were not consistent but were also not lower than the RITA estimate, this would provide some reassurance that the methodology used for the primary efficacy analysis did not overestimate the bHIV incidence rate.

Assessment

Differences in the Populations for the Evaluations of the bHIV Incidence Rate and the Observed HIV-1 Incidence Rate in the LEN Group

We investigated the available data to assess comparability by comparing the available baseline demographics and characteristics between the participants who tested HIV-1 positive or negative

at screening. The results are shown in Table 21 and Table 22. In PURPOSE 1 and PURPOSE 2, the percentage of participants who had a higher education level was relatively higher in the HIV-1 negative group, compared to that in the HIV-1 positive group. In PURPOSE 1, there were more people from South Africa than Uganda in the HIV-1 negative group, compared to the HIV-1 positive group. In PURPOSE 2, the percentage of Black or African American and Not Hispanic or Latino was relatively higher in the HIV-1 positive group compared to the HIV-1 negative group. Additionally, more people from South Africa than other countries were in the HIV-1 positive group.

Due to the limited data collected and the amount of the missing data at the screening stage, fully assessing the differences in baseline demographics and characteristics between the two groups was challenging.

We revisited the efficacy result in the subgroup analyses to investigate whether the same trend holds for those participants who were tested HIV-1 negative at the screening stage and randomized to treatment. Because of the small number of infections in the LEN group, we focused on the F/TDF group. The results are shown in Table 23 and Table 24. It appears that in PURPOSE 1, the education level has no obvious relationship to the incidence rate for participants received F/TDF. However, in PURPOSE 2, the trend still holds for education level, race, and ethnicity for participants who were treated with F/TDF.

Table 21. Baseline Demographics and Clinical Characteristics by Background HIV-1 Diagnosis, All Screened Set, PURPOSE 1

Characteristic		No HIV-1 Infection at Screening (N=7590)	HIV-1 Infection at Screening (N=504)	Diagnosis of HIV-1 [N+/N]
Age group	16 to <18	151 (1.99)	3 (0.60)	3/154 (1.9%)
	≥18	7439 (98.01)	501 (99.40)	501/7940 (6.3%)
Country	South Africa	6092 (80.26)	267 (52.98)	267/6359 (4.2%)
	Uganda	1498 (19.74)	237 (47.02)	237/1735 (13.7%)
Screening education level	<Some secondary school education	980 (12.91)	153 (30.36)	153/1133 (13.5%)
	Some secondary school education or higher	6094 (80.29)	169 (33.53)	169/6263 (2.7%)
	Missing	516 (6.80)	182 (36.11)	182/698 (26.1)
Modified VOICE risk score	<5	631 (8.31)	41 (8.13)	41/672 (6.1%)
	≥5	6260 (82.48)	280 (55.56)	280/6540 (4.3%)

Source: Reviewer's analysis using adsl.xpt.
Note: Some variables were not included due to large amount of missing data.
Abbreviation: HIV, human immunodeficiency virus; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

Table 22. Baseline Demographics and Clinical Characteristics by Background HIV-1 Diagnosis, All Screened Set, PURPOSE 2

Characteristic		No HIV-1 Infection at Screening (N=4256)	HIV-1 Infection at Screening (N=378)	Diagnosis of HIV-1 [N+/N]
Age group	16 to ≤25	1433 (33.67)	131 (34.66)	131/1564 (8.4%)
	>25 to <35	1685 (39.59)	167 (44.18)	167/1852 (9.0%)
	≥35	1138 (26.74)	80 (21.16)	80/1218 (6.6%))

Characteristic		No HIV-1 Infection at Screening (N=4256)	HIV-1 Infection at Screening (N=378)	Diagnosis of HIV-1 [N+/N]
Sex	Female	80 (1.88)	2 (0.53)	2/82 (2.4%)
	Male	4176 (98.12)	376 (99.47)	376/4552 (8.3%)
Race	Any black	1727 (40.58)	264 (69.84)	264/1991 (13.3%)
	Nonblack	2517 (59.14)	113 (29.89)	113/2630 (4.3%)
	Not permitted	12 (0.28)	1 (0.26)	1/13 (7.7%)
Gender identity	Cisgender man (CGM)	3302 (77.58)	283 (74.87)	283/3585 (7.9%)
	Gender nonbinary	235 (5.52)	17 (4.50)	17/252 (6.7%)
	Other, specify	12 (0.28)	1 (0.26)	1/13 (7.7%)
	Transgender man (TGM)	53 (1.25)	0 (0.00)	0
	Transgender woman (TGW)	654 (15.37)	77 (20.37)	77/731 (10.5%)
Sexual orientation	Bisexual	656 (15.41)	34 (8.99)	34/690 (4.9%)
	Gay	3090 (72.60)	298 (78.84)	298/3388 (8.8%)
	Lesbian	3 (0.07)	0 (0.00)	0
	Other, specify	143 (3.36)	6 (1.59)	6/149 (4.0%))
	Prefer not to disclose	35 (0.82)	3 (0.79)	3/38 (7.9%)
	Straight/heterosexual	329 (7.73)	37 (9.79)	37/366 (10.1%)
Ethnicity	Hispanic or Latino	2653 (62.34)	169 (44.71)	169/2822 (6.0%)
	Not Hispanic or Latino	1602 (37.64)	209 (55.29)	209/1811 (11.5%)
	Not permitted	1 (0.02)	0 (0.00)	0
Screening education level	< Some college or university degree	2066 (48.54)	191 (50.53)	191/2257 (8.5%)
	Some college or university degree	2076 (48.78)	92 (24.34)	92/2168 (4.2%)
	Missing	114 (2.68)	95 (25.13)	95/209 (45.5%)
Country	South Africa	521 (12.24)	164 (43.39)	164/685 (23.9%)
	Mexico	25 (0.59)	0	0
	United State	905 (11.01)	22 (5.82)	22/927 (2.4%)
	Peru	558 (13.11)	36 (9.52)	36/594 (6.1%)
	Thailand	458 (10.76)	28 (7.41)	28/486 (5.8%)
	Argentina	277 (6.51)	7 (1.85)	7/284 (2.5%)
	Brazil	1512 (35.53)	121 (32.01)	121/1633 (7.4%)
Body mass index (kg/m^2)	<25	1889 (44.38)	12 (3.17)	12/1901 (0.6%)
	>=25	1955 (45.94)	6 (1.59)	6/1961 (0.3%)
Any history of rectal gonorrhea, rectal chlamydia, or syphilis STI in the past 24 weeks	No	3727 (87.57)	337 (89.15)	337/4064 (8.3%)
	Yes	529 (12.43)	41 (10.85)	41/570 (7.2%)
Condomless receptive anal sex (CRAS) acts in the past 3 months prior to baseline	<=3	1901 (44.67)	7 (1.85)	7/1908 (0.4%)
	>3	1211 (28.45)	13 (3.44)	13/1224 (1.1%)
Taken drug before or during sex in past 12 weeks prior to baseline	Yes	961 (22.58)	4 (1.06)	4/965 (0.4%)
	No	2649 (62.24)	24 (6.35)	24/2673 (0.9%)
Used a needle to inject drugs in past 12 weeks	Yes	40 (0.94)	0	0
	No	3590 (84.35)	28 (7.41)	28/3618 (0.8%)

Characteristic		No HIV-1 Infection at Screening (N=4256)	HIV-1 Infection at Screening (N=378)	Diagnosis of HIV-1 [N+/N]
Six or more drinks on one occasion	Yes	2602 (61.13)	24 (6.35)	24/2626 (0.9%)
	Never	1001 (23.52)	4 (1.06)	4/1005 (0.4%)
Alcohol before or during sex in past 12 weeks	Yes	1994 (46.85)	14 (3.70)	14/2008 (0.7%)
	No	1615 (37.95)	14 (3.70)	14/1629 (0.9%)

Source: Reviewer's analysis using adsl.xpt.
Note: Some variables were not included due to large amount of missing data.
Abbreviation: STI, sexually transmitted infection.

Table 23. Efficacy Result by Highest Level of Education, Full Analysis Set, PURPOSE 1

Efficacy Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Highest level of education: < some secondary school education			
N	250	108	1133
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	236.83	105.00	
HIV-1 incidence per 100 person-years (95% CI)	0.000 (0.000, 1.558)	1.905 (0.231, 6.880)	3.520 (1.960, 6.322)
Highest level of education: some secondary school education or higher			
N	1882	959	6263
Number of HIV-1 diagnoses in study	0	14	
Person-years of follow-up	1700.96	842.88	
HIV-1 incidence per 100 person-years (95% CI)	0.000 (0.000, 0.217)	1.661 (0.908, 2.787)	1.262 (0.866, 1.841)

Source: Table 15.9.1.4.1 of the CSR
Abbreviations: bHIV, background HIV-1; CI, confidence interval; CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SC, subcutaneous.

Table 24. Efficacy Result by Highest Level of Education and Race, Full Analysis Set, PURPOSE 2

Efficacy Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Highest level of education: < Some College or University Degree			
N	1074	510	2257
Number of HIV-1 diagnoses in study	2	7	
Person-years of follow-up	931.75	448.05	
HIV-1 incidence per 100 person-years (95% CI)	0.215 (0.026 0.775)	1.562 (0.628, 3.219)	1.810 (1.003, 3.269)
Highest level of education: Some College or University Degree			
N	1104	574	2168
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	1006.24	517.30	
HIV-1 incidence per 100 person-years (95% CI)	0.000 (0.000,0.367)	0.387 (0.047,1.397)	1.927 (1.134,3.273)
Race: Black			
N	816	425	1991
Number of HIV-1 diagnoses in study	2	6	
Person-years of follow-up	802.10	405.46	
HIV-1 incidence per 100 person-years (95% CI)	0.249 (0.030, 0.901)	1.480 (0.543, 3.221)	3.254 (2.004, 5.285)

Efficacy Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Race: Non-Black			
N	1355	659	2630
Number of HIV-1 diagnoses in study	0	3	
Person-years of follow-up	1129.30	558.61	
HIV-1 incidence per 100 person-years (95% CI)	0.000 (0.000, 0.327)	0.537 (0.111, 1.569)	1.784 (1.066, 2.986)
Ethnicity: Hispanic			
N	1376	673	2822
Number of HIV-1 diagnoses in study	0	3	
Person-years of follow-up	1184.24	583.35	
HIV-1 incidence per 100 person-years (95% CI)	0.000 (0.000, 0.311)	0.514 (0.106, 1.503)	1.908 (1.106, 3.290)
Ethnicity: Non-Hispanic			
N	802	413	1811
Number of HIV-1 diagnoses in study	2	6	
Person-years of follow-up	752.83	383.20	
HIV-1 incidence per 100 person-years (95% CI)	0.266 (0.032, 0.960)	1.566 (0.575, 3.408)	3.184 (1.971, 5.143)

Source: Table 15.9.1.4.1 of the CSR.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SC, subcutaneous.

Effect on the Estimation of bHIV Incidence by Applying Different Sources and Cutoff on MDRI and FRR

For the primary analysis, the assay parameters given by (Kassanjee et al. 2016) were used for bHIV estimation. Table 25 lists the assay parameters and their rSEs for T =2 years (based on the RITA cutoffs pre-specified in the protocol). The assay parameters depend on the choice of the cutoff T, an explicit cutoff between true-recent and false-recent results. Additionally, alternative assay parameters for the Sedia LAg-EIA have been proposed recently by RAWG (Parkin et al.).

The Applicant conducted sensitivity analyses by using a shorter cutoff (T =1 year) and the alternative assay parameters proposed by Parkin. Table 26 and Table 27 listed the parameters of these two methods. Using these three methods, the estimate of bHIV incidence ranges from 2.025 to 2.407 (19% increase) for PURPOSE 1 and 1.894 to 2.374 (25% increase) for PURPOSE 2 as shown in Table 28.

Table 25. MDRI and FRR ((Kassanjee et al. 2016), 2016, T = 2 Years)[a]

	MDRI		FRR[b]	
Subtype	Days	rSE (%)	%	rSE (%)
A	170	17.3	2.7	98.7
B	146	13.1	1.3	98.7
C	163	8.3	1.4	100.3
D	241	22.5	0.0	NA[c]
AE	172.6	9.93	0.0	NA[c]

Source: Assay parameters for subtypes A, B, C and D are from (Kassanjee et al. 2016) ; parameters for subtype AE are not available in Kassanjee 2016, and are estimated using R package "inctools" (Grebe et al. 2022) based on data from (Klock et al. 2020) (see APPENDIX 2 for details).
[a] Based on the Sedia LAg-EIA and RITA cutoffs in Table 6-2 (i.e., an infection classified as recent if ODn ≤1.5 and HIV-1 RNA viral load >75 copies/mL).
[b] For untreated participants.
[c] For FRR =0%, rSE cannot be calculated; in this case, a standard error (instead of rSE) of zero will be used in the bHIV calculations.
Note: The Sedia LAg-EIA package insert refers to an MDRI of 130 days (95% CI 118-142, or rSE =4.7%) and an FRR of <1% for $T = 1$ using ODn cutoff of 1.5 and HIV-1 RNA viral load cutoff of 1000 copies/mL.
Abbreviations: bHIV, background HIV-1; FRR, false recency rate; LAg-EIA, limiting antigen avidity enzyme immunoassay; MDRI, mean duration of recent infections; ODn, normalized optical density; RITA, recent infection testing algorithm; rSE, relative standard error.

Table 26. MDRI and FRR ((Kassanjee et al. 2016), T =1 Year1)[a]

	MDRI		FRR[b]	
Subtype	Days	rSE (%)	%	rSE (%)
A	142	18.1	8.1	42.8
B	137	12.8	2.4	57.5
C	149	7.2	1.7	69.7
D	162	16.7	23.7	41.2

Source: (Kassanjee et al. 2016).
[a] Based on the Sedia LAg-EIA and RITA cutoffs: an infection classified as recent if ODn ≤1.5 and HIV-1 RNA viral load >75 copies/mL.
[b] For untreated participants.
Abbreviations: FRR, false recency rate; LAg-EIA, limiting antigen avidity enzyme immunoassay; MDRI, mean duration of recent infections; ODn, normalized optical density; RITA, recent infection testing algorithm; rSE, relative standard error.

Table 27. MDRI and FRR ((Parkin et al. 2023), T = 2 Year)[a]

	MDRI		FRR[b]	
Subtype	Days	rSE (%)	%	rSE (%)
A	212	14.0	2.6	98.7
B	189	12.7	1.8	99.1
C	194	7.0	1.4	99.3
D	262	20.2	NA	NA

Source: RAWG (Parkin et al. 2023).
[a] Based on the Sedia LAg-EIA and RITA cutoffs: an infection classified as recent if ODn ≤1.5 and HIV-1 RNA viral load >75 copies/mL.
[b] For untreated patients.
Abbreviations: FRR, false recency rate; LAg-EIA, limiting antigen avidity enzyme immunoassay; MDRI, mean duration of recent infections; NA, not available; ODn, normalized optical density; RITA, recent infection testing algorithm; rSE, relative standard error.

Table 28. RITA Estimate of the Background HIV-1 Incidence in the Incidence Phase (bHIV), All Screened Set

Incidence Parameter	PURPOSE 1 (N=8094)	PURPOSE 2 (N=4634)
Diagnosis of HIV-1 in Incidence Phase [N+/N]	504/8094 (6.2%)	378/4634 (8.2%)
Recency outcome available [N+,test/N+]	504/504 (100.0%)	376/378 (99.5%)
Recent HIV-1 infection (VL >75 copies/mL and ODn<=1.50) [Nrec/N+,test]	92/504 (18.3%)	45/376 (12.0%)
Estimated bHIV (/100PY) and 95% CI		
Based on assay parameters from (Kassanjee et al. 2016) T =2	2.407 (1.815-3.191)	2.374 (1.649-3.417)
Based on assay parameters from (Kassanjee et al. 2016) T =1	2.116 (1.334-3.355)	2.365 (1.601-3.492)
Based on assay parameters from (Parkin et al. 2023) [RAWG] T =2	2.025 (1.550-2.645)	1.894 (1.298-2.764)

Source: Table 15.9.1.3.1 of the CSRs.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; CSR, clinical study report; ODn, normalized optical density; VL, viral load; RITA, Recent Infection Testing Algorithm.

Effect of the Subtype Misclassification on the Estimation of bHIV Incidence

Using PURPOSE 1 as an example, we conducted some sensitivity analyses to assess the effect on the estimation of bHIV incidence of subtype misclassification by changing the subtype proportion within each country. The result is shown in Table 29. In the original analyses, the estimation of subtype distribution was 56% subtype A, 3% subtype C, and 41% subtype D. In our sensitivity analysis 1, we switched all the subtype A participants in Uganda to subtype D. This change led to the estimated bHIV incidence shifting from 2.41 to 2.20. In our sensitivity analysis 2, we switched all the subtype D participants in Uganda to subtype A. The estimated bHIV incidence increased to 2.60. In our sensitivity analysis 3, we switched all the subtype C participants in South Africa to subtype D. The estimated bHIV incidence decreased to 1.97. As shown in the sensitivity analyses, the bHIV incidence rate could vary substantially if the subtype data are mis-specified.

Table 29. Sensitivity Analysis by Modifying the Subtype Distribution Within Each Country, PURPOSE 1

					Subtype Distribution							
	MDRI		FRR		Purpose 1		Sensitivity 1		Sensitivity 2		Sensitivity 3	
Subtype	Days	rSE (%)	%	rSE (%)	ZAF	UGA	ZAF	UGA	ZAF	UGA	ZAF	UGA
A	170	17.3	2.7	98.7	0	0.56	0	0	0	0.97	0	0.56
C	163	8.3	1.4	100.3	1	0.03	1	0.03	1	0.03	0	0.03
D	241	22.5	0.0	NA	0	0.41	0	0.97	0	0	1	0.41
HIV-1 incidence per 100 person-years					**2.41**		**2.20**		**2.60**		**1.97**	
95% CI					**(1.82, 3.19)**		**(1.57 to 3.08)**		**(1.92, 3.52)**		**(1.29, 3.00)**	

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Abbreviations: FRR, false recency rate; MDRI, mean duration of recent infections; rSE, relative standard error.

Consistency of the RITA Estimation of the bHIV Incidence Rate Used for the Primary Efficacy Analysis With Alternative Methods to Estimate the bHIV Incidence Rate

To further assess the reliability of the RITA-estimated bHIV incidence rate used for the primary efficacy analyses in PURPOSE 1 and PURPOSE 2, we compared these bHIV incidence rates with those estimated using the following alternative methods:

- The modified VOICE risk score (PURPOSE 1 only): The Applicant used this HIV risk scoring tool derived from prior studies of African women to estimate bHIV incidence based on five demographic and behavioral risk components collected at screening: age <25 years =2 points; unmarried or not living with partner =2 points; partner does not provide financial or material support =1 point; primary partner has other partners (yes or don't know)=2 points; alcohol use in the past 3 months =1 point (Balkus et al. 2016). This was one of several modified versions of the VOICE risk score described in (Balkus et al. 2016), in which the authors calculated the incidence of HIV infection and its 95% CI for each total score using the data from women who participated in the MTN 003/VOICE trial, an HIV-1 PrEP trial that enrolled women 18 to 45 years of age in South Africa, Uganda, and Zimbabwe between 2009-2011. The authors assessed the performance of the score using data from two other HIV-1 PrEP trials: HPTN 035, which enrolled women in Malawi, South Africa, United States, Zimbabwe, and Zambia from 2005 to 2009, and FEM-PrEP, which enrolled women from Kenya, South Africa, and Tanzania from 2009 to 2011. The Applicant used these risk factors to generate a modified VOICE risk score for all randomized participants to predict the incidence rate for PURPOSE 1 only. The generalization of the results in the Balkus paper to any HIV-1 PrEP trials is questionable, as HIV-1 incidence has changed over time and can vary widely even within countries. The predictability of the risk factors used in this method is another concern.
- Historical data on bHIV from the ECHO trial reported in 2019 (PURPOSE 1 only): This is the only recent trial in the related region available with estimation of bHIV from a trial (ECHO Trial Consortium 2019).
- Rectal Gonorrhea Incidence (PURPOSE 2 only): The Applicant estimated the bHIV incidence rate based on a regression model of rectal gonorrhea and HIV-1 incidence in the absence of HIV prophylaxis (Mullick and Murray 2020). Approximately 8 data points were used to fit a linear regression model to predict the HIV-1 incidence rate using rectal gonorrhea incidences. There is no validation for this model.
- F/TDF Adherence-Efficacy Relationship (PURPOSE 2 only): The Applicant used a Bayesian model developed by Glidden to estimate the counterfactual bHIV incidence rate using tenofovir diphosphate levels to estimate adherence in participants randomized to F/TDF (Glidden et al. 2021). The Bayesian model was used to estimate bHIV incidence rate using DBS Tenofovir diphosphate (TFV-DP) concentrations in the current trial (collected in a random 10% subset of study participants and in all participants who were diagnosed with HIV-1) and using the adherence-efficacy relationship based on the iPrEx trial data to predict efficacy. The strong assumption for this analysis is that the adherence-efficacy relationship observed in the iPrEx trial is similar to the PURPOSE 2 trial, which was conducted 15 years later. The three adherence categories (low, medium, and high) were determined by the TFV-DP concentration in DBS; the reliability of this method to estimate bHIV incidence is not established.

- HIV-1 infections occurring between the screening and randomization visits (PURPOSE 1 and PURPOSE 2): We estimated the bHIV incidence rate using the 8 infections in PURPOSE 1 and 9 infections in PURPOSE 2 diagnosed after screening and at the randomization visit and the total person-years of follow up for all randomized participants between the screening and randomization visits. Please see Section 16.4 for more details. This approach alleviated some of the concerns with respect to differences in risk factors between populations in the Incidence Phase and Randomization Phase mentioned in the efficacy review issue section (Section 6.3). However, the follow-up time is short, and the number of infections is too small to provide a robust estimate. In addition, there are missing follow-up data for participants who were not randomized or diagnosed with HIV-1.

The bHIV incidence rates estimated using alternative methods did not demonstrate consistency in the estimate (see Table 30 below). Different methodologies estimated a bHIV incidence rates that varied as much as four-fold. The RITA estimated bHIV incidence rates used for the primary endpoints were lower than the bHIV incidence rates estimated by all the other methods. However, these alternative methods have multiple limitations as outlined above and are not considered reliable.

Table 30. Estimated bHIV Incidence Rates Per 100 Person Years (95% CI) Using Different Methodologies

Methodology	PURPOSE 1	PURPOSE 2
RITA (used for primary endpoint)	2.407 (1.815, 3.191)	2.374 (1.649, 3.417)
Modified VOICE risk score	9.405 (8.150, 11.200)[a]	--
Historical data (ECHO trial)	3.81 (3.45, 4.21)	--
Rectal gonorrhea incidence	--	6.187[b] (3.528, 8.847)
F/TDF adherence-efficacy relationship	--	2.867[c] (1.089, 6.723)
HIV infections between the screening and randomization visits	2.771 (1.196, 5.459)	4.513 (1.732, 7.905)

Source: Reviewer's analysis using adsl.xpt and adtte.xpt and CSRs.
[a] Based on the overall randomized population.
[b] Based on the at-risk of HIV-1 infection in study population in the LEN group.
[c] Based on the F/TDF group in the full analysis set, excluding the 6 participants who were HIV-1 positive at baseline.
Abbreviations: bHIV, background HIV-1; CSR, clinical study report; ECHO, Evidence for Contraceptive Options and HIV Outcomes; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; RITA, recent infection testing algorithm; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

Conclusion

The populations for the evaluations of the bHIV incidence rate and the observed HIV-1 incidence rate in the LEN group were different with regards to demographics and baseline characteristics potentially related to HIV-1 incidence based on available data. In addition, the limited data collection of HIV-1 subtypes adds even greater uncertainty with regards to the comparability of the populations. Therefore, a direct comparison of incidence rates between these two populations raises concerns of a biased estimate of the treatment effect.

The estimate of the bHIV incidence rate can be affected significantly by applying the parameter estimates of MDRI and FRR from different sources. Additionally, it is questionable whether the derived parameters in Kassanjee et al. (Kassanjee et al. 2016) are still applicable to the data collected in PURPOSE 1 and PURPOSE 2. As shown in the sensitivity analyses, misclassification of the subtypes of individual participants could substantially affect the estimate of the bHIV incidence rate as well.

Alternative methods of estimating the bHIV incidence rate did not demonstrate consistency of the estimate. However, the RITA estimated bHIV incidence rates used for the primary endpoint were lower than the bHIV incidence rates estimated by all the other methods, suggesting they may not have overestimated the bHIV incidence rate. However, because of the limitations with all of the alternative methods, we cannot state with confidence that the RITA estimated bHIV incidence rates were not an overestimate. In addition, RITA estimates based on analyses performed at other laboratories may not be consistent with these findings.

Considering the concerns listed above, we recommend that the evidence of efficacy should be based on the finding that LEN demonstrated superiority over F/TDF in both pivotal trials. The data suggest that the methodology utilized to estimate the bHIV incidence rate in PURPOSE 1 and PURPOSE 2 may not have overestimated the bHIV rate, so the primary endpoint results are considered supportive for this application. However, we cannot conclude that in future trials an endpoint based on a comparison to a RITA-estimated bHIV incidence rate would be reliable enough to support an efficacy claim.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical studies to support the safety of LEN were submitted and reviewed under investigational new drug applications 136260 and 138311 and NDAs 215973 and 215974 for the treatment of HIV-1 in HTE adults with MDR HIV-1. Please refer to Section 13 for details on the juvenile toxicity study and a local tolerance study submitted with the current NDA.

In the juvenile toxicity study, other than elevated cholesterol levels detected at the end of the dosing period that showed signs of resolving at the end of the recovery period, there were no LEN-related effects on growth or development.

The local tolerance study in rabbits revealed injection site reactions of palpable masses consisting of granulomatous inflammation. These findings were similar to those observed in the nonclinical toxicity studies in rats and dogs that were previously reviewed under the LEN NDAs 215973 and 215974for the treatment of HIV-1 in the HTE population.

Overall, the nonclinical safety assessment for LEN was considered acceptable from a pharmacology/toxicology perspective to support approval for the present indication (HIV-1 PrEP).

Exposure Multiples

Exposure multiples, based on the proposed human dosing regimen are presented in Table 31.

Table 31. Lenacapavir Exposure Multiple

Study	Dose	Adverse Findings	AUC[a] (ng•hr/mL)	Exposure Multiple[b]
Repeat-dose studies (oral)				
4-week rat	30 mg/kg (NOAEL)	None	34,500	33[c]
4-week dog	30 mg/kg (NOAEL)	None	75,900	73[c]
Repeat-dose studies (subcutaneous)				
6-week rat (43-day)	100 mg/kg (NOAEL) (systemic effects)	None	583,000	40[d]
26-week rat (92-day)	100 mg/kg(NOAEL) (systemic effects)	None	307,000 284,000 211,000	10[e] 9[e] 7[e]
6-week dog (43-day)	30 mg/kg (NOAEL) (systemic effects)	Vocalization, barrel rolling	436,000	30[d]
9-month dog	40 mg/kg (NOAEL) (systemic effects)	None	352,000	11[e]
Reproductive toxicology studies				
Fertility and early embryonic development Rat (SC)	100 mg/kg (NOAEL)	None	270,000 (M) 192,000 (F)	9[e] 6[e]
Embryo-fetal development				
Rat (oral)	30 mg/kg (NOAEL)	None	22,000	21[c]
Rabbits (IV)	20 mg/kg (NOAEL)	Lower body weight gain	178,000	170[c]
Pre- and postnatal development				
Rat (SC)	300 mg/kg (NOAEL)	None	54,800	7[f]
Juvenile Toxicity study Rat	30 mg/kg (NOAEL)	None	42,600	40[c]
Carcinogenicity				
6-month transgenic mouse		None	8,310,000[h]	88[g]
2-year (104-week) Rat	300 mg/kg (NOAEL) 927 mg/kg (high dose)	Malignant sarcoma; combined benign fibroma; granulomatous inflammation	4,130,000	44[g]

Source: Nonclinical reviewer analysis based on findings and AUC values from individual study reports.
[a] AUC values for male and female animals combined unless otherwise noted.
[b] Based on AUC_{tau} values in humans at the proposed dosing regimen: Day 1: 600 mg (oral) +927 mg (SC); Day 2: 600 mg (oral); continuation: 927 mg (SC) every 6 months (b) (4) ($AUC_{Day1-Week26}$=188,108 ng•hr/mL).
[c] Calculated using AUC_{0-24h} × 30 days in a month × 6 (to adjust 24 hr to 6 months)/188,108 ng•hr/mL.
[d] Calculated using AUC_{0-336h} × 13 (to adjust 13 weeks to 6 months)/ 188,108 ng•hr/mL.
[e] Calculated using AUC_{0-672h} × 6 (to adjust 1 month to 6 months)/188,108 ng•hr/mL.
[f] Calculated using AUC_{0-192h} × 23 (to adjust 8 days to 6 months)/188,108 ng•hr/mL.
[g] Calculated using $AUC_{0-2184h}$ × 2 (to modify 13 weeks to 6 months) / 188,108 ng•hr/mL.
[h] AUC values taken from the single dose SC dosing range finding toxicity study in rasH2 transgenic mic (study report no TX-200-2045).
Abbreviations: AUC, area under the curve; F, female; IV, intravenous; LEN, lenacapavir; M, male; ND, not determined; NOAEL, no observed adverse effect level; SC, subcutaneous.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns for LEN were identified based on clinical experiences with LEN for HIV-1 treatment in the HTE population and from safety concerns identified with the previously approved long-acting injectable PrEP product, APRETUDE (a long-acting formulation of cabotegravir [CAB], an integrase strand transfer inhibitor). In the Phase 2/3 HIV-1 treatment trial CAPELLA (N=72) the most common adverse reactions (all Grades) reported in

at least 3% of LEN recipients were ISRs (65%) and nausea (4%). For APRETUDE, ISRs were also the most commonly reported adverse reactions, with 82% and 38% of participants reporting at least one ISR in the Phase 3 trials HPTN 083 and HPTN 084, respectively.

For long-acting injectable products such as LEN and CAB for HIV-1 PrEP, the prolonged exposures also carry the risk of development of HIV-1 resistance in participants who become infected, and a prolonged risk of drug interactions.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

No potential risks or new safety concerns for LEN were identified through postmarketing experience that were not already identified in clinical trials.

7.3.2. Expectations on Safety

See Section 7.2.

7.3.3. Additional Safety Issues From Other Disciplines

None.

7.4. FDA Approach to the Safety Review

The review team did not identify any major data quality or integrity issues that preclude performing a safety review. No major issues were identified with respect to recording, coding, or categorizing AEs. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in PURPOSE 1 and PURPOSE 2 were coded according to Version 27.0, reviewed, and found to be acceptable.

Definitions for PURPOSE 1 and PURPOSE 2

AEs were protocol-defined as any untoward medical occurrence in a clinical study participant administered a study drug, which does not necessarily have a causal relationship with the treatment. However, per protocol, an AE did not include HIV infection as the incidence of HIV infection is included as an outcome of the studies.

Treatment-emergent adverse events (TEAEs) were defined in the Applicant's analysis, and for the purpose of this review, as any event that began on or after study drug first dose date through the last exposure date for the study Phase.

Adverse drug reactions were defined for the purpose of this review as any TEAE that was considered by the investigator to be related to the study drug.

AEs of special interest (AESIs) were determined based on clinical experience and information from long-acting injectable drugs, and from SUNLENCA (LEN for treatment of HIV-1 in HTE population), and focused on injection site reactions (ISRs).

A serious adverse event (SAE) was protocol defined as an event that, at any dose, resulted in the following:

- Death
- A life-threatening situation
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medical important event or reaction
- Of note, for PURPOSE 1, mother-to-child transmission in women who become HIV infected on study drug is considered medically important and therefore "serious." However, no such events occurred.

Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (NIH 2017).

Data Used for Clinical Safety Assessment

The primary safety analyses are based on the Applicants interim data, which was a prespecified analysis performed once 50% of the planned number of participants completed at least 52 weeks of follow-up or prematurely discontinued from the study. As the data met the prespecified interim efficacy stopping criteria, the interim analysis serves as the primary analysis. The trial transitioned from the RBP to the OL Phase after the interim analysis met the study stopping criteria. In addition, a 90-day safety update report (SUR) was submitted. The SUR included a summary of new deaths, SAEs, AESIs, AEs leading to study drug discontinuation, HIV-1 infections, and pregnancies for events in the RBP that occurred after the data cutoff for the interim analysis as well as those in the OL Phase up through the SUR data cutoff date. With the exception of ISR data, the SUR did not include data from the F/TAF group in PURPOSE 1, but only the LEN and F/TDF groups, as F/TDF was the active comparator and F/TAF was an additional experimental group in this trial. For that same reason, only the comparison to F/TDF was included in labeling, except for ISRs (for which all data were included for a more robust comparison as ISRs would be expected to occur due to the placebo injection rather than F/TDF or F/TAF).

A summary of available trial data by date is provided in Table 32 below.

Table 32. Summary of Ongoing Trials Providing Key Clinical Safety Data for Lenacapavir as PrEP

Trial	Study Start Date (First Participant Screened)	Original NDA Submission Analysis End Date	Safety Update End Date
GS-US-412-5624	30 August 2021	08 May 2024	04 December 2024
GS-US-528-9023	28 June 2021	05 August 2024	03 January 2025

Source: Applicant's NDA Study Reports and Safety Update Report.
Abbreviation: PrEP, pre-exposure prophylaxis.

In addition, Phase 1 clinical trial data were reviewed to supplement the safety assessment for specific review issues (please see Section 7.7.2 and 7.7.3 below).

Approach to Assessment of Clinical Trial Data

The review approach for assessment of risk consisted of evaluation of the safety data from the Phase 3 trials separately, as well as the pooled safety data from both trials, to identify rarer safety signals. The separate analysis of the trials constituted the primary basis of the safety review because the trials enrolled different patient populations. The subpopulations of pregnant women and adolescents were also evaluated for safety and outcomes (see Sections 8.3 and 8.4).

Clinical trial data were independently analyzed using JMP and JMP Clinical software. Additional analyses were provided by the Clinical Data Scientist support team. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

7.5. Adequacy of the Clinical Safety Database

Overall, the safety database is adequate for a comprehensive safety assessment of LEN for the proposed indication, dosage regimen, duration, and patient populations. At the time of the NDA filing, 4,323 participants enrolled in PURPOSE 1 and PURPOSE 2 had received at least one dose of SC LEN.

PURPOSE 1 Clinical Safety Experience

In the Phase 3 trial PURPOSE 1, 2,140 participants received at least one dose of LEN in the randomized blinded Phase with a median duration of LEN exposure of 42.6 weeks at the interim analysis (see Table 33). The median duration of LEN exposure at the safety update was 75.8 weeks.

Table 33. Duration of Exposure, Safety Population, PURPOSE 1

Parameter	LEN N=2140	F/TAF N=2135	F/TDF N=1070
Duration of treatment, weeks			
Mean (SD)	47.2 (17.3)	47.1 (17.6)	46.3 (17.7)
Median (Q1, Q3)	42.6 (38.1, 53.4)	41.6 (38.1, 53.7)	41.4 (38.1, 53.3)
Min, max	0.1, 132.3	0.1, 131.6	0.1, 132.7
Total exposure (person years)	1934	1928	950
Participants treated, by duration, n (%)			
<26 weeks	125 (5.8)	144 (6.7)	86 (8.0)
≥26 to <39 weeks	604 (28.2)	575 (26.9)	282 (26.4)
≥39 to <52 weeks	603 (28.2)	601 (28.1)	310 (29.0)
≥52 to <65 weeks	553 (25.8)	548 (25.7)	264 (24.7)
≥65 to <78 weeks	122 (5.7)	126 (5.9)	63 (5.9)
≥78 to <91 weeks	97 (4.5)	108 (5.1)	50 (4.7)
≥91 weeks	36 (1.7)	33 (1.5)	15 (1.4)

Source: [Data Scientist] adex.xpt and adsl.xpt; Software: R.
Duration is 52 weeks.
Abbreviations: F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; max, maximum; min, minimum; N, number of participants in treatment arm; n, number of participants with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation.

PURPOSE 2 Clinical Safety Experience

In the Phase 3 trial PURPOSE 2, 2183 participants received at least one dose of LEN in the randomized blinded Phase with a median duration of exposure to study drug of 39.3 weeks at the interim analysis (see Table 34). The median duration of LEN exposure at the safety update was 54.1 weeks.

Table 34. Duration of Exposure, Safety Population, PURPOSE 2

Parameter	LEN N=2183	F/TDF N=1088
Duration of treatment, weeks		
Mean (SD)	45.5 (22.8)	46.2 (24.8)
Median (Q1, Q3)	39.3 (28.5, 54.1)	39.3 (28.3, 55.1)
Min, max	0.1, 167	0.9, 158.3
Total exposure (person years)	1902	963
Participants treated, by duration, n (%)		
<26 weeks	190 (8.7)	106 (9.7)
≥26 to <39 weeks	767 (35.1)	363 (33.4)
≥39 to <52 weeks	457 (20.9)	233 (21.4)
≥52 to <65 weeks	386 (17.7)	179 (16.5)
≥65 to <78 weeks	153 (7.0)	84 (7.7)
≥78 to <91 weeks	145 (6.6)	59 (5.4)
≥91 weeks	85 (3.9)	64 (5.9)

Source:[Data Scientist] adex.xpt and adsl.xpt; Software: R.
Duration is 52 weeks.
Abbreviations: F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; max, maximum; min, minimum; N, number of participants in treatment arm; n, number of participants with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation.

7.6. Safety Results

7.6.1. Safety Results, PURPOSE 1

7.6.1.1. Overview of Treatment-Emergent Adverse Events, PURPOSE 1

An overview of the TEAEs in PURPOSE 1 is presented in Table 35. Overall, LEN demonstrated a favorable safety profile. No deaths occurred in the LEN group. There was a similar percentage of SAEs and any AEs across groups. The rates of adverse events leading to discontinuation were low (<1% across treatment groups).

Table 35. Overview of Treatment-Emergent Adverse Events, Safety Population, PURPOSE 1

Event Category	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	Risk Difference % (95% CI) LEN vs. F/TAF	LEN vs. F/TDF	F/TAF vs. F/TDF
SAE	59 (2.8)	85 (4.0)	35 (3.3)	-1.2 (-2.3, -0.1) *	-0.5 (-1.9, 0.7)	0.7 (-0.7, 2.0)
SAEs with fatal outcome	0	6 (0.3)	0	-0.3 (-0.6, -0.1) *	0.0 (-0.4, 0.2)	0.3 (-0.1, 0.6)
Life-threatening SAEs	8 (0.4)	11 (0.5)	4 (0.4)	-0.1 (-0.6, 0.3)	-0.0 (-0.6, 0.4)	0.1 (-0.5, 0.6)
SAEs requiring hospitalization	45 (2.1)	56 (2.6)	27 (2.5)	-0.5 (-1.5, 0.4)	-0.4 (-1.7, 0.6)	0.1 (-1.2, 1.2)
SAEs resulting in substantial disruption of normal life functions	6 (0.3)	7 (0.3)	1 (0.1)	-0.0 (-0.4, 0.3)	0.2 (-0.3, 0.5)	0.2 (-0.2, 0.6)
Congenital anomaly or birth defect	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Other	17 (0.8)	31 (1.5)	12 (1.1)	-0.7 (-1.3, -0.0) *	-0.3 (-1.2, 0.3)	0.3 (-0.6, 1.1)
AE leading to permanent discontinuation of study drug	9 (0.4)	2 (0.1)	0	0.3 (0.0, 0.7) *	0.4 (0.1, 0.8) *	0.1 (-0.3, 0.3)
AE leading to dose modification of study drug	21 (1.0)	25 (1.2)	12 (1.1)	-0.2 (-0.8, 0.4)	-0.1 (-1.0, 0.6)	0.0 (-0.9, 0.8)
AE leading to interruption of study drug	21 (1.0)	25 (1.2)	12 (1.1)	-0.2 (-0.8, 0.4)	-0.1 (-1.0, 0.6)	0.0 (-0.9, 0.8)
AE leading to reduction of study drug	0	0	0	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
AE leading to dose delay of study drug	0	0	0	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Any AE	1893 (88.5)	1779 (83.3)	881 (82.3)	5.1 (3.1, 7.2) *	6.1 (3.5, 8.8) *	1.0 (-1.7, 3.8)
Severe and worse	92 (4.3)	97 (4.5)	52 (4.9)	-0.2 (-1.5, 1.0)	-0.6 (-2.2, 0.9)	-0.3 (-2.0, 1.2)
Moderate	1137 (53.1)	1045 (48.9)	500 (46.7)	4.2 (1.2, 7.2) *	6.4 (2.7, 10.1) *	2.2 (-1.5, 5.9)
Mild	664 (31.0)	637 (29.8)	329 (30.7)	1.2 (-1.6, 3.9)	0.3 (-3.1, 3.6)	-0.9 (-4.3, 2.4)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event; SC, subcutaneous.

7.6.1.2. Deaths, PURPOSE 1

The six deaths in PURPOSE 1 were all in the F/TAF group and no deaths were reported among LEN participants. Details regarding deaths in PURPOSE 1 have been added in Table 36 below. No deaths were assessed by the investigators to be related to F/TAF. Following review of the submitted case narratives, the clinical review team agrees that none of the deaths appear to have been drug related.

Table 36. Listing of All Individual Participant Deaths, Safety Population, PURPOSE 1

Study Arm	Participant ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death	
						Preferred Term	Verbatim Term
F/TAF	(b) (6)	20	F	138	138	Hemorrhage	Hemorrhage (unk site)
						Road traffic accident	Motor bike accident
F/TAF		19	F	74		Asphyxia	Asphyxia secondary to strangulation
						Victim of homicide	Victim of homicide
F/TAF		23	F	91	106	Thermal burn	Non-accidental burn injury-total burn surface are approximately 50% (head, face, neck, back, upper chest and right thigh)
						Victim of homicide	Victim of homicide
F/TAF		21	F	110	140	Ischaemic cardiomyopathy	Ischaemic cardiomyopathy
F/TAF		22	F	585	585	Stab wound	Knife stab to chest
F/TAF		25	F	36	36	Ovarian cancer	Advanced ovarian cancer

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Abbreviations: F/TAF, emtricitabine/tenofovir alafenamide; F, female; ID, identifier; SC, subcutaneous; unk, unknown.

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The SUR included three new deaths, two in the LEN open label extension Phase and one in the F/TDF group in the RBP. All narratives were reviewed. The two deaths in the LEN group are considered treatment-emergent; one participant died due to “natural causes” with further details that the participant was a chronic user of methamphetamines, and one participant died due to hypovolemic shock following a ruptured ectopic pregnancy. The death reported in the F/TDF group was from a gunshot wound and was considered non-treatment emergent due to the time since the last dose of F/TDF and the reported AE. None of the deaths reported in the SUR are assessed by the investigators to be related to study drug, and the clinical review team agrees.

In conclusion, the deaths reported in the NDA filing and in the SUR do not identify a new safety signal.

7.6.1.3. Serious Treatment-Emergent Adverse Events, PURPOSE 1

Overall, the proportion of participants experiencing SAEs was similar across groups. There were no major imbalances in SAE preferred terms (PTs) across treatment groups. A total of 2.8% of participants in the LEN group experienced SAEs, compared to F/TDF where rates of SAEs occurred in 3.3% of participants, and F/TAF where 4.0% of participants experienced SAEs. The most common SAE PT was spontaneous abortion in all groups, reported in 15 (0.7%), 9 (0.8%), and 28 (1.3%) of participants in the LEN, F/TDF, and F/TAF groups, respectively. No other SAE was reported in ≥0.2% of LEN recipients. No system organ class (SOC) or PT was disproportionally reported as an SAE to suggest a pattern. A complete tabulation of SAEs can be found in Section 17.1.1.

The only drug-related SAE PT reported was spontaneous abortion. These drug-related SAEs of spontaneous abortion were rare, occurred in all groups, and were balanced between groups (reported in <0.1% of participants in each group). While safety in pregnancy and lactation are specifically addressed in Section 8.4, the clinical review team concludes that the rates of spontaneous abortion are consistent with the background rates seen in the countries of the participators and are not clearly associated with study drugs.

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The SUR data for PURPOSE 1 includes additional SAEs in the LEN group for an additional 22 participants and in the F/TDF group for an additional 9 participants, bringing totals to 81 participants in the LEN group (3.8%) and 44 participants in the F/TDF group (4.1%). When including the data from the SUR, the most reported SAE PT continues to be spontaneous abortion however, the rates are now 0.8% in the LEN group and 1.2% in the F/TDF group.

The clinical review team does not find concerning safety signals based on the SAEs reported in the NDA filing and the SUR.

7.6.1.4. Adverse Events and OND Custom Medical Queries Leading to Treatment Discontinuation, PURPOSE 1

AEs leading to treatment discontinuation are summarized in Table 37 below. The incidence of AEs leading to discontinuation are low, with 9 participants (0.4%) in the LEN group, 2 participants (0.1%) in the F/TAF group, and 0 participants in the F/TDF group discontinuing due to AEs. As shown, the primary PTs leading to discontinuation in the LEN group are ISR-related, (0.2%). In the LEN group, the only AEs leading to discontinuation that were assessed by the investigator to be related to LEN were also ISR-related. ISRs are described in more detail in Section 7.6.4, and additional details on AEs leading to treatment discontinuation can be found in Section 17.1.2.

Table 37. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	Risk Difference % (95% CI) LEN vs. F/TAF	 LEN vs. F/TDF	 F/TAF vs. F/TDF
Any AE leading to discontinuation	9 (0.4)	2 (0.1)	0	0.3 (0.0, 0.7) *	0.4 (0.1, 0.8) *	0.1 (-0.3, 0.3)
Gastrointestinal disorders (SOC)	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Nausea	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
General disorders and administration site conditions (SOC)	4 (0.2)	0	0	0.2 (0.0, 0.5) *	0.2 (-0.2, 0.5)	0.0 (-0.4, 0.2)
Injection site nodule	4 (0.2)	0	0	0.2 (0.0, 0.5) *	0.2 (-0.2, 0.5)	0.0 (-0.4, 0.2)
Injection site pain	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Injury, poisoning and procedural complications (SOC)	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Overdose	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Investigations (SOC)	2 (0.1)	0	0	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Creatinine renal clearance decreased	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Hepatic enzyme increased	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Pregnancy, puerperium and perinatal conditions (SOC)	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Abortion spontaneous	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Psychiatric disorders (SOC)	1 (0.0)	1 (0.0)	0	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Major depression	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Suicide attempt	1 (0.0)	1 (0.0)	0	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Depressive symptom	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Skin and subcutaneous tissue disorders (SOC)	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Angioedema	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)

Source:[Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

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The Applicant reports an additional four participants experienced AEs leading to discontinuation in the SUR, two participants in the LEN group and two participants in the F/TDF group. The participants in the LEN group discontinued due to one event of nonserious seizure, and one event of psoriasis. Neither event was assessed by investigators to be related to LEN. Two participants in the F/TDF group discontinued prematurely due to nonserious ISR-related events, which are assessed as related to study drug. ISRs will be described in labeling; the clinical review team does not find any other safety signals based on the AEs leading to discontinuation reported in the NDA filing and the SUR.

7.6.1.5. Treatment-Emergent Adverse Events, PURPOSE 1

Please refer to Section 17.1.3 for a tabulation of TEAEs occurring in at least 0.5% of participants in any arm. In this section, TEAEs considered at least possibly related to study drug (i.e., adverse drug reactions, ADRs) are discussed. ADRs reported in at least 2% of participants in any group are presented in the Table 38 below. The most common ADRs were ISR-related and these events were markedly more common among LEN participants than among F/TDF or F/TAF participants. Overall ISRs occurred in 1472 (68.8%) of LEN recipients, 363 (33.9%) of F/TDF recipients, and 753 (35.3%) of F/TAF recipients. These events are discussed in detail in Section 7.6.4. Apart from ISRs, ADRs occurring in at least 2% of participants were either balanced between groups or favored LEN, with less GI-related PTs such as nausea and vomiting in the LEN group. Nausea occurred in 103 (4.8%) of LEN recipients, 113 (10.6%) of F/TDF recipients, and 182 (8.5%) of F/TAF recipients. Vomiting occurred in 84 (3.9%) of LEN recipients, 70 (6.5%) of F/TDF participants, and 152 (7.1%) of F/TAF recipients.

ADRs to be included in labeling are those that occurred in at least 2% of participants in the LEN and F/TDF groups and include ISRs, headache, nausea, dizziness, vomiting, and diarrhea.

Table 38. Participants With Adverse Events Assessed by Investigator as Treatment-Related, Showing Terms Occurring in at Least 2% of Participants in Any Group, Safety Population, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	Risk Difference (%) (95% CI) LEN vs. F/TAF	 LEN vs. F/TDF	 F/TAF vs. F/TDF
Any AE	1377 (64.3)	987 (46.2)	513 (47.9)	18.1 (15.2, 21.0) *	16.4 (12.8, 20.0) *	-1.7 (−5.4, 1.9)
Gastrointestinal disorders (SOC)	254 (11.9)	359 (16.8)	214 (20.0)	-4.9 (−7.1, −2.9) *	-8.1 (−11.0, −5.4) *	-3.2 (−6.1, −0.4) *
Diarrhoea	84 (3.9)	94 (4.4)	42 (3.9)	-0.5 (−1.7, 0.7)	-0.0 (−1.5, 1.4)	0.5 (−1.1, 1.9)
Vomiting	84 (3.9)	152 (7.1)	70 (6.5)	-3.2 (−4.6, −1.8) *	-2.6 (−4.4, −1.0) *	0.6 (−1.3, 2.4)
Nausea	103 (4.8)	182 (8.5)	113 (10.6)	-3.7 (−5.2, −2.2) *	-5.7 (−7.9, −3.8) *	-2.0 (−4.3, 0.1)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	Risk Difference (%) (95% CI) LEN vs. F/TAF	 LEN vs. F/TDF	 F/TAF vs. F/TDF
General disorders and administration site conditions (SOC)	1242 (58.0)	658 (30.8)	322 (30.1)	27.2 (24.3, 30.1) *	27.9 (24.4, 31.3) *	0.7 (−2.7, 4.1)
Injection site nodule	1142 (53.4)	290 (13.6)	157 (14.7)	39.8 (37.2, 42.3) *	38.7 (35.6, 41.6) *	-1.1 (−3.7, 1.4)
Injection site pain	581 (27.1)	439 (20.6)	203 (19.0)	6.6 (4.0, 9.1) *	8.2 (5.1, 11.1) *	1.6 (−1.4, 4.4)
Injection site induration	83 (3.9)	19 (0.9)	8 (0.7)	3.0 (2.1, 4.0) *	3.1 (2.1, 4.1) *	0.1 (−0.6, 0.8)
Injection site pruritus	43 (2.0)	23 (1.1)	9 (0.8)	0.9 (0.2, 1.7) *	1.2 (0.3, 2.0) *	0.2 (−0.6, 0.9)
Injection site swelling	84 (3.9)	113 (5.3)	47 (4.4)	-1.4 (−2.6, −0.1) *	-0.5 (−2.1, 0.9)	0.9 (−0.7, 2.4)
Metabolism and nutrition disorders (SOC)	22 (1.0)	50 (2.3)	25 (2.3)	-1.3 (−2.1, −0.6) *	-1.3 (−2.5, −0.4) *	0.0 (−1.2, 1.1)
Nervous system disorders (SOC)	223 (10.4)	237 (11.1)	137 (12.8)	-0.7 (−2.5, 1.2)	-2.4 (−4.8, −0.1) *	-1.7 (−4.2, 0.6)
Headache	157 (7.3)	166 (7.8)	85 (7.9)	-0.4 (−2.0, 1.2)	-0.6 (−2.7, 1.3)	-0.2 (−2.2, 1.7)
Dizziness	89 (4.2)	98 (4.6)	59 (5.5)	-0.4 (−1.7, 0.8)	-1.4 (−3.1, 0.2)	-0.9 (−2.7, 0.6)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous.

7.6.1.6. Laboratory Findings, PURPOSE 1

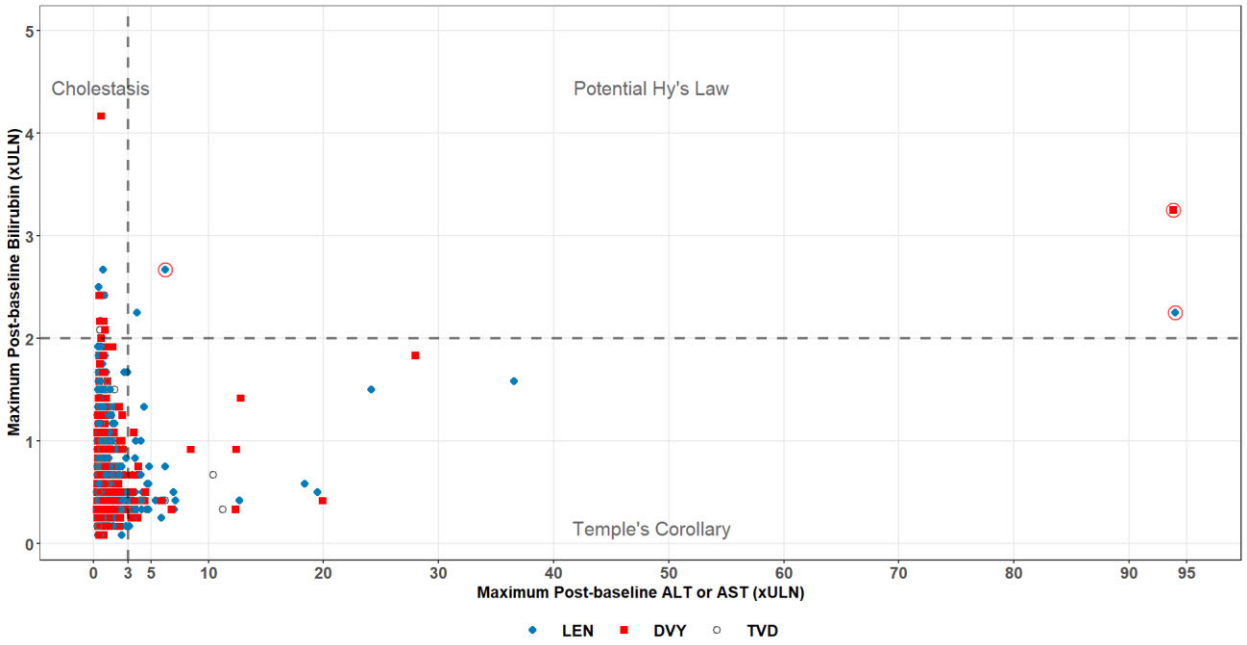
There were no clinically relevant differences between groups in chemistry, hematology, or kidney function laboratory parameters in PURPOSE 1. For a complete listing of laboratory outliers, please see Section 17.1.4.

Juvenile rat toxicity studies showed elevated cholesterol levels which resolved with maturity. In PURPOSE 1, lipid parameters were checked every 26 weeks. No evidence of cholesterol increases in the LEN group were seen through Week 130, and there were no clinically relevant differences in lipid parameters between groups. Please see Section 17.1.4 for more details.

7.6.1.7. Assessment of Drug-Induced Liver Injury, PURPOSE 1

Figure 8 shows a screening assessment for potential cases of serious drug-induced liver injury (DILI). Table 39 shows the participants in each quadrant for potential hepatocellular DILI screening plot.

Figure 8. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, PURPOSE 1



Source: [Data Scientist] adlb.xpt; Software: R.
Each data point represents a participant plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those participants who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All participants with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of participants in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot …" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening…."
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; ULN, upper limit of normal.

Table 39. Participants in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, PURPOSE 1

Quadrant	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)
Potential Hy's Law (right upper)	3/2127 (0.1)	1/2118 (0)	0/1058 (0)
Cholestasis (left upper)	6/2127 (0.3)	6/2118 (0.3)	4/1058 (0.4)
Temple's corollary (right lower)	43/2127 (2)	26/2118 (1.2)	11/1058 (1)
Total	52/2127 (2.4)	33/2118 (1.6)	15/1058 (1.4)

Source: [Data Scientist] adlb.xpt; Software: R.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

Of the three LEN participants who met Potential Hy's Law, the clinical review team does not find a likely relationship between the laboratory abnormalities and the use of LEN, particularly as laboratory abnormalities improved while still on therapy in all three. Participant (b) (6) had a single mild elevation of alanine aminotransferase (ALT) on Study Day 104, and 80 days

later a single grade 2 elevated bilirubin, both of which resolved. Participant (b) (6) experienced grade 4 ALT and aspartate aminotransferase (AST) elevations with grade 2 elevated bilirubin on Study Day 27, which all resolved by Study Day 42. The laboratory changes were attributed to alcohol use, as the participant reported drinking alcohol several days in a row prior to the laboratory visit, and the abnormalities resolved despite continuation of LEN and oral contraceptives. Participant (b) (6) experienced transient grade 3 ALT elevation, with grade 2 AST elevation and grade 3 hyperbilirubinemia on Study Day 196. Bilirubin remained to a grade 1 elevation through Study Day 274, however all other parameters resolved on Study Day 202. The participant reported a history of alcohol use at roughly 9 bottles of beer daily for at least 4 days per week and occasional cannabis use.

In addition, the clinical review team does not find a likely relationship between the laboratory abnormalities that meet Temple's Corollary cases and the use of LEN. The ALT or AST elevations found were transient, improved while on LEN, and often had plausible alternative etiologies (concomitant medications such as oral contraceptives or alcohol use). Additionally, ALT and AST measurements did not increase over time in the LEN group overall (please see Figure 51 and Figure 52 in Section 17.1.4 for more details).

7.6.1.8. Vital-Sign Analyses, PURPOSE 1

Trends in vital signs and body weight in PURPOSE 1 were reviewed. No clinically relevant changes from baseline or in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature or weight were seen.

7.6.2. Safety Results, PURPOSE 2

7.6.2.1. Overview of Treatment-Emergent Adverse Events, PURPOSE 2

An overview of the TEAEs is presented in Table 40. Incidence of Deaths, SAEs, AEs, and severity of AEs are generally similar between groups. The overall rates of adverse events leading to discontinuation are small, and the majority of AEs are considered mild to moderate. As in PURPOSE 1, the primary AEs leading to discontinuation of study drug in the LEN group are ISR-related, and these events are covered in detail in Section 7.6.4.

Table 40. Overview of Adverse Events, Safety Population, PURPOSE 2

Event Category	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
SAE	71 (3.3)	43 (4.0)	-0.7 (-2.2, 0.6)
SAEs with fatal outcome	4 (0.2)	1 (0.1)	0.1 (-0.3, 0.4)
Life-threatening SAEs	14 (0.6)	7 (0.6)	-0.0 (-0.7, 0.5)
SAEs requiring hospitalization	61 (2.8)	39 (3.6)	-0.8 (-2.2, 0.4)
SAEs resulting in substantial disruption of normal life functions	13 (0.6)	7 (0.6)	-0.0 (-0.8, 0.5)
AE leading to permanent discontinuation of study drug	32 (1.5)	10 (0.9)	0.5 (-0.3, 1.3)

Event Category	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
AE leading to dose modification of study drug	28 (1.3)	16 (1.5)	-0.2 (-1.2, 0.6)
AE leading to interruption of study drug	28 (1.3)	16 (1.5)	-0.2 (-1.2, 0.6)
AE leading to reduction of study drug	0	0	0.0 (-0.4, 0.2)
AE leading to dose delay of study drug	0	0	0.0 (-0.4, 0.2)
Any AE	2029 (92.9)	976 (89.7)	3.2 (1.2, 5.4) *
Severe and worse	104 (4.8)	66 (6.1)	-1.3 (-3.1, 0.3)
Moderate	1200 (55.0)	587 (54.0)	1.0 (-2.6, 4.6)
Mild	725 (33.2)	323 (29.7)	3.5 (0.1, 6.8) *

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
The Applicant's CSR reports 2 deaths in the F/TDF group on Table 18. The additional death was an "intracranial hemorrhage" and was not marked as treatment-emergent because "the participant's last dose was 128 days preceding the death." [CSR, pg. 113].
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event; SC, subcutaneous.

7.6.2.2. Deaths, PURPOSE 2

The five deaths, four in the LEN group and one in the F/TDF group, are summarized in Table 41. In the Applicant supplied Clinical Study Report, one additional death was reported in the F/TDF group, but this death (intracranial hemorrhage) was considered non-treatment emergent as the participant's last dose of study drug was 128 days prior to death.

No death was assessed by the investigators as related to study drug. The clinical team reviewed the submitted case narratives and agrees with the assessment that none of the deaths are related to study drugs. There was no clustering of AEs leading to death, and the AEs had plausible alternative explanations. For example, the participant who died of "cerebrovascular accident" while in the LEN group was a 35-year-old male with a medical history of smoking, obesity, hypertension, and diabetes mellitus and was also found on autopsy to have a pulmonary embolism. The participant had ongoing use of cyproterone acetate, which carries a risk of arterial thrombosis, stroke, and venous thromboembolism. In addition, the participant had ongoing use of estradiol, which may also increase the risk of thrombosis. This death was confounded by past medical history and concomitant medication exposures.

Table 41. Listing of All Individual Participant Deaths, Safety Population, PURPOSE 2

Study Arm	Participant ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death	
						Preferred Term	Verbatim Term
LEN	(b) (6)	35	M	179	338	Cerebrovascular accident	Cerebrovascular accident
LEN		27	M	2	126	Road traffic accident	Death by car crash
LEN		28	M	2	162	Death	Found dead - cause of death unknown

Study Arm	Participant ID	Age	Sex	Dosing Duration (Days)	Study Day of Death	Cause of Death	
						Preferred Term	Verbatim Term
LEN	(b) (6)	34	F	205	238	Completed suicide	Suicide
F/TDF		44	M	272		Death	Found dead - cause of death unknown

Source [Data Scientist]: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
The Applicant's CSR reports two deaths in the F/TDF group on Table 18. The additional death was an "intracranial hemorrhage" and was not marked as treatment-emergent because "the participant's last dose was 128 days preceding the death." [CSR, pg. 113].
Abbreviations: CSR, clinical study report; F, female; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; ID, identifier; LEN, lenacapavir; M, male; SC, subcutaneous.

90-Day Safety Update Report

The SUR included three new deaths in PURPOSE 2. All narratives were reviewed. One participant in the LEN group is reported to have died from cardiopulmonary arrest from malignant neoplasm of the esophagus. One participant in the LEN to open-label F/TDF group died from a traffic accident. One participant in the F/TDF to LEN open-label extension group died of a sudden cardiac arrest following a large consumption of alcohol at a party and did not have an autopsy. None of the deaths reported in the SUR are assessed by the investigators to be related to study drug and the clinical review team agrees.

In conclusion, the deaths reported in the NDA filing and in the SUR do not identify a new safety signal.

7.6.2.3. Serious Treatment-Emergent Adverse Events, PURPOSE 2

Overall, the proportion of participants experiencing SAEs was similar across groups. There were no major imbalances or apparent trends in SAE PTs higher in the LEN group. A total of 3.3% of participants in the LEN group experienced SAEs, compared to 4.0% of participants in the F/TDF group. The most common SAE PTs in the LEN group were appendicitis and suicide attempt (7 participants, 0.3%, each). In the F/TDF group the most common SAE PTs were appendicitis (6 participants, 0.6%) suicidal ideation (4 participants, 0.4%), and suicide attempt (3 participants, 0.3%). A complete tabulation of SAEs in PURPOSE 2 can be found in Section 17.2.1. No SAE was considered by investigators to be related to study drug in either group.

90-Day Safety Update

The SUR data for PURPOSE 2 includes additional SAEs in the LEN group for an additional 23 participants and in the F/TDF group for an additional 12 participants, bringing totals to 94 participants in the LEN group (4.3%) and 55 participants in the F/TDF group (5.1%).

The most common SAEs in the LEN group inclusive of the SUR are:

- Suicide attempt (9 participants [0.4%])
- Appendicitis (7 participants [0.3%])

- Hepatitis A (5 participants [0.2%])

The most common SAEs in the F/TDF group inclusive of the SUR data are:

- Appendicitis (6 participants [0.6%])
- Suicidal ideation (5 participants [0.5%])
- Suicide attempt (4 participants [0.4%])

The clinical review team does not find concerning safety signals based on the assessment of SAEs from the original NDA filing and the SUR.

7.6.2.4. Adverse Events and OND Custom Medical Queries Leading to Treatment Discontinuation, PURPOSE 2

AEs leading to treatment discontinuation are summarized in Table 42 below. The incidence of AEs leading to discontinuation are low in both groups, with 32 participants (1.5%) in the LEN group and 10 participants (0.9%) in the F/TDF group. The primary PTs leading to discontinuation in the LEN group are ISR-related. In addition, the only AEs leading to discontinuation that were assessed by the investigator to be related to LEN were also ISR-related. ISRs are described in more detail in Section 7.6.4. There were more treatment discontinuations in the F/TDF group due to creatinine renal clearance decreased (2 participants, 0.2%) compared to none in the LEN group, however, these were rare overall and this is a known safety issue with F/TDF.

There were no additional AEs that led to discontinuation of study drug in either LEN or F/TDF groups reported in the SUR. The risk of ISRs will be included in labeling; the clinical review team does not find any other safety signals based on the AEs leading to discontinuation reported in the original NDA filing and the SUR.

Table 42. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, PURPOSE 2

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Any AE leading to discontinuation	32 (1.5)	10 (0.9)	0.5 (-0.3, 1.3)
Gastrointestinal disorders (SOC)	1 (0.0)	3 (0.3)	-0.2 (-0.8, 0.0)
Abdominal pain	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Nausea	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Abdominal pain upper	0	1 (0.1)	-0.1 (-0.5, 0.1)
Diarrhoea	0	1 (0.1)	-0.1 (-0.5, 0.1)
General disorders and administration site conditions (SOC)	27 (1.2)	4 (0.4)	0.9 (0.2, 1.5) *
Injection site nodule	17 (0.8)	0	0.8 (0.4, 1.2) *
Injection site pain	8 (0.4)	2 (0.2)	0.2 (-0.3, 0.6)
Injection site induration	2 (0.1)	0	0.1 (-0.3, 0.3)
Injection site granuloma	1 (0.0)	0	0.0 (-0.3, 0.3)
Injection site ulcer	1 (0.0)	0	0.0 (-0.3, 0.3)
Oedema peripheral	1 (0.0)	0	0.0 (-0.3, 0.3)
Injection site mass	0	1 (0.1)	-0.1 (-0.5, 0.1)
Malaise	0	1 (0.1)	-0.1 (-0.5, 0.1)

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Infections and infestations (SOC)	2 (0.1)	0	0.1 (-0.3, 0.3)
Gastroenteritis	1 (0.0)	0	0.0 (-0.3, 0.3)
Onychomycosis	1 (0.0)	0	0.0 (-0.3, 0.3)
Investigations (SOC)	0	2 (0.2)	-0.2 (-0.7, -0.0) *
Creatinine renal clearance decreased	0	2 (0.2)	-0.2 (-0.7, -0.0) *
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.0)	0	0.0 (-0.3, 0.3)
Brain neoplasm	1 (0.0)	0	0.0 (-0.3, 0.3)
Nervous system disorders (SOC)	0	1 (0.1)	-0.1 (-0.5, 0.1)
Headache	0	1 (0.1)	-0.1 (-0.5, 0.1)
Renal and urinary disorders (SOC)	0	1 (0.1)	-0.1 (-0.5, 0.1)
Nephropathy	0	1 (0.1)	-0.1 (-0.5, 0.1)
Skin and subcutaneous tissue disorders (SOC)	3 (0.1)	0	0.1 (-0.2, 0.4)
Rash	1 (0.0)	0	0.0 (-0.3, 0.3)
Urticaria	1 (0.0)	0	0.0 (-0.3, 0.3)
Vasculitic rash	1 (0.0)	0	0.0 (-0.3, 0.3)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; incl, including; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

7.6.2.5. Treatment-Emergent Adverse Events, PURPOSE 2

Please refer to Section 17.2.2 for a complete tabulation of TEAEs occurring in at least 0.6% of participants in either arm. TEAEs considered at least possibly related to study drug (i.e., adverse drug reactions, ADRs) and occurring in at least 2% of participants in either group are shown in Table 43. The most common ADRs were ISR-related and these events were more common among LEN participants than among F/TDF participants. ISRs occurred in 1816 (83.2%) of LEN recipients and 756 (69.5%) of F/TDF participants. These events are discussed in detail in Section 7.6.4. Apart from ISRs, ADRs occurring in at least 2% of participants were either balanced between groups or favored LEN, with less GI-related PTs such as nausea in the LEN group. Nausea occurred in 46 (4.2%) of recipients of F/TDF and 48 (2.2%) of recipients of LEN.

ADRs to be included in labeling are those that occurred in at least 2% of participants in the LEN and F/TDF groups and include ISRs, headache, nausea, and diarrhea.

Table 43. Participants With Adverse Events Assessed by Investigator as Treatment-Related, Showing Terms Occurring in at Least 2% of Participants in Any Group, Safety Population, PURPOSE 2

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Any AE	1785 (81.8)	761 (69.9)	11.8 (8.7, 15.0) *
Gastrointestinal disorders (SOC)	114 (5.2)	82 (7.5)	-2.3 (−4.2, −0.6) *
Diarrhoea	43 (2.0)	25 (2.3)	-0.3 (−1.5, 0.7)
Nausea	48 (2.2)	46 (4.2)	-2.0 (−3.5, −0.8) *
General disorders and administration site conditions (SOC)	1751 (80.2)	724 (66.5)	13.7 (10.4, 17.0) *
Injection site nodule	1334 (61.1)	416 (38.2)	22.9 (19.3, 26.4) *
Injection site induration	337 (15.4)	108 (9.9)	5.5 (3.1, 7.8) *
Injection site pain	1171 (53.6)	550 (50.6)	3.1 (−0.5, 6.7)
Injection site pruritus	69 (3.2)	28 (2.6)	0.6 (−0.7, 1.7)
Injection site warmth	50 (2.3)	24 (2.2)	0.1 (−1.1, 1.1)
Injection site bruising	63 (2.9)	34 (3.1)	-0.2 (−1.6, 0.9)
Injection site erythema	373 (17.1)	210 (19.3)	-2.2 (−5.1, 0.6)
Injection site swelling	144 (6.6)	101 (9.3)	-2.7 (−4.8, −0.7) *
Nervous system disorders (SOC)	73 (3.3)	47 (4.3)	-1.0 (−2.5, 0.4)
Headache	39 (1.8)	27 (2.5)	-0.7 (−1.9, 0.3)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

7.6.2.6. Laboratory Findings, PURPOSE 2

There were no clinically relevant differences between treatment groups in chemistry, hematology, or kidney function laboratory parameters. Please refer to Section 17.2.3 for more details.

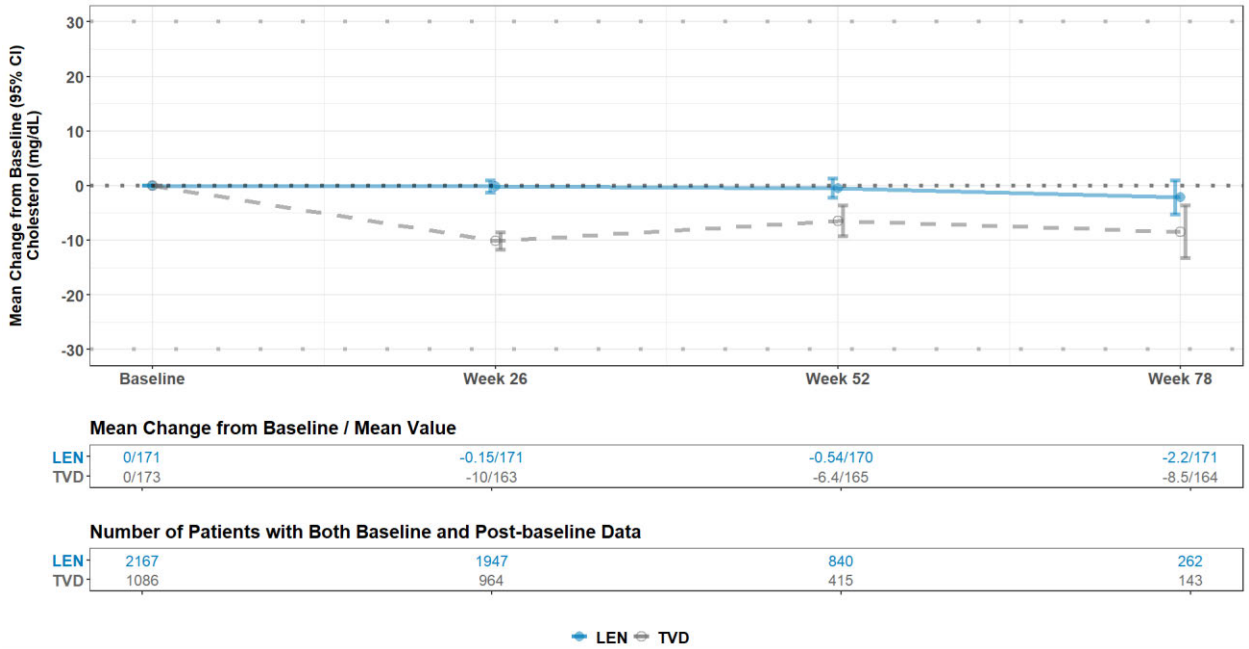
As previously stated, juvenile rat toxicity studies showed elevated cholesterol levels which resolved with maturity. In PURPOSE 2, lipid parameters were checked every 26 weeks. The proportion of participants with lipid parameter outliers are displayed in Table 44 below. A higher proportion of LEN recipients had elevated total cholesterol (24.7% in the LEN group, 19% in the F/TDF group, for total cholesterol >200 mg/dL) and mildly high LDL (20.7% in the LEN group, 17.1% in the F/TDF group, for LDL >130 mg/dL). A higher proportion of F/TDF recipients had mildly low HDL. However, the mean change from baseline of each lipid analyte over time in the LEN group does not reflect a clinically significant finding. Figure 9 displays the mean cholesterol change from baseline over time, Figure 10 displays the mean LDL change over time, and Figure 11 displays the mean HDL change from baseline over time. No clinically relevant differences were seen between groups. The clinical review team does not find concerning safety signals based on evaluation of the lipid parameters.

Table 44. Participants With One or More Lipid Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 2

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	485/1963 (24.7)	186/977 (19.0)	5.7 (2.5, 8.7) *
Level 2 (>210)	363/1963 (18.5)	128/977 (13.1)	5.4 (2.6, 8.1) *
Level 3 (>225)	224/1963 (11.4)	76/977 (7.8)	3.6 (1.4, 5.8) *
HDL, males, low (mg/dL)			
Level 1 (<40)	673/1924 (35.0)	408/957 (42.6)	-7.7 (-11.5, -3.9) *
Level 2 (<30)	141/1924 (7.3)	84/957 (8.8)	-1.4 (-3.7, 0.6)
Level 3 (<20)	5/1924 (0.3)	4/957 (0.4)	-0.2 (-0.8, 0.3)
HDL, females, low (mg/dL)			
Level 1 (<50)	25/37 (67.6)	14/20 (70.0)	-2.4 (-25.8, 23.8)
Level 2 (<40)	14/37 (37.8)	5/20 (25.0)	12.8 (-13.6, 35.3)
Level 3 (<20)	1/37 (2.7)	0/20 (0)	2.7 (-13.8, 14.0)
LDL, high (mg/dL)			
Level 1 (>130)	405/1961 (20.7)	167/975 (17.1)	3.5 (0.5, 6.4) *
Level 2 (>160)	110/1961 (5.6)	40/975 (4.1)	1.5 (-0.2, 3.1)
Level 3 (>190)	30/1961 (1.5)	11/975 (1.1)	0.4 (-0.6, 1.2)
Triglycerides, high (mg/dL)			
Level 1 (>150)	517/1962 (26.4)	225/977 (23.0)	3.3 (-0.0, 6.6)
Level 2 (>300)	93/1962 (4.7)	40/977 (4.1)	0.6 (-1.0, 2.1)
Level 3 (>500)	25/1962 (1.3)	7/977 (0.7)	0.6 (-0.3, 1.3)

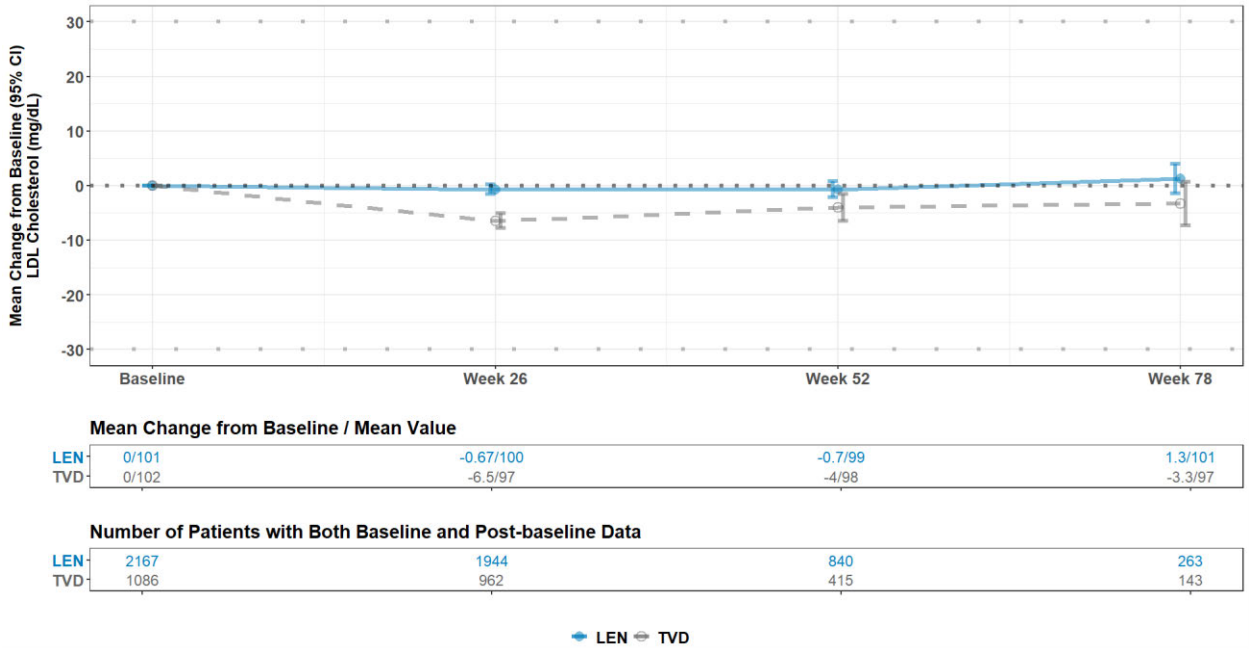
Source: [Clinical Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: F/TDF, emtricitabine/tenofovir disoproxil fumarate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data.

Figure 9. Mean Change From Baseline, Total Cholesterol, Safety Population, PURPOSE 2



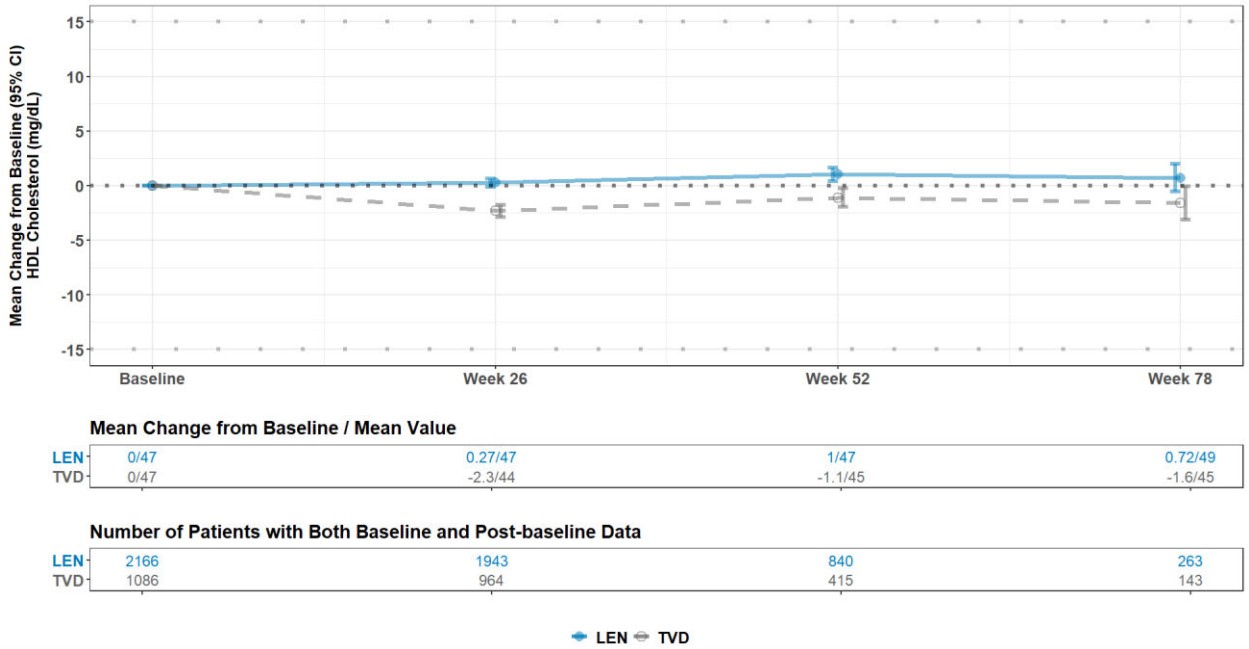
Source: [Clinical Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

Figure 10. Mean Change From Baseline, LDL Cholesterol, Safety Population, PURPOSE 2



Source: [Clinical Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

Figure 11. Mean Change From Baseline, HDL Cholesterol, Safety Population, PURPOSE 2

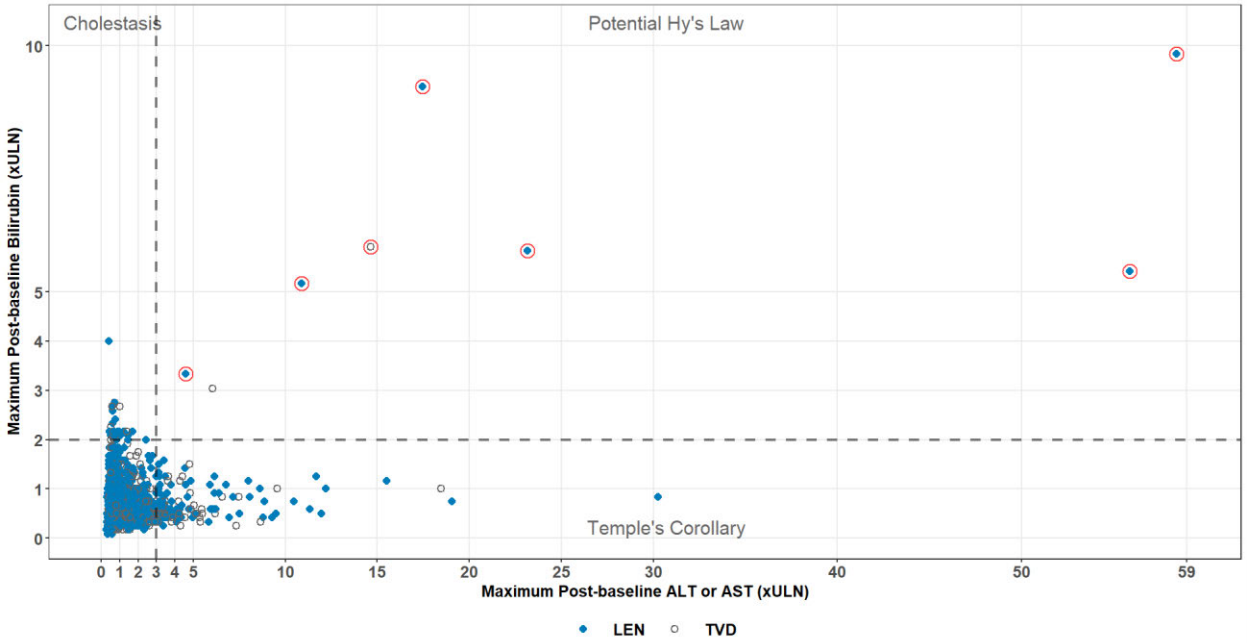


Source: [Clinical Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

7.6.2.7. Assessment of Drug-Induced Liver Injury, PURPOSE 2

Figure 12 shows a screening assessment for potential cases of serious drug-induced liver injury (DILI). Table 45 shows the participants in each quadrant for potential hepatocellular DILI screening plot.

Figure 12. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, PURPOSE 2



Source: [Data Scientist] adlb.xpt; Software: R.
Each data point represents a participant plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those participants who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All participants with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of participants in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot …" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening…."
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate; ULN, upper limit of normal.

Table 45. Participants in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, PURPOSE 2

Quadrant	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)
Potential Hy's Law (right upper)	6/2153 (0.3)	2/1073 (0.2)
Cholestasis (left upper)	23/2153 (1.1)	10/1073 (0.9)
Temple's corollary (right lower)	85/2153 (3.9)	47/1073 (4.4)
Total	114/2153 (5.3)	59/1073 (5.5)

Source: [Data Scientist] adlb.xpt; Software: R.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

There are no concerning imbalances between groups in hepatocellular DILI screening. Of the six LEN participants who met Potential Hy's Law, five of the six were diagnosed with Hepatitis A at the time of the laboratory abnormalities. The remaining participant experienced abnormal liver

function tests on Study Day 130 with concomitant systemic symptoms of fever, nausea, vomiting, and dark urine. The participant had rapid improvement in the abnormal liver laboratory parameters and continued to have a second dose of LEN on Study Day 183. As the liver laboratory parameters improved despite continued exposure to LEN, the investigators have assessed that the abnormalities are not related to LEN. The clinical review team also does not find a likely relationship between the liver related laboratory abnormalities and the use of LEN.

7.6.2.8. Vital-Sign Analyses, PURPOSE 2

No clinically relevant changes from baseline or in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature or weight were seen.

7.6.3. Safety Results, Pooled Analyses, PURPOSE 1 and PURPOSE 2

The LEN and F/TDF treatment groups from PURPOSE 1 and PURPOSE 2 were pooled to look for rare safety signals. A thorough safety review did not reveal any safety signals that had not been previously identified in the safety analyses of PURPOSE 1 and PURPOSE 2 separately. Please see Section 17.3 for more details.

7.6.4. Adverse Events of Special Interest: Injection Site Reactions

Background

The only AESI for either PURPOSE 1 or PURPOSE 2 were ISRs. ISRs are a concern for all medications administered via SC injection and were the most commonly reported adverse drug reactions in the studies supporting approval of SC LEN as a component of HIV-1 treatment in the HTE population.

Summary

ISRs were the most commonly reported adverse drug reaction in PURPOSE 1 and PURPOSE 2 (reported in 69% and 83% of LEN recipients, respectively), and were markedly more common among participants receiving SC LEN compared to participants receiving SC placebo injections of polyethylene glycol 400 (b) (4) Most ISRs in participants receiving SC LEN were Grade 1 or Grade 2 in severity and none of the ISRs were serious. ISRs leading to premature discontinuation of SC LEN were uncommon. The most commonly reported ISR among participants receiving SC LEN were injection site nodule events, which had a median duration of close to one year (after Day 1 [SC Injection 1]). Injection site induration events, although reported less frequently, also had a long duration with a median duration of approximately 3 to 6 months (after Day 1 [SC Injection 1]). Other ISRs (excluding injection site nodule and induration), such as erythema, pain, and swelling, resolved more quickly with a median duration of approximately one week.

The majority of data presented below is from the original NDA submissions. For the calculations of the duration of ISRs which did not all resolve by the data cutoff (i.e., nodules and induration),

the maximum duration was defined as the greater of either the longest resolved duration or the longest duration of follow-up for an unresolved event (written as > longest follow-up time); data from the SUR were used to calculate the durations for nodules and indurations after the Day 1 injections (SC Injection 1).

Although cross-trial comparisons are generally discouraged, ISRs of erythema, induration, and pain were less frequently reported among participants in PURPOSE 1 compared to participants in PURPOSE 2. This could be explained by the different demographics of the populations in these two trials (PURPOSE 1 was conducted exclusively in adolescent girls and young women in Africa whereas PURPOSE 2 was conducted in a cisgender men and gender-diverse people at sites in South America, North America, Africa, and Asia), which could impact subcutaneous fat thickness, skin tone/color, and ISR reporting rates.

A small number of serious cases of injection site necrosis and injection site ulcer have been reported in the postmarketing setting following improper administration (intradermal injection) of SC LEN injections (SUNLENCA). In PURPOSE 1 and PURPOSE 2, a total of 14 participants (<0.5%) who received SC LEN reported injection site ulcer, and no participant reported injection site necrosis. The development of injection site ulcer in some of the PURPOSE 1 and PURPOSE 2 participants was determined to be attributable to improper administration technique, resulting in intradermal injection rather than the specified subcutaneous injection. Despite the rare occurrence of injection site ulcer, these observations underscore the importance of administering SC LEN in strict adherence to labeling instructions and employing appropriate injection techniques. Injection site ulcer and injection site necrosis, which have been associated with the improper administration (intradermal injection) of SC LEN, are adequately labeled under WARNINGS AND PRECAUTIONS and clear step-by-step preparation and administration instructions along with pictures are provided in Section 2.6 *Preparation and Administration of Subcutaneous Injection* in the USPI.

7.6.4.1. PURPOSE 1

A total of 10,158 SC LEN injections and 15,171 SC placebo injections were administered to participants. ISRs were reported in 1,472 of 2,140 participants (68.8%) who received LEN injections and 1,116 of 3,204 participants (34.8%) who received placebo injections. Of note, one participant randomized to F/TAF did not receive placebo injections on Day 1.

As shown in Table 46, the most commonly reported ISRs in PURPOSE 1 (occurring in >10% of LEN participants) among LEN participants were injection site nodule (63.8%) and injection site pain (31.3%). See Section 17.6 for full details.

Table 46. Injection Site Reactions (All Grades) Reported in ≥2% of Participants Receiving LEN, Safety Population, Randomized Blinded Phase, PURPOSE 1

Preferred Term	LEN N=2140 n (%)	F/TDF+F/TAF[a] N=3205 n (%)	LEN vs. F/TDF+F/TAF[a] Risk Difference[b] (%) (95% CI)
Number of participants with any ISR	1472 (68.8)	1116 (34.8)	34.0 (31.4, 36.5)
Injection site nodule	1365 (63.8)	530 (16.5)	47.2 (44.8, 49.6)
Injection site pain	669 (31.3)	758 (23.7)	7.6 (5.2, 10.1)
Injection site swelling	96 (4.5)	171 (5.3)	-0.8 (−2.0, 0.4)
Injection site induration	91 (4.3)	32 (1.0)	3.3 (2.4, 4.2)
Injection site pruritus	50 (2.3)	38 (1.2)	1.2 (0.4, 2.0)

Source: Clinical Reviewer and Clinical Data Scientist; adae.xpt; Software: R, JMP v17.2.0.
[a] Participants received subcutaneous placebo injections.
[b] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate (coformulated TRUVADA); F/TAF, emtricitabine/tenofovir alafenamide (coformulated DESCOVY); ISR, injection site reaction; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event.

Most ISRs were Grade 1 or 2 in severity, with Grade 3 ISRs reported in 4 participants (0.2%) who received LEN injections and 4 participants (0.1%) who received placebo injections. There were no Grade 4 ISRs and none of the ISRs were serious. The Grade 3 ISRs reported after LEN injections were injection site ulcer (3 participants [0.1%]) and injection site nodule (1 participant [<0.1%]). The Grade 3 ISRs reported after placebo injections were injection site ulcer (3 participants [0.1%]) and injection site pain (1 participant [<0.1%]).

Overall, four participants (0.2%) who received LEN injections and zero participants who received placebo injections prematurely discontinued study drugs due to ISRs. The ISRs leading to discontinuation of LEN were injection side nodule (4 participants [0.2%]) and injection site pain (1 participant [<0.1%]).

The incidence of ISRs in participants who received LEN injections decreased with subsequent injections:

- After the Day 1 injection (SC Injection 1): 1325 of 2140 participants (61.9%)
- After the Week 26 injection (SC Injection 2): 898 of 1930 participants (46.5%)
- After the Week 52 injection (SC Injection 3): 266 of 862 participants (30.9%)

The incidence of ISRs in participants who received placebo injections decreased with subsequent injections:

- After the Day 1 injection (SC Injection 1): 844 of 3204 participants (26.3%)
- After the Week 26 injection (SC Injection 2): 447 of 2883 participants (15.5%)
- After the Week 52 injection (SC Injection 3): 153 of 1274 participants (12.0%)

Overall, the number of reported ISRs appears to decrease after subsequent injections. While this finding is reassuring, one cannot confidently conclude the reason for the decreased reporting is due to absence of ISR events. It is conceivable that participants stopped reporting ISRs because of increased tolerance and not because of the lack of ISR events.

Injection Site Nodule

Overall, injection site nodule events were reported as follows:

- LEN injections: 1,365 of 2,140 participants (63.8%)
- Placebo injections: 530 of 3,205 participants (16.5%)

Of the total 10,158 SC LEN injections administered, 4,056 injection site nodule events (39.9%) were reported. Of the total 15,171 SC placebo injections administered, 845 injection site nodule events (5.6%) were reported. All but one injection site nodule event was Grade 1 or 2 in severity. The Grade 3 injection site nodule event was reported in one participant in the LEN group.

At Day 1 (SC Injection 1), injection site nodules were reported in 56.4% of participants who received LEN (9.4% had one nodule per participant and 46.6% had two nodules per participant) and 13.3% of participants who received placebo injections (7.4% had one nodule per participant and 5.8% had two nodules per participant).

The median (Q1, Q3) of the maximum observed nodule diameter from each participant was 3.0 (2.0, 3.5) cm in participants who received LEN and 1.0 (0.5, 2.0) cm in participants who received placebo injections. The median (Q1, Q3) of the maximum observed nodule diameter per event was 2.0 (1.5, 3.0) cm in participants who received LEN and 1.0 (0.5, 1.5) cm in participants who received placebo injections.

The duration (days) of injection site nodule events after Day 1 (SC Injection 1):

- LEN injections:
  - Median: 350
  - Interquartile range (IQR): 182, 470
  - Range: 2, >854
- Placebo injections:
  - Median: 75
  - IQR: 44, 141
  - Range: 2, 636

The most common skin findings associated with injection site nodules among participants who received LEN or placebo injection were as follows:

- LEN injections: tenderness (5.6%, 565 of 10,158 injections), swelling (2.5%, 254 injections), and other (1.4%, 143 injections)
- Placebo injections: tenderness (0.9%, 129 of 15,171 injections), swelling (0.3%, 38 injections), and other (0.2%, 35 injections)

Injection Site Induration

Overall, injection site induration events were reported as follows:

- LEN injections: 91 of 2,140 participants (4.3%)
- Placebo injections: 32 of 3,204 participants (1.0%)

Of the total 10,158 SC LEN injections administered, 159 injection site induration events (1.6%) were reported. Of the total 15,171 placebo injections administered, 43 injection site induration events (0.3%) were reported. All injection site induration events were Grade 1 or 2 in severity.

At Day 1 (SC Injection 1), injection site indurations were reported in 3.1% of participants who received LEN (1.1% had 1 induration per participant and 2.0% had 2 indurations per participant) and 0.7% of participants who received placebo injections (13 participants had 1 induration per participant and 9 participants had 2 indurations per participant).

The median (Q1, Q3) of the maximum observed induration diameter per participant was 3.0 (2.0, 3.6) cm in participants who received LEN and 3.5 (1.0, 5.0) cm in participants who received placebo injections. The median (Q1, Q3) of the maximum observed induration diameter per event was 2.5 (1.5, 3.0) cm in participants who received LEN and 3.0 (2.3, 4.0) cm in participants who received placebo injections.

The duration (days) of injection site induration events after Day 1 (SC Injection 1):

- LEN injections:
  - Median: 162
  - IQR: 20, 270
  - Range: 3, 739
- Placebo injections:
  - Median: 8
  - IQR: 3, 37
  - Range: 2, >511

The most common skin findings associated with injection site indurations among participants who received LEN or placebo injection were as follows:

- LEN
  - tenderness (0.5%, 46 of 10,158 injections), and swelling and other (each 0.2%, 23 injections)
- Placebo
  - tenderness (<0.1%, 11 of 15,171 injections), erythema (<0.1%, 9 injections), and swelling (<0.1%, 7 injections)

Other Notable Injection Site Reactions

Injection site ulcers were reported in 3 participants (0.1%) who received LEN SC injections and 4 participants (0.1%) who received placebo SC injections. Injection site necrosis was reported in 2 participants (<0.1%) who received placebo SC injections. The Grade 3 injection site ulcer in one participant who received LEN injections and Grade 3 injection site ulcer and Grade 2 injection site necrosis in one participant who received placebo injections were assessed by the Applicant to be associated with incorrect (intradermal) injection technique. One additional participant who received placebo injections had Grade 3 injection site sterile abscess which was also confirmed to be associated with incorrect (intradermal) injection technique; this event was initially coded as “injection site abscess” but was corrected to “injection site sterile abscess” after

database finalization. Injection site necrosis and injection site ulcer are adequately described as serious ISRs associated with the improper administration (intradermal injection) under the WARNINGS AND PRECAUTIONS section (5.4 *Serious Injection Site Reactions with Improper Administration*) in the YEZTUGO labeling.

Other Injection Site Reactions

The duration (days) of any ISRs (excluding nodules and indurations) associated with all SC study drug doses was similar in both groups:

- LEN injections
  - Median: 9
  - IQR: 4, 29
  - Range: 1, 435
- Placebo injections
  - Median: 7
  - IQR (Q1, Q4): 3, 15
  - Range: 1, 385

7.6.4.2. PURPOSE 2

A total of 10,094 LEN and 5,145 placebo injections were administered to participants. ISRs were reported for 1,816 of 2,183 participants (83.2%) who received LEN injections and 756 of 1,088 participants (69.5%) who received placebo injections.

As shown in Table 47, the most commonly reported ISRs in PURPOSE 2 (occurring in >10% of LEN participants) among LEN participants were injection site nodule (63.4%), injection site pain (56.4%), injection site erythema (17.3%), and injection site induration (15.7%). See Section 17.6 for full details.

Table 47. Injection Site Reactions (All Grades) Reported in ≥2% of Participants Receiving LEN, Safety Population, Randomized Blinded Phase, PURPOSE 2

Preferred Term	LEN N=2183 n (%)	F/TDF[a] N=1088 n (%)	LEN vs. F/TDF[a] Risk Difference[b] (%) (95% CI)
Participants with any ISR	1816 (83.2)	756 (69.5)	13.8 (10.7, 17.0)
Injection site nodule	1383 (63.4)	427 (39.2)	24.1 (20.5, 27.6)
Injection site pain	1231 (56.4)	581 (53.4)	3.0 (−0.6, 6.6)
Injection site erythema	377 (17.3)	211 (19.4)	-2.1 (−5.0, 0.7)
Injection site induration	342 (15.7)	110 (10.1)	5.6 (3.1, 7.9)
Injection site swelling	149 (6.8)	104 (9.6)	-2.7 (−4.9, −0.8)
Injection site pruritus	74 (3.4)	30 (2.8)	0.6 (−0.7, 1.8)
Injection site bruising	67 (3.1)	42 (3.9)	-0.8 (−2.3, 0.5)
Injection site warmth	51 (2.3)	24 (2.2)	0.1 (−1.1, 1.2)

Source: Clinical Reviewer and Clinical Data Scientist; adae.xpt; Software: R, JMP v17.2.0.
[a] Participants received subcutaneous placebo injections.
[b] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate (coformulated TRUVADA); F/TAF, emtricitabine/tenofovir alafenamide (coformulated DESCOVY); ISR, injection site reaction; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event.

Most ISRs were Grade 1 or 2 in severity, with Grade 3 ISRs reported in 14 participants (0.6%) who received LEN injections and 1 participant (<0.1%) who received placebo injections. The Grade 3 ISRs reported after LEN injections were injection site pain (4 participants [0.2%]), injections site ulcer (4 participants [0.2%]), injection site erythema (3 participants [0.1%]), injection site dermatitis (1 participant [<0.1%]), and injection site edema (1 participant [<0.1%]). The only Grade 3 ISR reported after placebo injections was injection site pain (1 participant [<0.1%]). There were no Grade 4 ISRs and none of the ISRs were serious.

Overall, 26 participants (1.2%) who received LEN injections and 3 participants (0.3%) who received placebo injections prematurely discontinued study drugs due ISRs. The ISRs leading to discontinuation of LEN injections were injection site nodule (17 participants [0.8%]), injection site pain (8 participants [0.4%]), injection site induration (2 participants [<0.1%]), injection site granuloma (1 participant [<0.1%]), injection site mass (1 participant [<0.1%]), and injection site ulcer (1 participant [<0.1%]). The ISRs leading to discontinuation of placebo injections were injection site pain (2 participants [0.2%]) and injection site mass (1 participant [<0.1%]).

The incidence of ISRs in participants who received LEN decreased with subsequent injections:

- After the Day 1 injection (SC Injection 1): 1616 of 2183 participants (74.0%)
- After the Week 26 injection (SC Injection 2): 1292 of 1859 participants (69.5%)
- After the Week 52 injection (SC Injection 3): 433 of 744 participants (58.2%)

The incidence of ISRs in participants who received placebo injections decreased with subsequent injections:

- After the Day 1 injection (SC Injection 1): 628 of 1088 participants (57.7%)
- After the Week 26 injection (SC Injection 2): 468 of 946 participants (49.5%)
- After the Week 52 injection (SC Injection 3): 155 of 379 participants (40.9%)

Overall, the number of reported ISRs appears to decrease after subsequent injections. While this finding is reassuring, one cannot confidently conclude the reason for the decreased reporting is due to absence of events. It is conceivable that participants stopped reporting ISRs because of increased tolerance and not because of the lack of events.

Injection Site Nodule

Overall, injection site nodule events were reported as follows:

- LEN injections: 1,383 of 2,183 participants (63.4%)
- Placebo injections: 427 of 1,088 participants (39.2%)

Of the total 10,094 SC LEN injections administered, 4,797 injection site nodule events (47.5%) were reported. Of the total 5,145 placebo injections administered, 1,085 injection site nodule events (21.1%) were reported. All AEs of injection site nodule were Grade 1 or 2 in severity.

At Day 1 (SC Injection 1), injection site nodules were reported in 55.8% of participants who received LEN (6.9% had 1 nodule per participant and 48.8% had 2 nodules per participant) and 30.9% of participants who received placebo injections (9.3% had 1 nodule per participant and

21.6% had 2 nodules per participant). The incidence of injection site nodule events decreased with subsequent injections in both the LEN and placebo groups.

The median (Q1, Q3) of the maximum observed nodule diameter per participant was 3.0 (2.0, 4.0) cm in participants who received LEN and 2.0 (1.0, 2.5) cm in participants who received placebo injections. The median (Q1, Q3) of the maximum observed nodule diameter per event was 2.0 (1.5, 3.0) cm in participants who received LEN and 1.2 (1.0, 2.0) cm in participants who received placebo injections.

The duration (days) of injection site nodules after Day 1 (SC Injection 1):

- LEN injections:
  - Median: 297
  - IQR: 176, 423
  - Range: 1, >1145
- Placebo injections:
  - Median: 60
  - IQR: 29, 120
  - Range: 1, >700

The most common skin findings associated with injection site nodules among participants who received LEN or placebo injection were as follows:

- LEN injections: tenderness (6.1%, 618 of 10,094 injections), erythema (3.6%, 367 injections), and swelling (2.4%, 247 injections)
- Placebo injections: tenderness (3.1%, 160 of 5,145 injections), erythema (2.5%, 130 injections), and bruising (1.1%, 57 injections)

Injection Site Induration

Overall, injection site induration events were reported as follows:

- LEN injections: 342 of 2,183 participants (15.7%)
- Placebo injections: 110 of 1,088 participants (10.1%)

Of the total 10,094 SC LEN injections administered, 838 injection site induration events (8.3%) were reported. Of the total 5,145 placebo injections administered, 293 injection site induration events (5.7%) were reported. All AEs of injection site induration were Grade 1 or 2 in severity.

At Day 1 (SC Injection 1), injection site indurations were reported in 12.2% of participants who received LEN (3.2% had 1 induration per participant and 9.0% had 2 indurations per participant) and 8.5% of participants who received placebo injections (2.5% had 1 induration per participant and 6.0% had 2 indurations per participant).

The median (Q1, Q3) of the maximum observed induration diameter per participant was 3.0 (2.0, 4.0) cm in participants who received LEN and 2.5 (1.0, 5.0) cm in participants who received placebo injections. The median (Q1, Q3) of the longest induration diameter per event was 2.0 (1.0, 3.0) cm in participants who received LEN and 2.5 (1.0, 4.0) cm in participants who received placebo injections.

The duration (days) of injection site indurations after Day 1 (SC Injection 1):

- LEN injections:
  - Median: 92
  - IQR: 11, 282
  - Range: 1, >639
- Placebo injections:
  - Median: 11
  - IQR: 7, 56
  - Range: 1, >814

The most common skin findings associated with injection site indurations among participants who received LEN or placebo injection were as follows:

- LEN
  - tenderness (1.3%, 127 of 10,094 injections), erythema (0.4%, 36 injections), and other (0.3%, 29 injections)
- Placebo
  - tenderness (0.8%, 40 of 5,145 injections), erythema (0.4%, 19 injections), and bruising (0.2%, 12 injections)

Other Notable Injection Site Reactions

Injection site ulcers were reported in 11 participants (0.5%) who received LEN injections and 1 participant (<0.1%) who received placebo injections. There were no Grade 4 injection site ulcers and none of the injection site ulcers were SAEs. Grade 3 injection site ulcers were reported in 7 participants (0.3%) who received LEN injections and no participant who received placebo injections. Overall, one participant (<0.1%) who received LEN injections and no participant who received placebo injections prematurely discontinued study drugs due to injection site ulcer. Of note, the Applicant assessed that Grade 3 injection site ulcers that occurred in 2 of the 11 participants who received LEN were confirmed to be associated with the incorrect injection technique (intradermal injection). Injection site necrosis and ulcer are adequately described as serious ISRs associated with the improper administration (intradermal injection) under the WARNINGS AND PRECAUTIONS section (5.4 *Serious Injection Site Reactions with Improper Administration*) in the YEZTUGO labeling.

Other Injection Site Reactions

The duration (days) of any ISRs (excluding nodules and indurations) associated with all SC study drug doses was similar in both groups:

- LEN injections
  - Median: 4
  - IQR: 2, 8
  - Range: 1, 854

- Placebo injections
  - Median: 3
  - IQR: 2, 7
  - Range: 1, 745

90-Day Safety Update Report

Overall, the ISR profile of LEN in the SUR was consistent with the profile in the original NDA submissions and no new ISR concerns for SC LEN were noted. The SUR provided longer-term information on the duration of ISRs; therefore, the data on duration of ISRs from the SUR has been incorporated into the durations of ISR types that took longer to resolve (i.e., nodules and induration) mentioned above.

7.7. Key Safety Review Issues

7.7.1. HIV-1 Resistance Development and/or Delayed HIV-1 Diagnosis in Participants Who Become HIV-1 Infected While on LEN

Issue

Undiagnosed HIV-1 infections present at the initiation of antiretroviral (ARV)-based pre-exposure prophylaxis (PrEP), or infections that occur during PrEP use, result in monotherapy that could select for ARV-resistant virus. These resistant viruses may be cross-resistant with other ARVs in the same class, potentially limiting future treatment options. Another potential concern is that the presence of an active ARV during an undiagnosed infection, even when present only as monotherapy, might prolong the time before HIV-1 diagnostic assays can detect the infection.

Background

The selection of viruses resistant to lenacapavir (LEN), the first and currently only member of the HIV-1 capsid inhibitor class of ARVs (see the NDA 215973/215974 Integrated Review dated December 22, 2022 (FDA 2022a)), could affect the efficacy of future antiretroviral therapies (ART) that include a capsid inhibitor. However, LEN is currently approved only for treating highly treatment-experienced individuals with HIV-1, not as part of a first-line regimen or switch option, limiting the impact of LEN resistance.

Another potential concern is that LEN may delay HIV-1 diagnosis in individuals who are infected or who become infected during use. Antiretroviral-based PrEP products can affect the ability of HIV-1 diagnostic assays to detect infection (Donnell et al. 2017), likely due to suppressed viral replication and delayed development of high-affinity anti-HIV-1 antibodies (Parker et al. 2021). Delayed HIV-1 diagnoses have been reported for currently approved PrEP products, including oral emtricitabine/tenofovir disoproxil fumarate (F/TDF) (Donnell et al. 2017) and injectable long acting cabotegravir (CAB LA) (Marzinke et al. 2021; Eshleman et al. 2022) (Section 7.7.1 of the Integrated Review of NDA 215499 (FDA 2021)). Notably, CAB

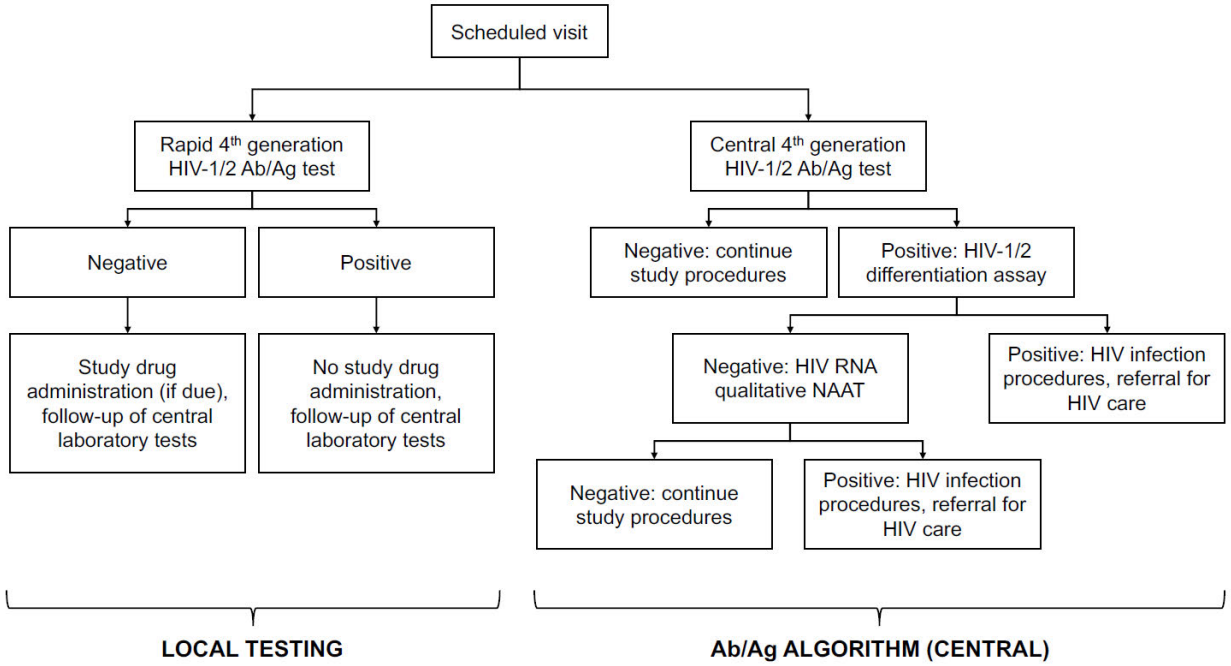
LA's impact on infection diagnosis is greater than F/TDF's, both in duration and affected assay types, presumably due to higher adherence and more durable antiretroviral activity.

Assessment

HIV Diagnostics

The HIV testing algorithm used for both PURPOSE 1 (Bekker et al. 2024) and PURPOSE 2 (Kelley et al. 2025) is illustrated in Figure 13 (from Figure S1 of (Bekker et al. 2024)). All participants were tested using assays conducted by the local clinical site and by a central laboratory (b) (4) at Screening, Baseline (Day 1), and at each on-study visit. The local site used a point-of-care antigen/antibody (Ag/Ab) rapid test (Abbott Determine™ HIV-1/2 Ag/Ab COMBO; FDA-approved, Premarket Application number [PMA] BP120037 (CBER 2022)) and the central laboratory used an instrumented, laboratory-based HIV-1/2 Ag/Ab assay (Siemens ADVIA Centaur® HIV Ag/Ab Combo Assay; FDA approved, PMA BP140103 (CBER 2020a)) and a quantitative reverse transcriptase polymerase chain reaction (RT-PCR)-based assay (Roche Cobas® HIV-1; FDA approved, PMA BP150262 (CBER 2020b)) at Screening and Baseline. The local site also used the point-of-care HIV-1/2 Ag/Ab rapid test at subsequent study visits, while the central laboratory used the laboratory-based HIV-1/2 Ag/Ab assay. In all cases, positive results by the central laboratory's Ag/Ab assay were confirmed with an HIV-1/2 antibody differentiation assay (Bio-Rad Geenius™ HIV 1/2 Supplemental Assay; FDA approved, BLA 125670 (CBER 2019)) that, unlike the Ag/Ab assays, can distinguish between HIV-1 and HIV-2 infections. Discordant serological results were further tested using a qualitative HIV-1 RNA RT-PCR assay (described as the "Cobas Ampliprep-cobas TaqMan 2.0", which may refer to the Roche Cobas® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test, v. 2.0, an assay that has been described by the World Health Organization but does not appear to have been approved or cleared by the FDA under this name) (WHO 2016). Quantitative plasma HIV-1 RNA testing (assay not identified) was conducted using samples stored from the preceding study visit(s) for any participants diagnosed with HIV-1 infection to estimate the time of infection.

Figure 13. HIV Testing Algorithm



Source: (Bekker et al. 2024).
Abbreviations: Ab/Ag, antibody/antigen; HIV, human immunodeficiency virus; NAAT, nucleic acid amplification test; RNA, ribonucleic acid.

HIV infections were considered prevalent if the date of diagnosis was retrospectively determined to be Day 1 (i.e., the participant was infected before beginning PrEP). All HIV testing results indicating a potential incident infection (i.e., those that occurred after initiating PrEP) were reviewed by a blinded adjudication committee. The committee determined whether results indicated infection, false-positive results, or ambiguous results requiring further testing. They also established the date of HIV diagnosis, defined as the earliest study day with evidence of infection in participants with incident infections.

Positive point-of-care Ag/Ab rapid test results were deemed false positives if the central laboratory's Ag/Ab assay was negative, and a contemporaneous quantitative plasma HIV-1 RNA assay detected no RNA. Positive central laboratory Ag/Ab test results were considered false positives if two consecutive (one contemporaneous and one follow-up) quantitative plasma HIV-1 RNA assays detected no RNA.

HIV Infections in PURPOSE 1 and PURPOSE 2

Thirteen participants randomized to the LEN groups of PURPOSE 1 (n=6) and PURPOSE 2 (n=7) were exposed to the drug while HIV-1 infected (Table 48); no HIV-2 infections were observed. Of these, 62% (8/13) had prevalent infections, (i.e., undiagnosed at baseline), including four participants in each trial. The remaining participants experienced incident infections (occurring during PrEP use): two in PURPOSE 1 and three in PURPOSE 2. Additionally, 53 infections (one prevalent and 52 incident) occurred among participants randomized to the F/TAF group in PURPOSE 1, and 39 infections (four prevalent and 35 incident) among participants randomized to the F/TDF groups across both trials (Table 48). Of note, HIV-1 infections that occurred after the data cutoff date for the efficacy analysis, but which were reported in the SUR, are included in these numbers.

Table 48. HIV-1 Infections, PURPOSE 1 and PURPOSE 2

	PURPOSE 1			PURPOSE 2	
	LEN	F/TAF	F/TDF	LEN	F/TDF
Infections	n (%)	n (%)	n (%)	n (%)	n (%)
HIV-1 Infections	6	53	26	7	13
Prevalent	4 (67)	1 (02)	2 (08)	4 (57)	2 (15)
Incident	2 (33)	52 (98)	24 (92)	3 (43)	11 (85)
HIV-1 Subtypes					
A		2 (04)			
A1	1 (17)	2 (04)	2 (08)		
A/C			1 (04)		
A/D		1 (02)			
B					5 (38)
C	2 (33)	32 (60)	14 (54)	5 (71)	5 (38)
D	1 (17)	1 (02)			
F1					1 (08)
Missing	2 (33)	15 (28)	9 (35)	2 (29)	2 (15)

Source: PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h), 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b).
Abbreviations: F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV-1, human immunodeficiency virus 1; LEN, lenacapavir.

Most HIV-1 infections in the PURPOSE trials occurred in South Africa (ZAF) and were associated with HIV-1 subtype C, including 81% (48/59) of the subtyped infections in PURPOSE 1 and 56% (9/16) in PURPOSE 2 (Table 49). The subtype distributions are consistent with the known epidemiology of HIV-1, with subtypes B, C, and F being prevalent in Brazil (BRA, (Graf et al. 2021)), subtype B being prevalent in Peru (PER, (Yabar et al. 2012; Trebelcock et al. 2019)) and the USA (Kline et al. 2019), and subtypes A, D, and A/D being prevalent in Uganda (UGA, (Nazziwa et al. 2013; Yebra et al. 2015; Lamers et al. 2020)). Notably, LEN demonstrated comparable levels of antiviral activity against multiple HIV-1 isolates, including subtypes A, B, C, D, and F, when evaluated in cell culture (see the NDA 215973/215974 Integrated Review dated February 8, 2022 (FDA 2022a)), so LEN is expected to demonstrate efficacy consistently across subtypes.

Table 49. HIV-1 Subtypes vs. Country

	PURPOSE 1		PURPOSE 2				
HIV-1 Subtype	UGA	ZAF	BRA	PER	THA	USA	ZAF
A	2						
A1	5						
A/C		1					
A/D	1						
B			1	1		3	
C		48	1				9
D	2						
F1			1				
Missing	7	19	1		1		2

Source: PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h), 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b), adsl.xpt datasets for PURPOSE 1 (Gilead Sciences 2024b) and PURPOSE 2 (Gilead Sciences 2024e).
Abbreviations: BRA, Brazil; HIV-1, human immunodeficiency virus 1; PER, Peru; THA, Thailand; UGA, Uganda; USA, United States of America; ZAF, South Africa.

HIV-1 Diagnosis, Effect of LEN on Diagnosis, and LEN Resistance

Key information for the HIV-1 infections among participants randomized to receive LEN for PrEP is presented in Table 50, including HIV-1 diagnostic assay results at each timepoint, LEN dosing times, LEN plasma concentrations (when available), ART initiation time, and genotypic data (viral subtype and LEN resistance-associated substitutions [RAS]).

Table 50. HIV-1 Infections, LEN Group, PURPOSE 1 and PURPOSE 2

				Local		Central					
ID	Day	Visit	[LEN] (ng/mL)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	LEN RAS	Potential LEN RAS
Prevalent Infections											
PURPOSE 1											
(b) (6)	-14	Screen		-	-		-				
	1	LEN Injection		-	+	-	+	4,540,000	C	NR	
	6	Initiate ART									
	8	Unscheduled		+			+	26,500		NR	
	29	30-Day FU					+	195			
	91	90-Day FU					+	<20			
	-24	Screen		-	-		-				
	1	LEN Injection		-	+	-	+	105,000,000	A1	NR	T54M, L111T
	9	Unscheduled			+	+	+	227,000		N74D	T54M, L111T
	141	Initiate ART									
	176	30-Day FU					+	271		N74D	T54M, L111T
	269	90-Day FU					+	168			
	361	9 Month FU					+	90			
	-15	Screen		-	-		-				
	1	LEN Injection		-	+	-	+	80,500,000	D	NR	L56M, L69V
	29	Unscheduled		+							
	46	Initiate ART									
	75	30-Day FU			+	+					
	166	Unscheduled					+	119			
	271	6 Month FU					+	127,000		N74D	L56M, L69V
	347	9 Month FU					+	12,300			
	-25	Screen		-	-		-				
	1	LEN Injection		-	-		+	129,000	C	NR	T54S
	15	HIV Infection					+	269,000			
	24	Initiate ART									
	29	30-Day FU					+	353		T107A	T54S
	95	90-Day FU					-	ND			

				Local		Central					
ID	Day	Visit	[LEN] (ng/mL)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	LEN RAS	Potential LEN RAS
PURPOSE 2											
(b) (6)	-28	Screen		-	-		-				
	1	LEN Injection		-	+	-	+	67,300,000	C	NR	
	20	30-Day FU			+	+	+	4,340			
	111	Unscheduled					+	65,400		N74D	Q67R, I73V
	112	Initiate ART									
	184	6-Month FU					+				
	258	9-Month FU					-				
	-34	Screen		-	-		-				
	1	LEN Injection		-	+	-	+	77,900,000	C	NR	
	27	HIV Infection					+	618		NR	
	27	Initiate ART									
	62	30-Day FU					+	36			
	126	90-Day FU					+	27			
	-28	Screen		-	-		-				
	1	LEN Injection		-	-		+	452	ND	ND	ND
	16	Unscheduled			-		+	<20			
	32	HIV Infection					-				
	43	Initiate ART									
	71	30-Day FU					-				
	122	90-Day FU					-				
	-21	Screen		-	-		-				
	1	LEN Injection		-	-		+	31			
	13	Unscheduled		-							
	21	Unscheduled		-	-		+	189,000	C	NR	T54G
	29	Week 4		-	-		+	944,000			
	64	Initiate ART									
	77	30-Day FU					+	78,600		N74D	T54G, A105V
	119	90-Day FU					+	166			

				Local		Central					
ID	Day	Visit	[LEN] (ng/mL)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	LEN RAS	Potential LEN RAS
Incident Infections											
PURPOSE 1											
(b) (6)	-11	Screen		-	-		-				
	1	LEN Injection		-	-		-				
	29	Week 4	28.1	-	-						
	57	Week 8	54.1	-	-						
	92	Week 13	47.6	-	-						
	183	LEN Injection	11.3	-	-						
	271	Week 39	60.5	-	-						
	579	F/TDF OLE	1.19		-		-				
	670	Week 91	0.65	+	+	+	+	134,000	ND	NR	ND
	670	Unscheduled					+	200,000			
	674	Initiate ART									
	732	Week 104	BLQ				+	114			
	876	Week 125					+	38			
	-28	Screen		-	-		-				
	1	LEN Injection		-	-		-				
	30	Week 4	33.5	-	-						
	57	Week 8	75.5	-	-						
	92	Week 13	63.8	-	-						
	183	LEN Injection	31.8	-	-						
	274	Week 39	81	-	-		-				
	365	LEN Injection	44.6	-	-		+	47			
	456	OLE Week 13	106	-	+	±	+	78			
	464	Discontinuation	92	-	+	±	+	<20			
	492	30-Day FU	71.6				+	82			
PURPOSE 2											
(b) (6)	-12	Screen		-	-		-				
	1	LEN Injection		-	-		-				
	28	Week 4	26	-	-		-				
	56	Week 8	25.4	-	-		-				
	93	Week 13	23.8	+	+	±	+	934,000	C	N74D	ND
	93	Week 13					+	699,000			

				Local		Central					
ID	Day	Visit	[LEN] (ng/mL)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	LEN RAS	Potential LEN RAS
(b) (6)	-25	Screen		-	-		-				
	1	LEN Injection		-	-		-				
	30	Week 4	10.6	-	-						
	60	Week 8	5.08	-	-						
	92	Week 13	15.1	-	-		-				
	185	LEN Injection	25.2	-	+	±	+	14,100	C	N74D	Q50T, T54A
	-15	Screen		-	-		-				
	1	LEN Injection		-	-		-				
	29	Week 4	150	-	-						
	56	Week 8	166	-	-						
	85	Week 13	139	-	-						
	176	LEN Injection	17.4	-	-						
	267	Week 39	76.4	-	-		-				
	352	LEN Injection	14.2	-	+	-	+	2,020,000	ND	Q67H, K70R	ND
	360	Unscheduled					+	7,150			
	364	Unscheduled					+	1,550			
	391	30-Day FU	178								

Source: adcm.xpt datasets for PURPOSE 1 (Gilead Sciences 2024a) and PURPOSE 2 (Gilead Sciences 2024d); adsl.xpt datasets for PURPOSE 1 (Gilead Sciences 2024b) and PURPOSE 2 (Gilead Sciences 2024e); lb.xpt datasets for PURPOSE 1 (Gilead Sciences 2024c) and PURPOSE 2 (Gilead Sciences 2024f); PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h); 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b).
Abbreviations: Ab, HIV antibody test; Ag/Ab, HIV antigen/antibody test; ART, time of initiating antiretroviral therapy (dolutegravir, lamivudine, and tenofovir disoproxil fumarate); BLQ, below the assay's limit of quantification (0.5 ng/mL); F/TDF, emtricitabine/tenofovir disoproxil fumarate (Truvada); FU, post-HIV-1 infection follow-up visit; HIV, human immunodeficiency virus; ID, participant identifier; Lab, laboratory-based assay; LEN, lenacapavir; ND, no data; NR, no resistance-associated substitutions detected; OLE, Open-Label Extension; RNA, ribonucleic acid; +, positive assay result, -, negative assay result, ±, indeterminate assay result.

Potential LEN PrEP Failures

Two participants in PURPOSE 1 and three participants in PURPOSE 2 experienced incident infections representing potential PrEP failures. The narratives of these participants were reviewed for factors associated with increased risk of HIV-1 acquisition, including LEN plasma concentrations below the targeted minimum level (15.5 ng/mL) and STI or reported intravenous drug use near the time of HIV-1 acquisition.

PURPOSE 1, ID (b) (6): LEN injections were administered on Day 1 and Day 183. The Day 365 visit was missed. Open-label oral F/TDF was initiated on Day 579. HIV-1 infection was diagnosed on Day 670 when LEN concentrations had fallen to 0.65 ng/mL, well below the target LEN concentration. HIV-1 acquisition likely occurred after LEN levels fell below effective concentrations and during a period of non-adherence to daily oral F/TDF. No LEN RAS were detected, consistent with LEN concentrations having been too low to inhibit replication.

PURPOSE 1, ID (b) (6): LEN injections were administered on Day 1, Day 183, and Day 365. The participant had an undiagnosed acute HIV-1 infection on Day 365 that was acquired despite receiving on-time LEN injections and having achieved target plasma LEN concentrations at the time of HIV-1 infection. Chlamydia was reported as an adverse event on Day 378, potentially indicating an active STI at the time of HIV-1 infection. Viral loads were too low for resistance analysis. This case represents PrEP failure.

PURPOSE 2, ID (b) (6): An LEN injection was administered on Day 1. HIV-1 infection was diagnosed on Day 93 despite having achieved target plasma LEN concentrations. Resistance analysis of the Week 13 sample revealed an HIV-1 variant expressing the N74D LEN RAS. This case represents PrEP failure.

PURPOSE 2, ID (b) (6): LEN injections were administered on Day 1 and Day 185. HIV-1 infection was diagnosed on Day 185 by the central laboratory. The participants plasma LEN concentrations did not achieve the target concentration until Day 92, despite confirmation of the oral LEN loading doses were taken. No abnormalities to study drug injection were noted by the site staff. Resistance analysis of the Day 185 sample revealed an HIV-1 variant expressing the N74D LEN RAS. This case represents PrEP failure.

PURPOSE 2, ID (b) (6): LEN injections were administered on Day 1, Day 176, and Day 352. HIV-1 infection was diagnosed on Day 352 despite receiving on-time LEN injections and having achieved target plasma LEN concentrations. Resistance analysis of the Day 352 sample revealed an HIV-1 variant expressing Q67H and K70R LEN RAS. This case represents PrEP failure.

Four of the five incident infections represent PrEP failures.

Diagnostic Assay Sensitivity

The RNA assay was the most sensitive for detecting infections, as expected since viral RNA is the first detectable viral analyte (Cohen et al. 2010), and was used to determine the time of diagnosis. In comparison, the central laboratory Ag/Ab assay detected 69% (9/13) of infections in the LEN groups as early as the RNA assay, including 63% (5/8) of the prevalent infections, initially missing those without high viremia levels, and 80% (4/5) of incident infections (Table 51). The central laboratory's Ag/Ab assay detected 81% (43/53) of infections in the F/TAF group, including the only prevalent infection (1/1) and 81% (42/52) incident infections, and 74% (29/39) of infections in the F/TDF groups, including 50% (2/4) of the prevalent infections and

77% (27/35) of incident infections (refer to Table 117 in Section 18 for a summary of the F/TAF and F/TDF diagnostics data).

Table 51. Relative Assay Sensitivity for Detecting the Earliest Time of Infection

	PURPOSE 1						PURPOSE 2				PURPOSE 1+2			
	LEN		F/TAF		F/TDF		LEN		F/TDF		LEN		F/TDF	
Assay	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
HIV-1	6		53		26		7		13		13		39	
Infections														
Cen Ag/Ab	4	(67)	43	(81)	19	(73)	5	(71)	10	(77)	9	(69)	29	(74)
Local Ag/Ab	1	(17)	28	(53)	14	(54)	1	(14)	4	(31)	2	(15)	18	(46)
Prevalent	4		1		2		4		2		8		4	
Cen Ag/Ab	3	(75)	1	(100)	1	(50)	2	(50)	1	(50)	5	(63)	2	(50)
Local Ag/Ab	0		0		0		0		0		0		0	
Incident	2		52		24		3		11		5		35	
Cen Ag/Ab	1	(50)	42	(81)	18	(75)	3	(100)	9	(82)	4	(80)	27	(77)
Local Ag/Ab	1	(50)	28	(54)	14	(58)	1	(33)	4	(36)	2	(40)	18	(51)

Source: adsl.xpt datasets for PURPOSE 1 (Gilead Sciences 2024b) and PURPOSE 2 (Gilead Sciences 2024e); lb.xpt datasets for PURPOSE 1 (Gilead Sciences 2024c) and PURPOSE 2 (Gilead Sciences 2024f); PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h); 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b).
Abbreviations: Ab, HIV antibody test; Ag/Ab, HIV antigen/antibody test; Cen, central laboratory; F/TDF, emtricitabine/tenofovir disoproxil fumarate (Truvada); HIV, human immunodeficiency virus; LEN, lenacapavir; Local, local site.

The local point-of-care Ag/Ab rapid test demonstrated lower sensitivity for detecting early infections. The local site diagnosed 15% (2/13) of infections in the LEN groups as early as the central laboratory, including 0% (0/8) of the prevalent infections and 40% (2/5) of incident infections, 53% (28/53) of infections in the F/TAF group, including 0% (0/1) of the prevalent infections and 54% (28/52) of incident infections, and 46% (18/39) of infections in the F/TDF groups, including 0% (0/4) of the prevalent infections and 51% (18/35) of incident infections. Given the relatively limited sensitivity of the point-of-care test used by local sites, we recommend confirming negative point-of-care Ag/Ab assay results with a more sensitive assay, preferably an RNA-specific assay, when screening for HIV-1 infections before and during LEN for PrEP use.

In PURPOSE 1 and PURPOSE 2, there was a delay of at least 1 study visit between HIV-1 diagnosis by the local site relative to that of the central laboratory for 85% (11/13) of cases in the LEN groups and 54% (21/39) in the F/TDF groups. This difference raises concerns that LEN may lead to a delay in HIV-1 diagnosis, as observed in trials evaluating cabotegravir (CAB) for PrEP, HPTN 083 (NIH 2024b) and HPTN 084 (NIH 2024a). In HPTN 083, participants who were assigned to the CAB arm and experienced prevalent or incident infections had delays in time to diagnosis, with 69% (11/16) of cases in the CAB arm and 24% (10/42) in the F/TDF group demonstrating at least 1 study visit where the local site failed to detect an infection concurrently with central laboratory (Marzinke et al. 2021). When including data from HPTN 084 (Eshleman et al. 2022), 60% (12/20) of cases in the CAB arms and 23% (18/77) of cases in the F/TDF groups had a delay of at least 1 visit before the local site detected HIV-1 infection relative to the central laboratory (these data are also summarized in Section 7.7.1 of the Integrated Review of NDA 215499 (FDA 2021)).

In general, the diagnostic delays observed in the LEN trials are less pronounced than those described in the CAB trials. For example, the HIV diagnosis time of the central laboratory Ag/Ab assay was later than that of the RNA assay in all cases (12/12) of the CAB trials, but only

in 31% (4/13) of cases in the LEN trials. CAB use was also shown to delay, or even to transiently reverse, the detection of HIV-1 across multiple clinical visits in some cases. LEN appears to have exerted less interference, with the central laboratory Ag/Ab assay detecting infection concurrently with the RNA assay in most cases. Additionally, there is less evidence that LEN monotherapy could efficiently suppress viral replication, and fewer instances of prolonged periods where LEN interfered with the performance of diagnostic assays.

The disparity between LEN and CAB in interfering with diagnostic assays could be attributed to differences in their antiviral activities. For example, LEN might have a lower barrier to resistance, reducing the duration of viral suppression and the associated diagnostic delay. However, differences in trial design might also explain these disparities. The LEN trials tested all baseline samples with a central laboratory RNA assay, while the CAB trials did not. This difference may have increased the risk of longer drug exposure before diagnosis for participants with acute baseline infections in the CAB trial, but it also extended the window for observing the effect of CAB monotherapy on viral replication and diagnosis. Additionally, the LEN trials tested all samples with the central laboratory Ag/Ab assay, while the HPTN trials relied on point-of-care rapid tests and local laboratory Ag/Ab assays, using central laboratory assays only after detection by a local site. Detection may have been delayed if the local site Ag/Ab assay was less sensitive than the central laboratory assay.

Chance might also have had a role in the apparent differences between the drugs. For example, many of the prevalent infections in the LEN trials were associated with high viral loads, while those in the CAB trials were generally lower. High viral load infections are more likely to be diagnosed, while lower viral loads are more likely to be suppressed by monotherapy.

The HIV testing frequency also varied between the trials. The LEN trials tested every 13 weeks, while the CAB trials tested approximately every 6 weeks (at 8-week injection visits and 2-week post-injection safety visits). This difference could have affected the ability to detect disparate outcomes between assay types, as less frequent testing increases the likelihood of missing the acute Phase of infection or interference with Ag/Ab assays early after infection.

In summary, LEN appears to have had some impact on the time to diagnosis of infection. However, it is difficult to compare the magnitude of this effect to that of CAB, which has been comparatively well characterized.

Resistance

Genotypic data were generated using the GenoSure® GAG PRO assay (Monogram Biosciences, Inc.), an Illumina-MiSeq next-generation sequencing (NGS) platform. The FDA conducted an independent assessment using the NGS data to confirm the findings. Genotypic data were available for isolates from 11 of the 13 participants (Table 52, a summary of the relevant information from Table 50). The data are stratified by infection time (prevalent versus incident) and summarize known and potential LEN RAS. Known LEN RAS, as listed in the SUNLENCA label (Gilead Sciences 2022), include L56I, M66I, Q67H/K/N, K70N/R/S, N74D/H/S, and T107A/S/N. Potential LEN RAS are defined as novel substitutions at amino acid positions of known LEN RAS or substitutions at amino acid positions within 4 Å of LEN, potentially interacting directly with the drug (FDA analysis). Potential RAS include novel substitutions occurring at L56, M66, Q67, K70, N74, and T107, as well as substitutions at amino acid positions Q50, N53, T54, N57, Q63, L69, I73, A105, and Y130.

Table 52. Genotypic Analysis of HIV-1 Isolates From Participants Receiving LEN

Infection Timing	Trial	ID	HIV-1 Subtype	Day	LEN RAS	Potential LEN RAS
Prevalent	PURPOSE 1	(b) (6)	C	1	NR	
				8	NR	
			A1	1	NR	T54M, L111T
				9	N74D	T54M, L111T
				176	N47D	T54M, L111T
			D	1	NR	L56M, L69V
				271	N74D	L56M, L69V
			C	1	NR	T54S
				29	T107A	T54S
	PURPOSE 2		C	1	NR	
				111	N74D	Q67R, I73V
			C	1	NR	
				27	NR	
			ND	1	ND	ND
			C	21	NR	T54G
				77	N74D	T54G, A105V
Incident	PURPOSE 1		ND	670	NR	ND
			ND		ND	ND
	PURPOSE 2		C	93	N74D	
			C	185	N74D	Q50T, T54A
			ND	352	Q67H, K70R	ND

Source: adsl.xpt datasets for PURPOSE 1 (Gilead Sciences 2024b) and PURPOSE 2 (Gilead Sciences 2024e); lb.xpt datasets for PURPOSE 1 (Gilead Sciences 2024c) and PURPOSE 2 (Gilead Sciences 2024f); PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h), 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b).
Abbreviations: HIV, human immunodeficiency virus; LEN, lenacapavir; ND, no data; NR, no resistance-associated substitutions detected or reported; RAS, resistance-associated substitution.

Two participants (b) (6) had insufficient plasma HIV-1 RNA at sample collection for successful nucleotide sequencing. Only data related to known LEN RAS, rather than complete genotypic data, were provided for three participants who became infected after the primary efficacy analysis timepoint (b) (6)

No LEN RAS were detected in isolates from two participants with prevalent infections (b) (6) and one participant with an incident infection (b) (6) For the two participants with baseline infections, the absence of resistance may be attributed to their relatively short exposure (<1 month) to LEN monotherapy. In the case of the incident infection, the lack of resistance likely resulted from insufficient selective pressure by LEN, suggesting infection occurred after LEN concentrations decreased below the threshold for variant selection (Table 50).

Eight participants developed variants harboring at least one known LEN RAS:

- Six with variants expressing N74D (b) (6)
- One with Q67H+K70R (b) (6)
- One with T107A (b) (6)

T107A, while not associated with reduced LEN susceptibility in cell culture, is in the LEN binding site and has emerged in clinical isolates from individuals failing LEN-containing regimens. Therefore, FDA considers T107A to be an LEN RAS, perhaps as a precursor to other LEN RAS.

Two participants developed variants with potential LEN RAS, (b) (6) (Q67R+I73V) and (b) (6) (A105V). These substitutions emerged alongside N74D, a known LEN RAS, indicating a possible compensatory role in LEN resistance. These substitutions were unique to these isolates in PURPOSE 1 or PURPOSE 2.

The LEN resistance profile observed in the PURPOSE trials aligns with findings from other LEN development programs.

Resistance in the F/TAF and F/TDF groups are discussed in Section 18.

Conclusion

- LEN may have delayed HIV-1 diagnosis in the PURPOSE trials, though quantifying this effect is challenging due to a robust HIV testing algorithm.
- The point-of-care Ag/Ab rapid test showed limited sensitivity compared to the laboratory-based Ag/Ab and RNA assays. Consequently, Section 2.1 of the label includes a recommendation to confirm negative test results from a point-of-care rapid test with more sensitive assays.
- LEN resistance patterns in the PURPOSE trials align with other LEN development programs. However, we recommend that the Applicant evaluate the effects of newly identified potential LEN substitutions. The following Post-Marketing Commitment is being negotiated to achieve this goal:

Conduct a study to determine the phenotype of LEN against the following HIV-1 capsids: 1) subtype A1 containing the L111T substitution; 2) subtype C containing the T54A, Q67R, I73V, and A105V substitutions, 3) subtype C containing the T54S and T107A substitutions, and 4) subtype D containing the L56M and L69V substitutions, assessed individually and in the context in which these were identified. In your study, use a wildtype control and known resistance-associated substitutions, such as a subtype B capsid with the K70N substitution (24-fold change in EC_{50} value) representing the range of reductions in susceptibility for comparison.

7.7.2. Appropriate LEN Injection Sites

Issue

The Applicant proposed that SC LEN injections be administered by healthcare professionals at the following anatomical sites: the abdomen, thigh, (b) (4). In addition, the Applicant proposed (b) (4)

Background

In PURPOSE 1, almost all (>99%) SC LEN injections in the Randomized Blinded Phase were administered into the abdomen. For each SC LEN dose into the abdomen, the second injection

was administered at least 4 inches away from the previous injection site. For pregnant participants who consented to remain on study drug, bilateral thigh injections (one injection into each thigh) were provided as an alternative injection site. The alternative approach using the thigh was implemented when the investigator determined that abdominal injections for pregnant participants were no longer feasible because of a gravid abdomen. Among 32 pregnant participants in PURPOSE 1, a total of 65 SC LEN injections were administered into the thigh. ISRs after SC LEN injections into the thigh were reported in 5 of the 32 pregnant participants (15.6%) with a total of 11 ISR events (all were Grade 1 in severity and none were serious). The 11 ISRs reported after 65 SC LEN injections into the thigh included the following: nodule (n=6/65 [9.2%]), induration (n=2/65 [3.1%]), swelling (n=2/65 [3.1%]), and pain (n=1/65 [1.5%]).

In PURPOSE 2, all SC LEN injections in the Randomized Blinded Phase were administered into the abdomen. For each SC LEN dose, the second injection was administered at least 4 inches away from the previous injection site.

In the Phase 2/3 CAPELLA and Phase 2 CALIBRATE studies, which were used to support the approval of SUNLENCA, all SC LEN injections were administered into the abdomen. For each SC LEN dose, the second LEN injections were administered at least 4 inches apart from the previous injection site.

Assessment

Pharmacokinetics

LEN PK at alternate sites of injection were characterized from plasma concentration data generated from intensive PK sampling in Study GS-US-200-4540 and sparse PK in PURPOSE 1 (participants who became pregnant). The Applicant also conducted a population pharmacokinetics (PopPK) analysis to evaluate the effect of injection sites on the PK of LEN to further support their proposal. PopPK analysis included the following data from Phase 1 studies in healthy participants: GS-US-200-4329 (single intravenous LEN dose of 10 mg or 20 mg), GS-US-200-4538 (single dose cohorts of 309 mg and 927 mg administered into the abdomen), and GS-US-200-4540 (single dose of 927 mg administered to alternative injection sites and abdomen).

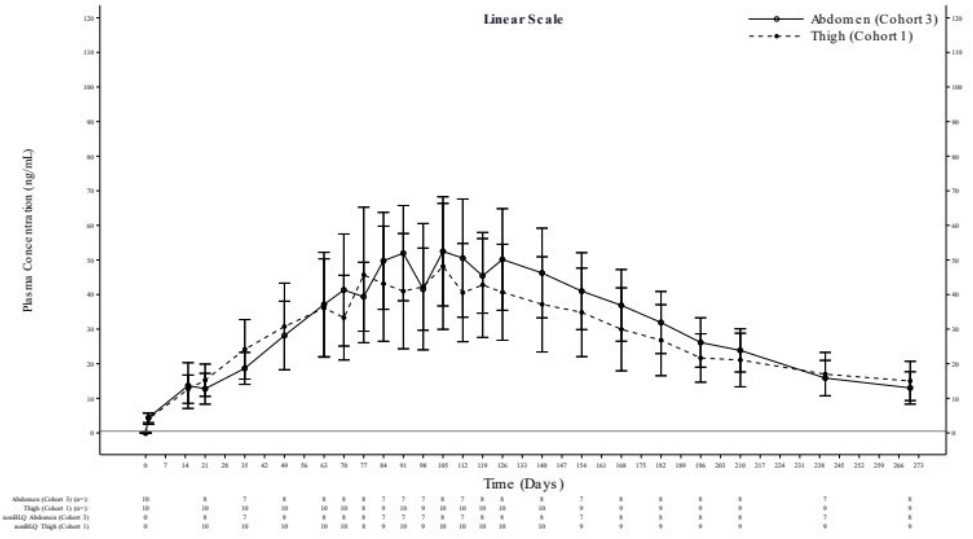
Study GS-US-200-4540

The primary objective of the Phase 1 study GS- US –200-4540 was to assess the PK of a single 927 mg dose of LEN injection (309 mg/ml, 2x 1.5 mL injection) into alternate injection sites (thigh, upper arm, and gluteal region) in comparison to the abdomen. For more details on this study, please see Section 14.2.1.

Thigh

The LEN concentration versus time profile and key summative PK following injections in the thigh compared to the abdomen are described in Figure 14 and Table 53 below.

Figure 14. Mean (90% CI) LEN Plasma Concentration vs. Time Profiles in the Thigh Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540



BLQ = below the limit of quantitation; CI = confidence interval; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SC = subcutaneous
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
The LLOQ is defined as 0.5 ng/mL for LEN.
Reference line indicates LLOQ. Postdose concentration values less than or equal to the LLOQ are not presented on the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.
Source: Study GS-US-200-4540 Final Clinical Study Report, Figure 2.

Table 53. Statistical Comparison of LEN PK Parameters in the Thigh Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540

PK Parameter	Geometric Mean (95%CI)		GLSM Ratio (%) (90% CI)
	Thigh (Test) (n = 10)	Abdomen (Reference) (n = 8[a])	
$AUC_{0\text{-}6\ month}$ (ng•h/mL)	121,870.6[b] (73,386.10, 202,387.8)	143,812.7 (105,610.3, 195,834.2)	84.74 (57.43, 125.1)
AUC_{last} (ng•h/mL)	164,198.8[b] (108,828.2, 247,741.4)	187,431.9 (142,882.4, 245,871.7)	87.60 (62.12, 123.6)
AUC_{inf} (ng•h/mL)	267,025.1[c] (203,680.1, 350,070.5)	222,761.0 (168,062.6, 295,261.8)	119.9 (86.59, 166.0)
C_{max} (ng/mL)	52.1 (33.6, 80.7)	56.7 (40.8, 78.6)	91.92 (61.41, 137.6)
T_{max} (h)	2495 (1990, 2831)	2663 (2076, 3167)	—
T_{last} (h)	6456 (6456, 6456)	6458 (6458, 6458)	—
$t_{1/2}$ (h)	1426[c] (1136, 1832)	1443 (1215, 1866)	—
C_{6mo} (ng/mL)	22.6[b] (13.9, 36.7)	28.6 (17.9, 45.6)	—

%CV = percentage coefficient of variation; CI = confidence interval; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a PK parameters are not available for N = 2 who prematurely discontinued after Days 5 and 10.
b N = 9 for $AUC_{0\text{-}6\ month}$, AUC_{last}, and C_{6mo} as these PK parameters were not available for N = 1 who prematurely discontinued after Day 140.c N = 6 for AUC_{inf} and $t_{1/2}$ due to inadequate characterization of the terminal phase for N = 4. Six months is Day 182 or Week 26.
Results reported as median (Q1, Q3) for T_{max}, T_{last}, and $t_{1/2}$.
Source: Study GS-US-200-4540 Final Clinical Study Report, Table 8.

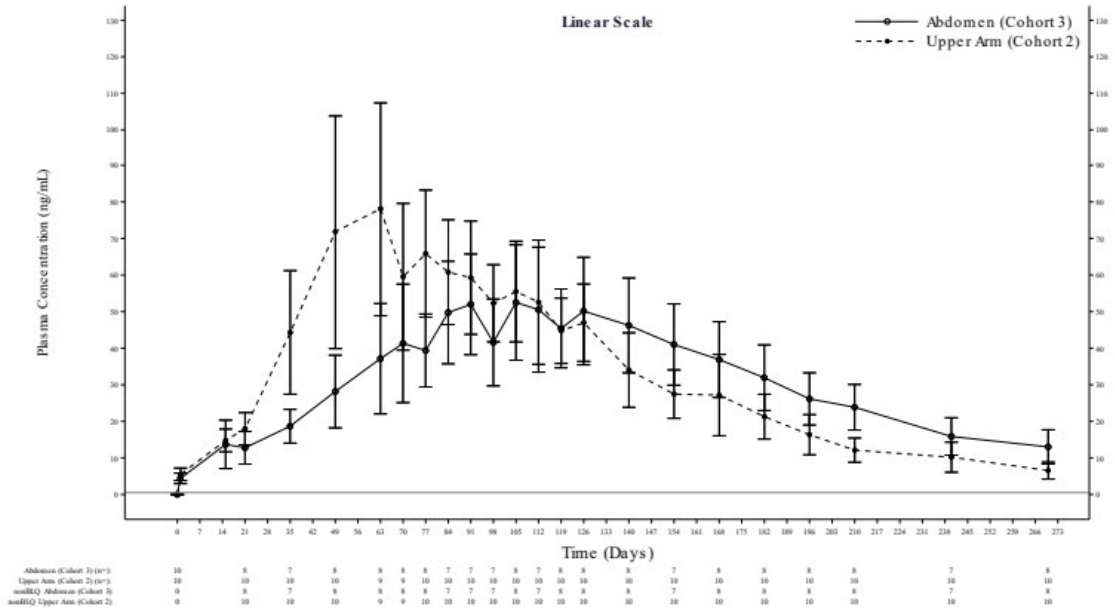
Overall concentration-time profiles observed exposure as measured by area under the concentration-time curve $(AUC)_{last}$ and AUC_{inf}, concentrations at 6 months, and half-life ($t_{1/2}$) between thigh and abdominal sites were comparable.

LEN C_{6mo} concentrations after thigh and abdominal injections from Study US-GS-200-4540 were compared with LEN trough concentrations (C_{trough}) after abdominal injections reported in the pivotal Phase 3 PURPOSE 1 and PURPOSE 2 trials. LEN C_{6mo} were within the C_{trough} (mean, [90% CI]) range observed in the pre-selected 10% subset of adult participants from PURPOSE 1 (34.1ng/ml [31.5,36.6] and PURPOSE 2 (22.8 ng/ml [26.1, 24.1]).

Upper Arm

The LEN concentration versus time profile and key summative PK following injections in the upper arm compared to the abdomen are described in Figure 15 and Table 54 below.

Figure 15. Mean (90% CI) LEN Plasma Concentration vs. Time Profiles in the Upper Arm Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540



BLQ = below the limit of quantitation; CI = confidence interval; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SC = subcutaneous
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
The LLOQ is defined as 0.5 ng/mL for LEN.
Reference line indicates LLOQ. Postdose concentration values less than or equal to the LLOQ are not presented on the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.
Source: Study GS-US-200-4540 Final Clinical Study Report, Figure 3.

Table 54. Statistical Comparison of LEN PK Parameters in the Upper Arm Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540

LEN PK Parameter	Geom. Mean 95% CI)		GLSM Ratio (%) (90% CI)
	Upper arm (Test) (n = 10)	Abdomen (Reference) (n = 8[a])	
$AUC_{0\text{-}6\ month}$ (ng•h/mL)	171,778.9 (125,962.5, 234,260.2)	143,812.7 (105,610.3, 195,834.2)	119.5 (81.70, 174.6)
AUC_{last} (ng•h/mL)	195,653.4 (144,905.1, 264174.8)	187,431.9 (142,882.4, 245,871.7)	104.4 (74.63, 146.0)
AUC_{inf} (ng•h/mL)	207,556.8 (153,843.5, 280,023.8)	222,761.0 (168,062.6, 295,261.8)	93.17 (70.02, 124.0)
C_{max} (ng/mL)	75.6 (51.7, 110.6)	56.7 (40.8, 78.6)	133.4 (89.11, 199.7)
T_{max} (h)	1992 (1152, 2494)	2663 (2076, 3167)	—
T_{last} (h)	6477 (6477, 6478)	6458 (6458, 6458)	—
$t_{1/2}$ (h)	1262 (1076, 1463)	1443 (1215, 1866)	—
C_{6mo} (ng/mL)	18.7 (12.6, 27.8)	28.6 (17.9, 45.6)	—

%CV = percentage coefficient of variation; CI = confidence interval; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a K parameters are not available for N = 2 who prematurely discontinued after Days 5 and 10.
Six months is Day 182 or Week 26.
Source: Study GS-US-200-4540 Final Clinical Study Report, Table 9.

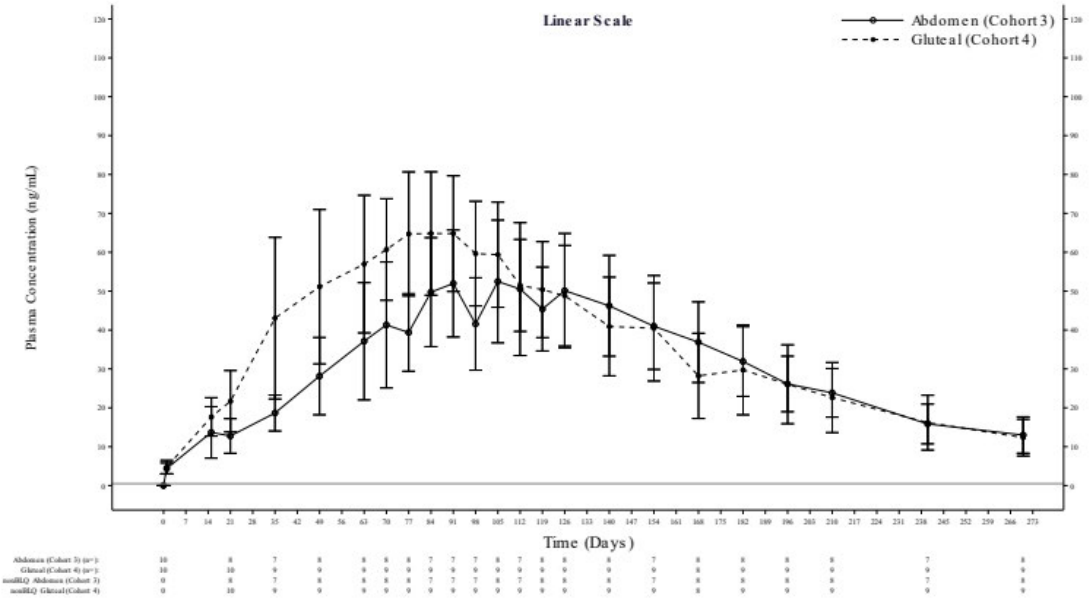
Time to maximum plasma concentration (T_{max}) appeared to occur faster after the upper arm injection relative to the abdomen suggesting potentially altered release kinetics from the injection depot which was accompanied by a 33% higher maximum plasma concentration (C_{max}).

Although AUC_{last} and AUC_{inf} appeared similar between cohorts, LEN C_{6mo} concentrations observed after upper arm injections were lower than those following abdominal injections and were the lowest across all injection site cohorts. When numerically compared to the LEN trough concentrations (C_{trough}) after abdominal injections reported in the pivotal Phase 3 PURPOSE 1 and PURPOSE 2 trials, LEN C_{6mo} after upper arm injections were lower than those observed in the pre-selected 10% subset of adult participants from PURPOSE 1 (34.1ng/ml [31.5,36.6] and PURPOSE 2 (22.8 ng/ml [26.1, 24.1]).

Gluteal Region

The LEN concentration versus time profile and key summative PK following injections in the gluteal region compared to the abdomen are described in Figure 16 and Table 55 below.

Figure 16. Mean (90% CI) LEN Plasma Concentration vs. Time Profiles in the Gluteal Region Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540



BLQ = below the limit of quantitation; CI = confidence interval; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SC = subcutaneous
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
The LLOQ is defined as 0.5 ng/mL for LEN.
Reference line indicates LLOQ. Postdose concentration values less than or equal to the LLOQ are not presented on the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.
Source: Study GS-US-200-4540 Final Clinical Study Report, Figure 4.

Table 55. Statistical Comparison of LEN PK Parameters in the Gluteal Region Compared With the Abdomen Following a Single Dose of SC LEN 927 mg, GS-US-200-4540

LEN PK Parameter	Geom. Mean (95% CI)		GLSM Ratio (%) (90% CI)
	Gluteal Region (Test) (n = 9[a])	Abdomen (Reference) (n = 8[b])	
$AUC_{0\text{-}6\ month}$ (ng•h/mL)	181,120.6 (137,613.3, 238383.0)	143,812.7 (105,610.3, 195,834.2)	125.9 (85.34, 185.9)
AUC_{last} (ng•h/mL)	220,422.0 (168,698.5, 288,004.0)	187,431.9 (142,882.4, 245,871.7)	117.6 (83.39, 165.9)
AUC_{inf} (ng•h/mL)	247,348.6 (190,088.6, 321,857.0)	222,761.0 (168,062.6, 295,261.8)	111.0 (82.86, 148.8)
C_{max} (ng/mL)	71.2 (52.0, 97.5)	56.7 (40.8, 78.6)	125.7 (83.14, 190.0)
T_{max} (h)	2163 (1656, 2497)	2663 (2076, 3167)	—
T_{last} (h)	6457 (6455, 6457)	6458 (6458, 6458)	—
$t_{1/2}$ (h)	1564 (1342, 1778)	1443 (1215, 1866)	—
C_{6mo} (ng/mL)	25.2 (15.7, 40.4)	28.6 (17.9, 45.6)	—

%CV = percentage coefficient of variation; CI = confidence interval; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a PK parameters are not available for N = 1 who prematurely discontinued after Day 21.
b PK parameters are not available for N = 2 who prematurely discontinued after Days 5 and 10.
Six months is Day 182 or Week 26.
Results reported as median (Q1, Q3) for T_{max}, T_{last}, and $t_{1/2}$.
Source: Study GS-US-200-4540 Final Clinical Study Report, Table 10.

T_{max} appeared to occur faster after the gluteal injection relative to the abdomen suggesting potentially altered release kinetics from the injection depot which was accompanied by a 26% higher C_{max}.

The C_{6mo} after the gluteal injection was comparable to the C_{6mo} achieved after abdominal injection however, the observed variability was large around the point estimate (geometric mean [90% CI]: 25.2 [15.7, 40.4]) for the gluteal region. This variability could be in part due to the small sample size used to calculate PK parameters or characteristics of the injection site (i.e. fat deposition or site vascularity), and ultimately limits the overall interpretation of PK data.

PURPOSE 1

PK data after thigh injection are available in 12 women who became pregnant while receiving LEN for HIV-1 PrEP and consented to remain on study drug. LEN plasma concentrations were described according to pregnancy trimester and relative to time since the last injection.

LEN plasma concentrations after the thigh injections were within the range of those observed overall in the participants who received LEN via abdominal injection. Following 0 to ≤13 weeks since the last injection, LEN plasma concentrations ranged from 71.1 to 97.5 ng/mL (N=2) during the second trimester and ranged from 37.2 to 114 ng/mL (N=5) during the third trimester. Following >13 to ≤28 weeks since the last injection, LEN plasma concentrations ranged from 33.5 to 40.5 ng/mL (N=2) and 42.4 to 65.0 ng/mL (N=4) during the second and third trimester,

respectively. Furthermore, none of the participants who received LEN via thigh injection developed incident HIV-1 infection.

Population PK Analysis of Alternate Sites of Injection Relative to Abdominal Reference

Model-predicted LEN exposures in individual participants from Study 4540 indicate that C_{trough} after upper arm injection was statistically lower at Week 26 compared to reference (abdomen, Table 56).

Table 56. Mixed Effects Modeling To Evaluate C_{trough} Between Test and Reference

Test Groups	Upper Arm N=10	Thigh N=9	Gluteal N=9	Abdomen N=8
GMR (90% CI)	0.58 (0.39-0.87)	0.85 (0.54-1.31)	0.88 (0.54-1.42)	Reference
Significant variable	Injection site (P=0.03)	None	None	Reference

Source: Reviewer analysis.
Mixed effects modeling between test and reference.
*p=0.0509 borderline significance with observed data.
Abbreviations: CI, confidence interval; C_{trough}, trough plasma concentration; GMR, geometric mean ratio; REF, reference.

Model based simulations of LEN PK using the final model estimates for adults from studies GS-US-200-4239, −4538, and −4540 are described below in Table 57. Concentrations were simulated at steady-state following six 927 mg SC doses administered into alternative injection sites. The upper arm and gluteal region potentially have lower predicted C_{trough} values at steady state, particularly at the lower bound of the 90% prediction interval, compared to the abdominal reference injection site.

Table 57. Simulated Median [90% PI] LEN PK at Steady State in Healthy Adults Receiving SC LEN Every 26 Weeks

Injection Site	C_{max} (ng/mL) Median (90%PI)	AUC_{tau} (h · ng/mL) Median (90%PI)	C_{trough} (ng/mL) Median (90%PI)
Abdomen	62.9 (35.1- 113.2)	199,923 (109,283-365,863)	28.7 (11.7- 63.5)
Thigh	55.6 (31.2- 99.7)	198,295 (108,819-363,818)	35.3 (16.0- 71.5)
Upper Arm	67.7 (37.7- 123.5)	199,602 (109,505-366,233)	23.4 (7.8- 56.9)
Glutes	67.0 (37.5- 122.9)	199,053 (109,618-364,814)	24.2 (7.9- 58.0)

Source: Population pharmacokinetic report (QP-2024-1091), Table 6.12.
Simulated steady state LEN exposures are presented. Steady state conditions represented after six 927 mg. subcutaneous LEN doses (2 x 1.5 mL injections, 309 mg/mL strength). 500 replicates of 100 adults randomly selected from the NHANES database were simulated.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; CV, coefficient of variation; LEN, lenacapavir; NHANES, National Health and Nutrition Examination Survey, PI, prediction interval.

Overall, LEN PK differed following administration at each of the alternate sites relative to the abdominal injection. Simulated PK results at week 26 and steady state revealed the potential for lower C_{trough} values (lower bound of the 90% CI < IQ4) after injection into the gluteal region and upper arm compared to the abdominal reference cohort. Although variability in PK may be expected due to injection site and participant characteristics including fat deposition or site vascularity, the small sample size to characterize LEN PK may further limit robust interpretation of the PK data, particularly at the gluteal and upper arm sites where the only PK data available across the LEN development program is from the Phase 1 study. The review team concluded that

the PK data from the Phase 1 GS-US-200-4540 coupled with the Phase 3 PURPOSE 1 studies can support the recommendation for the thigh to be an acceptable alternate site of injection.

Safety

The Phase 1 study GS-US-200-4540 evaluated the PK and safety of a single-dose SC LEN injection (927 mg [2 ×1.5 mL of LEN injection, 309 mg/mL]) into the thigh, upper arm, and gluteal region in comparison with the abdomen as the reference. A total of 40 participants were enrolled with 10 participants in each cohort (thigh, upper arm, gluteal region, and abdomen). SC LEN injections were administered bilaterally into the arms, thigh, and gluteal area. SC LEN injections into the abdomen were administered at least 4 inches away from the previous injection site. The reported study-drug related ISRs are included in Table 58.

Table 58. Study-Drug-Related Injection Site Reactions by Severity and Preferred Term, Safety Analysis Set, GS-US-200-4540

Injection Site Reactions	Thigh (n=10)	Upper Arm (n=10)	Gluteal Region (n=10)	Abdomen (n=10)	Total (N=40)
Number of participants who received at least 1 injection	10	10	10	10	40
Number (%) of participants with any study drug-related ISRs	9 (90.0%)	10 (100.0%)	9 (90.0%)	10 (100.0%)	38 (95.0%)
Grade 1	9 (90.0%)	10 (100.0%)	9 (90.0%)	10 (100.0%)	38 (95.0%)
Grade 2	7 (70.0%)	8 (80.0%)	4 (40.0%)	4 (40.0%)	23 (57.5%)
Grade 3	0	1 (10.0%)	0	0	1 (2.5%)
Grade 4	0	0	0	0	0
Number (%) of participants with any study drug-related ISRs by preferred term					
Injection site pain	9 (90.0%)	8 (80.0%)	9 (90.0%)	10 (100.0%)	36 (90.0%)
Injection site induration	8 (80.0%)	10 (100.0%)	3 (30.0%)	8 (80.0%)	29 (72.5%)
Injection site erythema	9 (90.0%)	8 (80.0%)	5 (50.0%)	6 (60.0%)	28 (70.0%)
Injection site nodule	4 (40.0%)	0	0	2 (20.0%)	6 (15.0%)
Injection site swelling	0	1 (10.0%)	1 (10.0%)	4 (40.0%)	6 (15.0%)
Injection site bruising	1 (10.0%)	1 (10.0%)	0	2 (20.0%)	4 (10.0%)
Injection site discoloration	2 (20.0%)	0	0	1 (10.0%)	3 (7.5%)
Injection site pruritus	1 (10.0%)	0	0	0	1 (2.5%)

Source: Applicant; GS-US-200-4540 Final Clinical Study Report, Table 15.11.2.1.4.
Adverse events were coded according to MedDRA Version 26.0.
Each SC dose consists of two SC injections (927 mg [2 ×1.5 mL of LEN injection, 309 mg/mL]).
Study drug-related ISR defined as an AE marked "Related" on the AE electronic case report form, high-level term = injection site reactions.
Preferred terms were presented by descending order of total frequencies.
Abbreviations: AE, adverse, event; ISR, injection site reaction; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.

Among all participants, a single Grade 3 AE was reported; one participant who received SC LEN in the upper arm experienced injection site erythema that resolved within 5 days without intervention.

Safety data from SC LEN injections into the thigh are available from a total of 42 participants across PURPOSE 1 and the Phase 1 Study GS-US-200-4540. Despite the limited safety data available for SC LEN injections into the thigh compared to the abdomen, the available data suggest that the incidence and severity of ISRs associated with SC LEN thigh injections in

pregnant participants and healthy adult volunteers is generally comparable to those observed with SC LEN injections into the abdomen.

The small number of participants receiving single doses of SC LEN (927 mg [2 ×1.5 mL of LEN injection, 309 mg/mL]) into the upper arm (n=10) and gluteal area (n=10) in the Phase 1 Study GS-US-200-4540, coupled with the absence of SC LEN injections administered into the upper arm or gluteal area across PURPOSE 1 (randomized blinded Phase), PURPOSE 2 (randomized blinded Phase), CAPELLA, and CALIBRATE, precludes a comprehensive evaluation of the safety profile for SC LEN administration in the upper arm or gluteal area. The ISRs observed in participants receiving abdominal injections in the Phase 1 Study GS-US-200-4540 were notably different than those reported in PURPOSE 1 and PURPOSE 2. A potential explanation for this discrepancy may be attributed to differences in the populations participating in the clinical studies and the small number of participants (n=10) who received abdominal injections in the Phase 1 study, thus accounting for the observed variations in ISRs.

In addition, the upper arm and gluteal area SC LEN injections in Study GS-US-200-4540 were administered bilaterally. Therefore, there are no safety data with SC LEN administered unilaterally into the upper arm or gluteal area.

There exists a potential for more extensive ISRs to intersect when administering SC LEN doses close together, particularly in cases involving injection site nodules or injection site indurations with large diameters. For each SC LEN dose administered into the abdomen in PURPOSE 1, PURPOSE 2, CAPELLA, CALIBRATE, and the Phase 1 study GS-US-200-4540, the second LEN injection was administered at least 4 inches apart from the previous injection site. For each SC LEN dose administered into the thigh in PURPOSE 1 (pregnant participants only) and the Phase 1 study GS-US-200-4540, SC LEN injections were administered bilaterally. For each SC LEN dose administered into the upper arm or gluteal region in the Phase 1 study GS-US-200-4540, SC LEN injections were administered bilaterally. Across PURPOSE 1 and PURPOSE 2, a total of 82 participants (1.9%) who received SC LEN had injection site nodules or indurations ≥5.1 cm (≥2 inches) in diameter. Although the incidence is relatively low, there exists a potential for more extensive ISRs to intersect when administering SC LEN doses if the second SC LEN injection is administered only 2 inches away from the first injection site.

Conclusion

The review team recommends limiting the administration of SC LEN injections to the abdomen (primary site) and thigh (alternative site). The review team does not recommend the upper arm and gluteal region injection based on the difference in PK observed as compared to SC LEN injections into the abdomen. The thigh was assessed as an acceptable alternative site because of the available data from the total of 42 participants from PURPOSE 1 and the Phase 1 Study GS-US-200-4540.

The review team recommends that SC LEN injections should be administered at least 4 inches apart because of the lack of available safety data for the administration of SC LEN with injection sites spaced apart by at least 2 to less than 4 inches. This recommendation aligns with the instructions for SC LEN administration into the abdomen in PURPOSE 1, PURPOSE 2, CAPELLA, CALIBRATE, and the Phase 1 Study GS-US-200-4540.

These recommendations are a prudent approach that prioritizes safety and ensures that SC LEN is administered into anatomic sites where there is sufficient evidence to support the use of SC

LEN, noting that the population receiving SC LEN for HIV-1 PrEP will generally consist of healthy individuals. Limiting the administration of SC LEN to the abdomen (primary site) and thigh (alternative site), while maintaining a minimum distance of 4 inches between injection sites, allows some flexibility for SC injection sites until further evidence can establish the safety and PK of additional anatomic sites of administration.

7.7.3. Co-Administration With Rifampin or Rifabutin and Recommended Dosing Adjustments

Issue

LEN is contraindicated with rifampin and not recommended with rifabutin in the SUNLENCA labeling (LEN for HIV-1 treatment, NDA 215973/215974) because rifampin and rifabutin are CYP3A and P-gp inducers that significantly reduce LEN concentrations. In the current submission, the Applicant proposes dosing recommendations for LEN when co-administered with rifampin or rifabutin. The Applicant's proposal is based primarily on physiologically based pharmacokinetics (PBPK) and PopPK modeling and simulation. They propose the administration of supplemental doses of oral (only for rifampin) and SC LEN to mitigate the expected drug-drug interactions and maintain sufficient LEN exposure for HIV-1 PrEP over the entire dosing interval. The proposal to administer supplemental LEN doses raised the following review issues: (1) whether the supplemental doses are sufficient to maintain adequate LEN exposure for HIV-1 PrEP over the entire dosing interval during concomitant therapy with rifampin or rifabutin; (2) whether there was an adequate safety margin, especially if supplemental LEN doses are to be administered near the C_{max} of LEN; and (3) the potential safety risk of prolonged and elevated LEN exposures in the event rifampin or rifabutin are discontinued soon after supplemental doses are administered. The team also considered whether available safety and PK analyses support the broader application of the proposed supplemental dosing strategy to all strong and moderate CYP3A inducers.

Background

Clinical drug-drug interactions studies with CYP3A inducers have only been conducted with oral LEN. In the presence of rifampin, oral LEN AUC and C_{max} were decreased by 84% and 55%, respectively. In the presence of efavirenz, oral LEN AUC and C_{max} were decreased by 56% and 36%, respectively. Based on these results, LEN is contraindicated with strong CYP3A inducers including rifampin and not recommended with moderate inducers including rifabutin. Please refer to the SUNLENCA labeling (Gilead Sciences 2022) and Integrated Review for NDA 215973/215974 for additional study details (FDA 2022a).

To manage the induction effects of rifampin and rifabutin, the Applicant proposes administering supplemental doses of oral and SC LEN with rifampin and rifabutin in addition to the scheduled every 6-month maintenance dosing in the following manner:

Rifampin

- In individuals receiving LEN, rifampin may be co-administered starting at least 2 days after LEN is first initiated.

- On the day rifampin is initiated, administer 927 mg of LEN SC (2 x 1.5 mL injections) and 600 mg of LEN orally (2 x 300 mg tablets), and
- On the day after rifampin initiation, administer 600 mg of LEN orally (2 x 300 mg tablets).
- If rifampin is co-administered for longer than 6 months, continue to administer additional doses of LEN as described above every 6 months following the day of rifampin initiation.

Rifabutin

- On the day rifabutin is initiated, administer 463.5 mg of LEN SC (1 x 1.5 mL injection). If rifabutin is co-administered for longer than 6 months, continue to administer additional doses of LEN as described above every 6 months following the day of rifabutin initiation.

After stopping rifampin or rifabutin, maintain the usual LEN dosing schedule.

These proposed recommendations are based on PBPK and PopPK modeling approaches. Based on these modeling and simulation approaches, the Applicant claimed that significant drug interactions between LEN and rifamycins can be mitigated by the proposed supplemental doses. After reviewing both modeling reports, the review team concluded that PBPK modeling alone is sufficient and adequate to support the proposed supplemental dose when LEN is administered with rifamycins. Therefore, the PopPK based modeling and simulation report was not reviewed to determine the acceptability of the proposed dosing regimen. In addition, while the Applicant proposed supplemental doses only when LEN is administered with rifampin and rifabutin, the review team evaluated whether the same recommendation could be made for other inducers with similar induction potential (i.e., moderate and strong CYP3A inducers).

Assessment

Pharmacokinetics

PBPK analyses were performed using GastroPlus version 9.8.3 and consisted of a full PBPK model and a mechanistic oral model. The LEN PBPK model was developed using in vitro data; physicochemical properties; human absorption, distribution, metabolism, and excretion studies; and clinical PK data. Systemic clearance of LEN was assumed to be mainly through P-gp-mediated clearance, metabolism by CYP3A and UGT1A1. The contribution of CYP3A and P-gp pathway was assigned and/or validated using clinical drug-drug interaction (DDI) data with cobicistat, voriconazole, rifampin, and efavirenz. Please see Section 14.5.1 for more details about the PBPK model.

In general, the limitation of using PBPK analysis to support DDI assessment for P-gp and CYP3A is the determination of the contributions of each pathway. In this submission, intravenous (IV) mass-balance data provided critical insight into hepatic P-gp–mediated clearance. When combined with the low absolute bioavailability of LEN (6–8%) and in vitro absorption data, these characteristics further supports P-gp–mediated clearance. PBPK models for cobicistat, voriconazole, rifampin and efavirenz were submitted and evaluated. The review team agreed with the Applicant that rifampin PBPK model was adequately verified for CYP3A and P-gp pathways as the model was extensively validated with clinical DDI studies covering a wide range of clinically relevant scenarios including single and multiple dosing of rifampin on CYP3A (mainly midazolam, IV and by mouth [PO]) and Pgp (digoxin and fexofenadine, IV and

PO) substrates. In comparison, less but adequate clinical validations were available for cobicistat, voriconazole, and efavirenz.

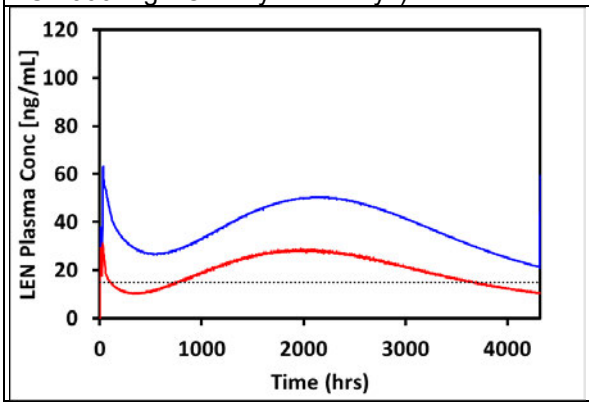
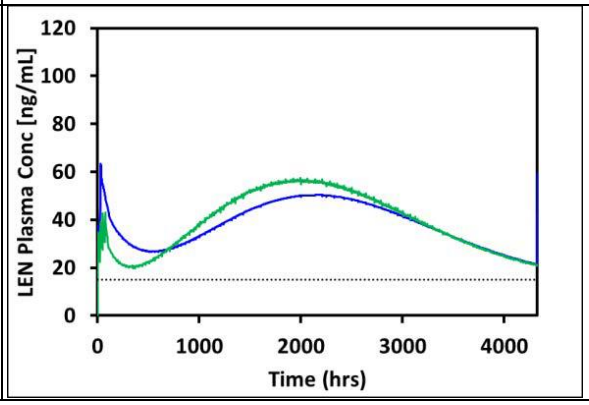
Overall, the review team considered the LEN PBPK model (both oral and SC) to be adequately validated for DDI assessment.

The Applicant's PBPK model evaluated the impact of 6-month rifampin treatment (600 mg orally once daily) or 6-month rifabutin treatment (300 mg orally once daily) on the PK of LEN. Based on the model, they propose a dose adjustment with the goal of maintaining sufficient LEN exposures throughout its dosing interval. The Applicant considered several scenarios regarding the impact of rifamycin therapy on LEN efficacy and safety. Since rifampin or rifabutin may be initiated at any time during the 6-month LEN dosing interval, the impact of supplemental doses of LEN with rifamycin treatment initiation near the start of LEN (Day 1 and/or 3) as well as near LEN C_{trough} were explored to illustrate the worst-case scenario in terms of efficacy. The Applicant also considered the worst-case scenario for safety by exploring the impact of supplemental LEN doses with rifamycins near LEN $C_{max.}$ as well as the scenario that the rifamycins were discontinued shortly after the supplemental doses of LEN.

Rifampin

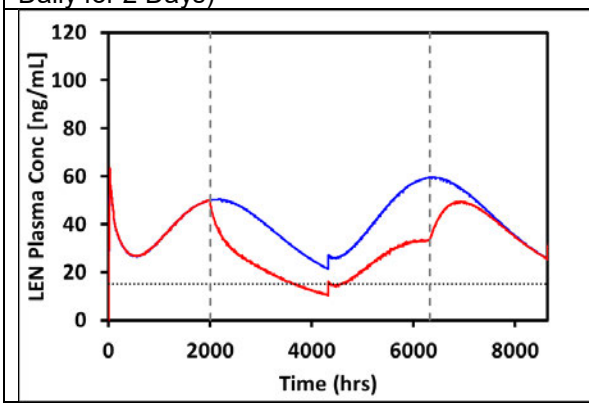
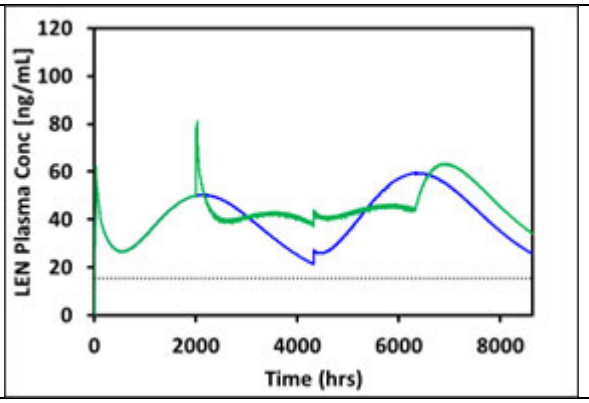
Figure 17, Figure 18, and Figure 19 (left panels) below present the impact of a 6-month rifampin treatment initiated at different time points—Day 1, C_{max}, and C_{min} —relative to LEN administration. The effect of supplemental dosing (LEN SC 927 mg dose [2 x 1.5 mL] +600 mg PO daily on Days 1 and 2) starting on Day 1 of rifampin treatment is also shown in the figures below on the right panels. As shown in these figures, the proposed supplemental doses would provide adequate LEN plasma concentrations; C_{trough} values are similar or higher than those observed when LEN is administered alone without inducers (described in blue in Figure 17). In some scenarios, the supplemental dosing would result in C_{max} values higher than those observed when LEN is administered alone without inducers (Figure 18). However, the review team concluded that such an increase in C_{max} would not pose a new or significant safety concern based on the range of C_{max} observed in prior clinical trials.

Figure 17. Impact of Rifampin Treatment and Proposed Additional[a] LEN Dosing, Day 1 Scenario

Impact of RIF 6-Month Treatment Regimen on Day 1 of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

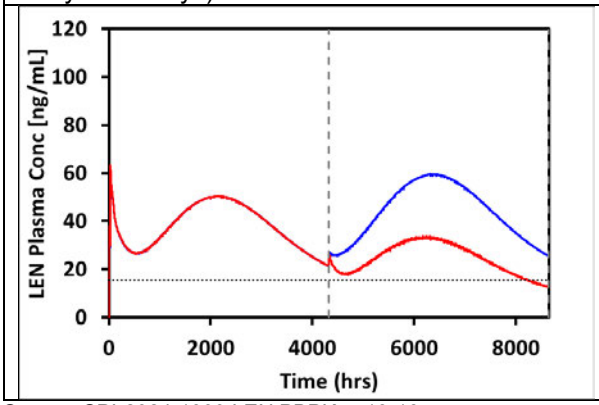
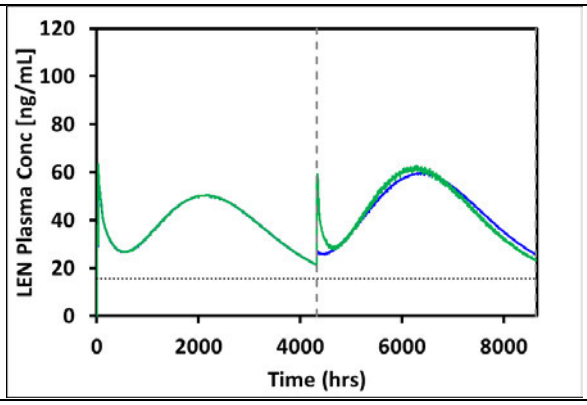
Source: SPI-2024-1099 LEN PBPK, Figures 13-16.
Blue line represents LEN PK when administered alone, red lines represent LEN PK with 6-month RIF treatment (600 mg QD), green line represents LEN PK with RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4).
[a] Here and throughout this section of the review, additional dosing (a term used by the Applicant throughout the submission) is used synonymously with supplemental dosing (review team's recommended terminology for labeling for the management of drug interactions with inducers).
Abbreviations: LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Figure 18. Impact of Rifampin Treatment and Proposed Additional LEN Dosing, C_{max} Scenario

Impact of RIF 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{max} of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

Source: SPI-2024-1099 LEN PBPK, Figures 13-16.
Blue line represents LEN PK when administered alone, red line represents LEN PK with 6-month RIF treatment (600 mg QD) starting at 2000 hrs after the start of LEN treatment, green line represents LEN PK with RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4), 2 vertical dashed lines outline the RIF treatment period.
Abbreviations: C_{max}, maximum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Figure 19. Impact of Rifampin Treatment and Proposed Additional LEN Dosing, C_{min} Scenario

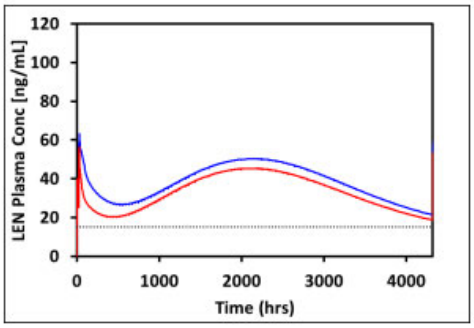
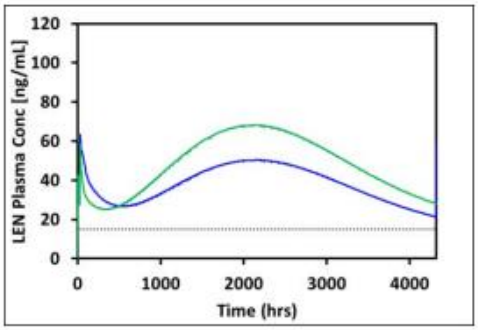
Impact of RIF 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{min} of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

Source: SPI-2024-1099 LEN PBPK, s 13-16.
Blue line represents LEN PK when administered alone, red line represents LEN PK with 6-month RIF treatment (600 mg QD) starting at 4320 hrs after the start of LEN treatment, green line represents LEN PK with RIF treatment + with additional LEN simplified regimen Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4), 2 vertical dashed lines outline the RIF treatment period.
Abbreviations: C_{min}, minimum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Rifabutin

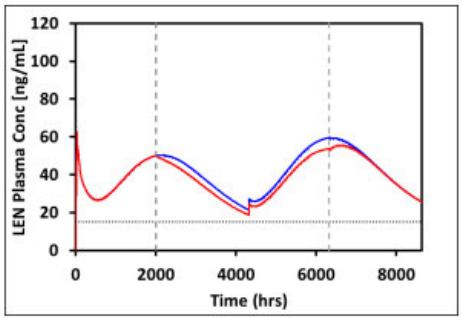
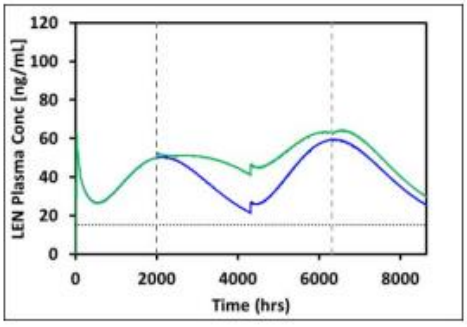
When co-administered with rifabutin, a supplemental SC injection at half the dose (463.5 mg [1 x 1.5 mL] on the day of rifabutin initiation was proposed. Figure 20, Figure 21, and Figure 22 (left panels) below present the impact of a 6-month rifabutin treatment initiated at different time points—Day 1, Cmax, and Cmin—relative to LEN administration. The effect of supplemental dosing (half dose LEN SC, 463.5 mg 1x 1.5 mL) starting on Day 1 of rifabutin treatment is also shown in the figures below on the right panels. Similar to the supplemental dosing for the administration of LEN with rifampin, the proposed supplemental doses of LEN when co-administered with rifabutin would provide adequate LEN plasma concentrations.

Figure 20. Impact of Rifabutin Treatment and Proposed Additional LEN Dosing, Day 1 Scenario

Impact of RIFAB 6-Month Treatment Regimen on Day 1 of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with Additional half dose LEN SC (463.5 mg SC) at the Start of RIFAB Treatment
	

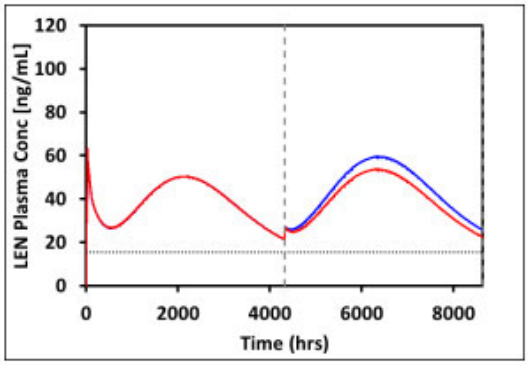
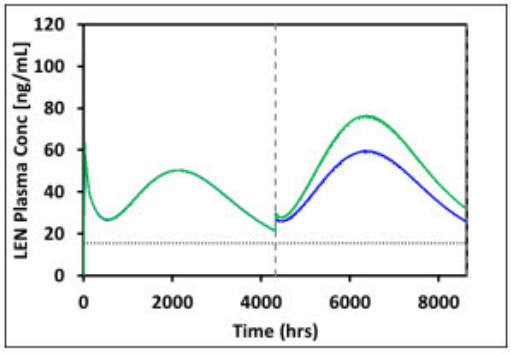
Source: SPI-2024-1099 LEN PBPK, Figures 17-20.
Blue lines represent LEN PK when administered alone, red lines represent LEN PK with 6-month RIFAB treatment (300 mg QD) green line represents LEN PK with 6-month RIFAB treatment (300 mg QD) starting at the same time as LEN treatment and additional half dose SC injection (1 x 1.5 mL of Q6M formulation) at the start of the RIFAB treatment. Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4), 2 vertical dashed lines outline the RIFAB treatment period.
Abbreviations: LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIFAB, rifabutin; SC, subcutaneous.

Figure 21. Impact of Rifabutin Treatment and Proposed Additional LEN Dosing, C_{max} Scenario

Impact of RIFAB 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{max} of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with additional half dose LEN SC (463.5 mg SC) at the Start of RIFAB Treatment
	

Source: SPI-2024-1099 LEN PBPK, Figures 17-20.
Blue lines represent LEN PK when administered alone, red lines represent LEN PK with 6-month RIFAB treatment (300 mg QD) starting at 2000hrs after the start of LEN, green line represents LEN PK with 6-month RIFAB treatment (300 mg QD) starting at 2000 hrs after the start of LEN treatment along with additional half dose LEN SC injection (1 x 1.5 mL of Q6M formulation) at the start of RIFAB treatment. Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4), 2 vertical dashed lines outline the RIFAB treatment period.
Abbreviations: C_{max}, maximum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIFAB, rifabutin; SC, subcutaneous.

Figure 22. Impact of Rifabutin Treatment and Proposed Additional LEN Dosing, C_{min} Scenario

Impact of RIFAB 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{min} of the LEN Simplified Regimen (927 mg SC +600 mg PO Daily for 2 Days)	LEN PK with additional half dose LEN SC (463.5 mg SC) at the Start of RIFAB Treatment
	

Source: SPI-2024-1099 LEN PBPK, Figures 17-20.
Blue lines represent LEN PK when administered alone, red lines represent LEN PK with 6-month RIFAB treatment (300 mg QD) starting at 4320hrs after the start of LEN, green line represents LEN PK with 6-month RIFAB treatment (300 mg QD) starting at 4320 hrs after the start of LEN treatment along with additional half dose LEN SC injection (1 x 1.5 mL of Q6M formulation) at the start of RIFAB treatment. Dotted horizontal line marks 15.5 ng/mL plasma concentration (IQ4), 2 vertical dashed lines outline the RIFAB treatment period.
Abbreviations: C_{min}, minimum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIFAB, rifabutin; SC, subcutaneous.

Safety

Additional data that support the safety of LEN at higher exposures have been reviewed to ensure the safety of LEN in situations where the administration of proposed supplemental LEN doses would result in higher-than-predicted LEN exposures. This includes situations where the co-administration of an inducer is significantly shorter than six months (e.g., premature discontinuation of rifampin due to tolerability issues) or co-administration of CYP3A inducers that have a less potent induction effect compared to rifampin.

Phase 1 Study: GS-US-200-5717

Preliminary safety findings from the Phase 1 Study GS-US-200-5717 were submitted by the Applicant. This is an ongoing Phase 1 study in healthy adult volunteers assessing the PK, safety, and tolerability of single doses of various potential LEN formulations dosed every 12 months. In this study, participants received a single dose of 1,800 to 5,000 mg LEN administered as IM or SC injections. Based on the available information provided by the Applicant, resultant exposures, namely C_{max}, from some of these dose cohorts are anticipated to be higher than the worst-case scenarios described for premature discontinuation of rifampin and rifabutin after receipt of supplemental LEN dosing.

TEAEs were reported in 306 of 318 participants (96.2%) and AEs considered related to study drug were reported in 301 of 318 participants (94.7%). ISRs were not assessed because the investigational formulations of LEN in Study GS-US-200-5717 are different from the currently marketed LEN formulation (309 mg/mL, LEN sodium). Non-ISR TEAEs reported in more than 2% of participants included headache (10.1%), back pain (4.7%), SARS-CoV-2 test positive (4.4%), COVID-19 (2.8%), arthralgia (2.5%), cough (2.5%), abdominal pain (2.2%), dizziness (2.2%), and oropharyngeal pain (2.2%). Most TEAEs were Grade 1 or Grade 2 in severity. Grade 3 TEAEs, excluding ISRs, were reported in seven participants, two of which were considered

related to study drug (one participant with syncope [and injection site pain] that was likely vasovagal due to micturition and pain, and one participant with syncope likely vasovagal due to pain and fasting). There were no Grade 4 AEs assessed as related to study drug. One participant death (Grade 5) occurred due to heroin overdose and was assessed as unrelated to study drug. No AEs, excluding ISRs, led to discontinuation of study drug.

Overall, 57 of 318 participants (17.9%) had maximum Grade 3 laboratory abnormalities and 7 of 318 participants (2.2%) had maximum Grade 4 lab abnormalities at the time of the data cut. As summarized by the Applicant, all returned to baseline/screening levels or normalized with ongoing exposure and without intervention, were deemed not clinically significant, and/or had likely non-study drug related alternative etiologies.

CAPELLA and CALIBRATE Studies

The Applicant submitted additional supportive data from participants in CAPELLA (Study GS-US-200-4625) and CALIBRATE (Study-GS-US-200-4334) who had higher observed LEN exposures. In CAPELLA and CALIBRATE combined, 77 and 131 participants had LEN concentrations exceeding the predicted worst-case scenario mean C_{max} for rifampin and rifabutin, respectively. These data were previously submitted as part of SUNLENCA supplemental NDAs 215973/S-06 and NDA 215974/S-08 for oral bridging, which were approved on November 25, 2024. The overall favorable safety profile observed in the CAPELLA and CALIBRATE studies, including a significant proportion of participants with higher LEN exposures, that could be experienced by people who prematurely discontinue rifampin or rifabutin, add additional supportive safety of LEN at higher exposures.

Phase 1 Studies: GS-US-200-5709 and GS-US-200-4332

Supratherapeutic exposures of LEN for short durations (weeks versus months) were evaluated in the following:

- GS-US-200-5709 (Cohort 3): LEN 600 mg was administered twice daily for 10 days from Days 1 to 10 followed by 600 mg in the morning on Day 11 to achieve supratherapeutic exposure.
- GS-US-200-4332: LEN 600 mg was administered twice daily for 8 days on Days 5 to 12 (600 mg on Day 12 morning) to achieve supratherapeutic exposure.

Lenacapavir $AUC_{0\text{-}12hr}$ in Studies GS-US-200-4332 and GS-US-200-5709 was up to 15-fold higher relative to the therapeutic exposure in PWH. LEN C_{max} in these studies was up to 9-fold higher than the therapeutic C_{max} in PWH. No deaths, SAEs, Grade 3 or higher TEAEs related study drug, or TEAEs leading to premature discontinuation of study drug were reported in participants with supratherapeutic exposures to LEN.

Application of Dosing Recommendations to All CYP3A Strong and Moderate Inducers (With and Without P-gp Induction)

The Applicant responded to a review team request and provided information to support the application of dosing recommendations proposed for LEN when administered with rifampin to other strong CYP3A inducers such as carbamazepine and phenytoin; and rifabutin to other moderate inducers of CYP3A (with and without P-gp induction) such as bosentan and modafinil. Following review of the Applicant's response, the review team concluded that dosing

recommendations may be extended to all strong and moderate inducers of CYP3A given the safety margins described of worst-case scenarios and the adequacy of PBPK analysis for DDI simulation. Because rifampin is among the most potent inducers of CYP3A and P-gp, it is mechanistically reasonable to extend the LEN dosing recommendation when administered with rifampin (a strong CYP3A and P-gp inducer) to other strong CYP3A inducers (e.g., carbamazepine and phenytoin). Similarly, it is reasonable to extend the LEN dosing recommendation when administered with rifabutin (a moderate CYP3A and P-gp inducer) to other moderate CYP3A inducers, with or without P-gp induction potential (e.g., bosentan and modafinil) based on observed and simulated data with efavirenz (a more potent CYP3A/P-gp inducer amongst moderate CYP3A inducers).

Conclusion

The proposal to administer supplemental doses of LEN in addition to regularly scheduled maintenance dosing is acceptable when co-administration of rifampin or rifabutin is planned in individuals already receiving LEN. The same dosing recommendation may be made for planned co-administration with any strong or moderate inducer of CYP3A in individuals already receiving LEN.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Studies assessing intrinsic factors including mass balance (GS-US-200-4329), renal impairment (GS-US-200-4330), and hepatic impairment (GS-US-200-4331) were previously submitted and reviewed under SUNLENCA for HIV-1 treatment NDA 215973/215974 (FDA 2022a). No dosage adjustment of SUNLENCA is recommended in patients with mild, moderate or severe renal impairment (estimated creatinine clearance greater than or equal to 15 mL per minute). SUNLENCA has not been studied in patients with end stage renal disease (estimated creatinine clearance less than 15 mL per minute). No dosage adjustment of SUNLENCA is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. SUNLENCA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No additional studies assessing intrinsic factors were submitted in the current NDA.

A LEN PopPK model (QP-2024-1082 LEN PopPK) was updated with data from PURPOSE 1 and 2 and several covariates, including age, sex, race/ethnicity, body weight, and pregnancy were assessed. Age, sex, race/ethnicity, or pregnancy/postpartum period were not statistically significant covariates on LEN PK.

Baseline body weight was correlated with LEN AUC_{tau}, C_{max}, C_{trough} exposure metrics. Participants with body weight 37.9 to 195.4 kg were included in the PopPK analysis. The impact of weight ranged from a 29% decrease at the 95th percentile (110 kg) to a 35% increase at the 5th percentile (49 kg) compared to the median weight of 72 kg. The review team noted the observed differences in mean LEN C_{trough} between PURPOSE 1 and PURPOSE 2, 34.1ng/ml and 22.8 ng/ml, respectively. Per the Applicant's PopPK analysis, the difference is explained by body weight, rather than sex. The median body weight in PURPOSE 1, which consisted of

females, was 60.2 kg versus PURPOSE 2, which consisted of males, was 77.6 kg. The review team did not deem these differences clinically relevant, and no dosage adjustments are necessary based on body weight.

8.2. Extrinsic Factors

Studies assessing extrinsic factors including food effect (GS-US-200-4071) and *in vitro* and *in vivo* drug interactions (GS-US-200-4333) were previously submitted and reviewed under SUNLENCA for HIV-1 treatment NDA 215973/215974 (FDA 2022a). SUNLENCA may be taken without regard to food. SUNLENCA may be a precipitant in drug interactions primarily with substrates of CYP3A4.

Drug Interactions With Hormone Therapies

Impact LEN on Hormone Therapy PK

Although not conducted as a clinical drug interaction study with intensive PK sampling, the impact of LEN on hormone therapies (long-acting hormonal contraceptives and gender affirming therapies) was assessed as an exploratory objective in participants receiving them as concomitant medications during PURPOSE 1 and PURPOSE 2. Sparse PK sampling was employed while participants received LEN and concomitant hormone therapies in both Phase 3 trials in the following schedule: Day 1, Weeks 4, 8, 13, and every 13 weeks thereafter to week 78.

Participants in PURPOSE 1 were permitted to take concomitant hormone therapies including long-acting hormonal contraceptives: medroxyprogesterone acetate, norethindrone, and etonogestrel. Concentrations of these long-acting contraceptives were compared at baseline prior to initiation of LEN and in the presence of LEN. The results indicate there is no clinically significant changes in exposure of long-acting contraceptives. In PURPOSE 2, participants were permitted to take concomitant hormone therapies including estradiol and testosterone. Concentrations of estradiol, testosterone, and dihydrotestosterone [active metabolite of testosterone] were measured and compared before and after LEN dosing. Comparisons of hormone therapy concentrations did not reveal LEN had a clinically relevant impact on the estradiol, testosterone, and dihydrotestosterone levels (See Section 14.2.2 and 14.2.3 for details).

Impact of Hormone Therapies on LEN PK

Population PK analyses were conducted to determine whether hormone therapies had a significant impact on LEN PK in participants receiving these therapies in PURPOSE 1 and PURPOSE 2. The analyses did not demonstrate a statistically significant impact of any hormone therapies on LEN PK. However, the conclusion that these therapies do not have an impact on LEN PK could not be established with the present data. LEN is a moderate inhibitor of CYP3A; therefore, plasma concentrations of some hormones (long-acting contraceptives and hormones used for gender-affirming therapy) may increase when co-administered with LEN. Study limitations should be noted such as (1) the dose of hormones and timing of hormone administration relative to the timing of LEN administration were not controlled and (2) the results may not be generalizable to hormone therapies that were not studied in PURPOSE 1 and 2. While the results suggest the effect of LEN on these studied hormones is unlikely to be significant, the review team agrees that these limitations of the data should be acknowledged and

preclude their inclusion as drugs without clinically significant interactions in the proposed LEN for HIV-1 PrEP label.

Drug Interactions With Rifamycins

SUNLENCA is contraindicated with strong inducers of CYP3A4 and not recommended with moderate inducers of CYP3A4 due to expected significant reductions in LEN exposure. Physiologically based pharmacokinetics (PBPK) and PopPK modeling were conducted to capture the interaction of LEN and rifamycins and provide guidance for dose adjustment of LEN in people who may require concomitant rifampin (strong CYP3A4 inducer) or rifabutin (moderate CYP3A4 inducer) therapy. A discussion of these data and recommendations are provided in Section 7.7.3.

8.3. Plans for Pediatric Drug Development

As outlined in the Agreed Initial Pediatric Study Plan (iPSP), LEN for PrEP was granted a full waiver in neonates, infants, and children from birth to less than 16 years of age. PURPOSE 1 and PURPOSE 2 enrolled a total of 128 adolescents, all 16 to 17 years of age: 124 adolescents in PURPOSE 1 and 4 adolescents in PURPOSE 2. The Applicant is seeking an indication in adolescents who weigh at least 35 kg in the YEZTUGO application. The available data to support an indication in adolescents are summarized below.

Pharmacokinetic Data

LEN plasma concentration data in all adolescent participants available at the 52-week interim analysis for PURPOSE 1 (excluding adolescent participants who became pregnant, participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection) are described in Table 59. Overall concentrations at week 26 in adolescents were comparable and within the range of concentrations observed in adult participants (a pre-selected random 10% subset of randomized adult participants in each respective study) as shown in Figure 23.

PK data were available for 2 adolescent participants in PURPOSE 2. Trough concentrations in these two adolescents at week 26 were 30.8 and 50.6 ng/ml- both of which were within the range of concentrations observed in the adult participants.

Population PK analysis was performed on data from adults and adolescents 16 years of age or older from the PURPOSE 1 and PURPOSE 2 trials, and simulations were then performed for a virtual group of adolescents 12 to <18 years of age and weighing at least 35 kg to inform dosing in the adolescent population. Population PK modeling provided an acceptable description of LEN concentrations in adults whose body weight was within the adolescent weight range >37 kg (lowest participant weight) and in adolescent participants 16 years or older. Further, simulated C_{trough} predictions in adolescents 12 to <18 years of age were reasonably aligned with observed adult participants.

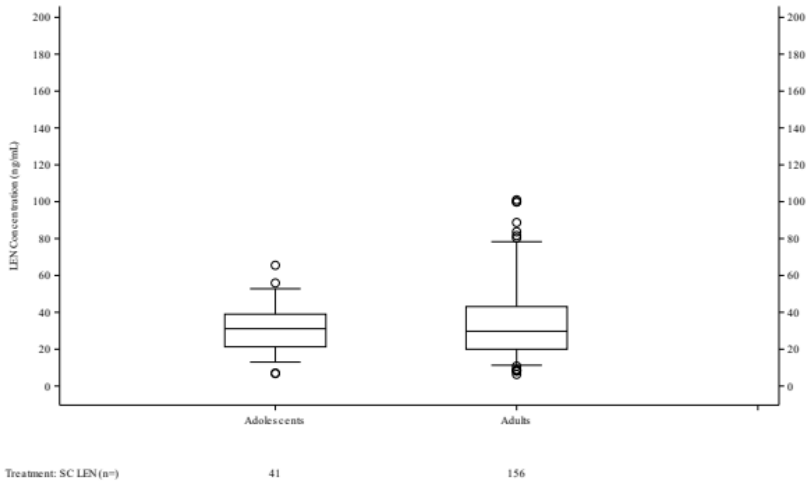
Based on the comparable observed and simulated PK between adolescents and adults, as well as the reasonable assumption that adolescents weighing at least 35 kg are not expected to have significantly different LEN PK compared to adults, the review team agrees with the Applicant's proposed indication to include adolescents weighing at least 35 kg for HIV-1 pre-exposure prophylaxis.

Table 59. Summary Statistics of LEN Plasma Concentrations in Adolescents by Study Visit, Randomized Blinded Phase, LEN PK Analysis Set[a], PURPOSE 1

Parameter	Week 4 (N = 48)	Week 8 (N = 49)	Week 13 (N = 50)	Week 26 (N = 41)	Week 39 (N = 26)	Week 52 (N = 9)
Mean (ng/mL)	25.8	50.7	66.3	31.4	87.6	30.9
90% CI (lower) (ng/mL)	22.3	42.6	55.8	27.7	75.7	22.3
90% CI (upper) (ng/mL)	29.3	58.8	76.8	35.0	99.6	39.5

CI = confidence interval; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s)
a Adolescents, excluding participants who became pregnant, participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection, as applicable.
Values were rounded to 3 significant figures, except for N.
Lower limit of quantitation was 0.5 ng/mL for LEN.
For injection visits, records with on-time injection (both injections administered in full dose within ± 2 weeks of targeted day relative to previous injection) were summarized.
For other visits, records collected per protocol-specified visit windows were summarized.
Values below the limit of quantitation were treated as 0 for summary statistics.
Source: Interim Week52 Clinical Study Reports for GS-US-412-5624, Table 23.

Figure 23. Boxplots of LEN Plasma Concentrations at Week 26 (Adolescents vs. Adults), Randomized Blinded Phase, LEN PK Analysis Set[a], PURPOSE 1



HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
a Excluding participants who became pregnant, participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection, as applicable.
Values below the limit of quantitation (0.5 ng/mL) were treated as 0 for summary statistics.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Interim Week52 Clinical Study Reports for GS-US-412-5624, Figure 10.

Safety Data

As stated above, PURPOSE 1 and PURPOSE 2 enrolled a total of 128 adolescents: 124 adolescents in PURPOSE 1 and 4 adolescents in PURPOSE 2, all 16 to 17 years of age. Across both trials, the safety data for the participants under 18 years of age show no concerning safety signals. There were no deaths in the adolescent population in either trial. Adolescents in PURPOSE 1 reported two SAEs in the LEN group; Food poisoning and Pyelonephritis, neither assessed by the investigators as related to study drug. There were no reported SAEs in the adolescent population in PURPOSE 2. The incidence of TEAEs and specific Preferred Terms

between treatment groups in the adolescent subset were consistent with findings in the overall population. Please see Section 17.4 for more details.

There were no HIV conversions in the adolescent population of PURPOSE 1 but one reported HIV-1 conversion in the adolescent population of PURPOSE 2. The 17-year-old male participant was randomized to the LEN group and was diagnosed with HIV-1 on Study Day 185. The participant was a cisgender gay man with history of rectal chlamydia diagnosed and treated at screening (no other on-study STI history) with a baseline BMI of 21.85 kg/m^2. All prospective HIV-1 testing was negative through Study Day 92. The participant's Study Day 185 rapid HIV-1 Ab/Ag testing was negative, though central HIV-1 testing Ab/Ag was positive. While Ab differentiation testing was indeterminate for HIV-1, the participant had a HIV-1 viral load 14100 copies/mL, with qualitative RNA positive for HIV-1. In addition, the participant was found to have a N74D capsid mutation on genotypic testing. A retrospective viral load from Study Day 92 was negative. The participant was referred to a local clinic for treatment of HIV-1 and initiated DTG/3TC/TDF. Following the HIV-1 diagnosis the participant withdrew study consent and requested never to be contacted again from the study site.

It is noted that LEN concentrations did not reach IQ4 until Week 13 in this participant despite confirmation of LEN administration (both the oral loading dose and SC injection) on Day 1. However, it is unclear whether the low LEN concentrations during the first 13 weeks contributed to HIV acquisition as the timing of HIV exposure and LEN concentration at the time of exposure to HIV are unknown. The LEN concentration at the time of HIV-1 diagnosis was higher than the IQ4 and similar to the LEN concentrations observed in other participants.

Conclusions

The overall observed adolescent PK was within range of observed adult PK (pre-selected random 10% of participants in RBP). The safety findings in adolescents in PURPOSE 1 and PURPOSE 2 were consistent with the findings for the overall population, with no safety signals unique to adolescents identified. The clinical pharmacology and clinical review teams note one HIV conversion in the adolescent age group but cannot draw any conclusions based on this single HIV conversion and the corresponding PK data. Safety, efficacy, model-based predictions, and PK exposure comparisons support the proposed dosage in the indicated adolescent population.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

PURPOSE 1 was conducted in cisgender adolescent girls and young women ≥16 to ≤25 years of age who were assigned female at birth, have sex with cisgender males and were able to become pregnant. Participants who became pregnant during PURPOSE 1 were allowed to remain on study drug after a discussion of potential risks and benefits and provision of additional informed consent. Participants were not unblinded at the time that pregnancy was diagnosed. The outcome of the pregnancy was reported to the Gilead Global Patient Safety database. In addition, participants 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.

Postpartum LEN concentrations during the first 28 weeks after delivery were collected for a subset of women who became pregnant (n=20). In women who breastfed, limited data on LEN concentrations in breast milk and infant plasma are also available. Multiple analyses were conducted relative to time of last injection, site of injection, pregnancy trimester, and postpartum period to characterize LEN PK during pregnancy and postpartum periods. First trimester is defined as estimated gestational age (EGA) of 1 to 84 days. Second trimester is defined as EGA of 85 to 189 days. Third trimester is defined as EGA >189 days. Postpartum period is defined as the time within 13 weeks after the end of pregnancy, whether following childbirth or pregnancy termination.

Pharmacokinetics in Pregnancy

All enrolled participants had a negative pregnancy test on study day 1. It is reasonable to assume participants who received SC LEN on Day 1 and who became pregnant while on study drug were exposed to LEN throughout the entirety of the pregnancy given the long half of SC LEN (8-12 weeks).

LEN plasma concentration versus time data were described in 181 pregnant women. LEN plasma concentrations during each pregnancy trimester relative to the LEN concentrations prior to pregnancy in the same participants were stratified by the time since last injection (0 to ≤13 weeks or >13 to ≤28 weeks) and summarized for the abdominal injection site in Table 60 below. LEN concentrations following the first and second SC injections were pooled for analysis as there were a limited number of participants available following the second SC injection at the time of the 52-week interim analysis. This was deemed acceptable by the review team as LEN is not reported to have significant accumulation after each successive injection over time.

In Table 60 below, average observed LEN concentrations after SC injections into the abdomen across pregnancy trimester were comparable to average concentrations prior to pregnancy in the same women when stratified by the time of last injection. When assessing LEN concentrations irrespective of injection site (abdomen or thigh) across pregnancy trimester relative to the same women's pre-pregnancy levels, concentrations remained within the range of those observed during the pre-pregnancy period (Figure 24 below). In comparison to women who did not become pregnant, observed LEN concentrations in women who became pregnant were similar prior to pregnancy, across each pregnancy trimester and during the postpartum period as shown in Figure 25 below.

A population PK analysis was conducted on the PK data from the PURPOSE 1 and PURPOSE 2 trials which contained data from 163 women on LEN who became pregnant before the data cutoff date of GS-US-412-5624 (PURPOSE 1). No statistically significant effect of pregnancy trimester, the periods before pregnancy or postpartum, or data from nonpregnant women on LEN PK was identified. Overall, model-predicted LEN exposures during pregnancy and postpartum were between −22% to +12% (C_{max}) and −10% to +15% (C_{trough}) of those observed in nonpregnant women (using time points with at least 5 participants per trimester or postpartum period).

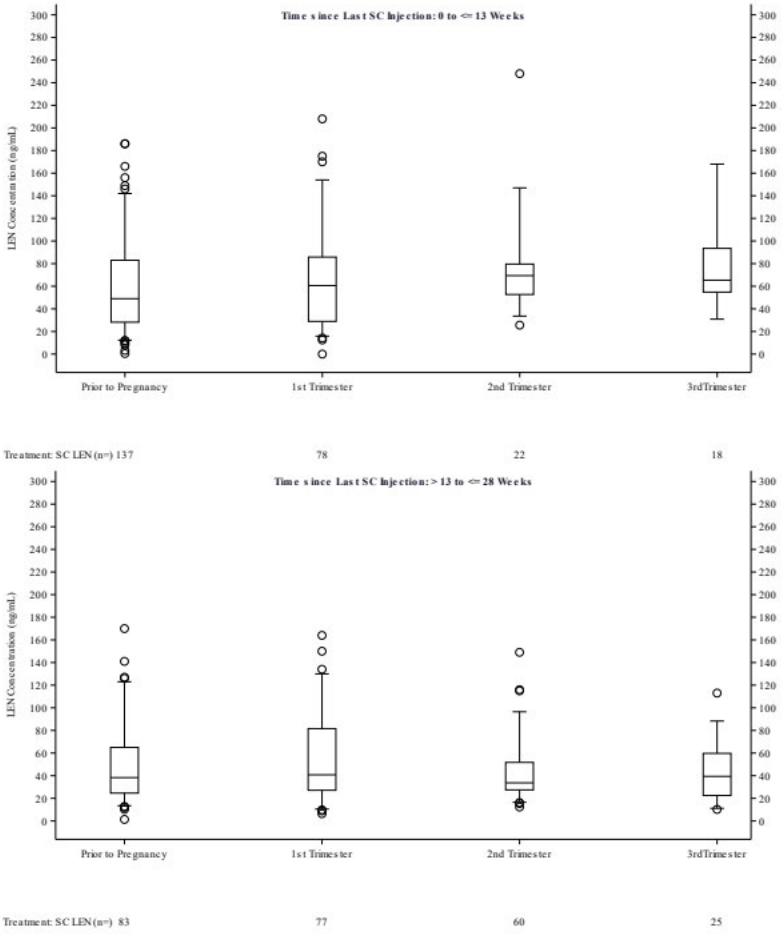
The review team agrees with the Applicant that pregnancy and postpartum periods do not appear to have a significant impact on LEN PK, and therefore, no dose adjustments of LEN are necessary for women during pregnancy or in the postpartum period.

Table 60. Summary Statistics of LEN Plasma Concentrations Prior to and During Pregnancy Following SC Dosing Into the Abdomen as Stratified by Time Since Last Injection, Randomized Blinded Phase, LEN PK Analysis Set, Participants Who Became Pregnant During the Study, PURPOSE 1

	Time Since Last SC LEN Injection							
	0 to ≤ 13 Weeks				> 13 to ≤ 28 Weeks			
Parameter	Prior to Pregnancy (N = 137)	First Trimester (N = 78)	Second Trimester (N = 20)	Third Trimester (N = 14)	Prior to Pregnancy (N = 83)	First Trimester (N = 77)	Second Trimester (N = 58)	Third Trimester (N = 21)
Mean (ng/mL)	60.8	64.4	77.3	81.8	48.9	52.1	44.3	40.0
90% CI (lower) (ng/mL)	55.1	56.2	58.3	63.7	42.7	45.5	38.1	30.1
90% CI (upper) (ng/mL)	66.5	72.5	96.4	99.9	55.0	58.8	50.6	50.0

CI = confidence interval; LEN = lenacapavir; PK = pharmacokinetic(s)
Values were rounded to 3 significant figures, except for N.
Lower limit of quantitation was 0.5 ng/mL for LEN.
Values below the limit of quantitation were treated as 0 for summary statistics.
On-time injection was defined as both injections administered in full dose within ± 2 weeks of targeted day relative to the previous injection.
For participants with more than one visit that fell into a summary category in a column, the latest visit was used in the summary.
Prior to pregnancy was defined as PK sample collection date ≤ last menstrual period date.
Source: US-GS-214-5624 Interim 52-week Clinical Study Report, Table 24.

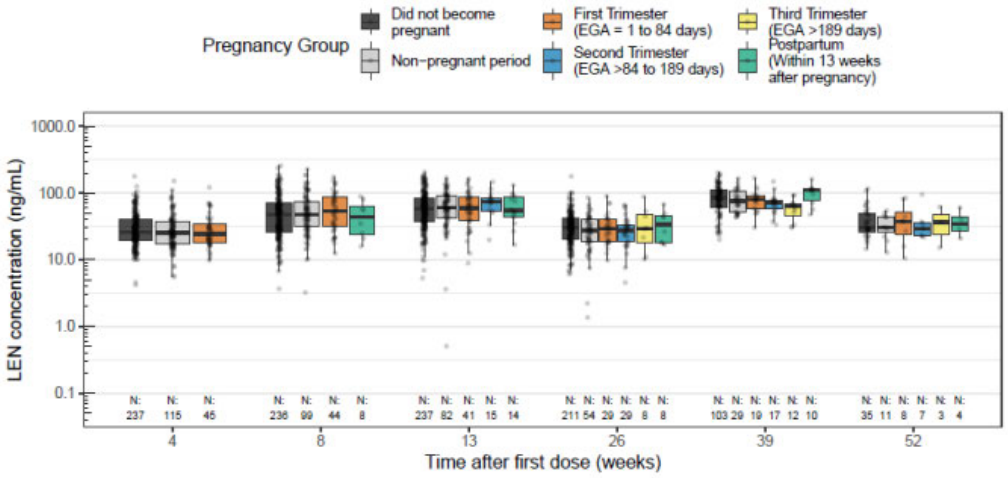
Figure 24. Boxplots of LEN Plasma Concentrations Irrespective of Injection Site Location During Pregnancy vs. Prior to Pregnancy as Stratified by Time Since Last Injection, Randomized Blinded Phase, LEN PK Analysis Set, Participants Who Became Pregnant During the Study, PURPOSE 1



LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (0.5 ng/mL) were treated as 0 for summary statistics.
For participants with more than one visit that fell into a summary category, the latest visit was used in the summary.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Prior to pregnancy was defined as PK sample collection date ≤ last menstrual period date.

Source: US-GS-214-5624 Interim 52-week Clinical Study Report, Figure 11.

Figure 25. Boxplots of Observed LEN Concentrations up to Week 52, Stratified by Pregnancy Groups, for Participants Who Took LEN On Time and Were Included in PopPK Analysis, PURPOSE 1



Source code: EDA−plots−box−plots−PrEP.R
Source graphic: deliv/figures/EDA/final/EDA−box−plots−5624.pdf page: 1

EGA = estimated gestational age; LEN = lenacapavir; PopPK = population pharmacokinetics; SC = subcutaneous
Figure includes observed LEN concentrations from participants in Study GS-US-412-5624 who received the Simplified Regimen on time and are included in the PopPK analysis (data cut of 28 February 2024 for Study GS-US-412-5624). On time was defined as participants who received 2 complete oral loading doses within 72 hours of Day 1 and the complete SC dose on Day 1. Additionally, data for those who received the complete Week 26 SC dose on time (± 2 weeks) were also included. For participants who did not receive the Week 26 dose on time but completed the oral loading and first SC dose on time, their data were included up until Week 26.
First trimester is defined as EGA of 1 to 84 days. Second trimester is defined as EGA of 85 to 189 days. Third trimester is defined as EGA > 189 days. Postpartum period is defined as the time within 13 weeks after the end of pregnancy, whether following childbirth or pregnancy termination. Nonpregnant period includes data from before pregnancy or after the postpartum period for participants who became pregnant up to the data cut date. N values in the plots are the number of participants in Study GS-US-412-5624 with quantifiable LEN concentration at that time point. Strata with < 2 participants were excluded.
Source: QP-2024-1082 LEN Population PK Report, Figure 6.6.

Safety in Pregnancy

Pregnancy Outcomes

A total of 798 confirmed pregnancies were reported in PURPOSE 1 from the RBP (inclusive of additional pregnancies reported in the SUR): 297 among LEN recipients, 159 among F/TDF recipients, and 342 among F/TAF recipients. Among the 297 pregnancies with exposure to LEN, 208 pregnancies have known outcomes, 88 are reported as ongoing pregnancies and 1 with an unknown outcome. Among the 208 pregnancies with known outcomes, 130 pregnancies 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. A consult was requested of the Division of Pediatrics and Maternal Health (DPMH) to help assess the pregnancy outcomes. Table 61 displays the pregnancy outcomes data as generated by the DPMH reviewer across treatment groups, and is inclusive of the pregnancy data provided in the SUR.

Table 61. DPMH-Generated Table of Pregnancy Outcomes, Randomized Blinded Phase, 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)	0 (0%)	2/122=1.6% (95% CI 0.2, 5.8)
Major congenital malformations (MCMs)	VSD: 2 (1.5%) (95% CI 0.18, 5.4)		club foot: 1 (0.8%)
Minor CAs	polydactyly: 1 (0.8%) umbilical hernia: 1 (0.8%) hemangioma: 1 (0.8%)		bilateral hydrocele: 1 (0.8%)
Neonatal problem	6/132=4.5% (95% CI 1.7, 9.6)	2/61=3.3% (95% CI 0.4, 11.2)	1/122=0.8% (95% CI 0.02, 4.5)
	jaundice: 3 omphalitis/sepsis: 1 TTN: 1 respiratory distress: 1	meconium: 1 low birth weight: 1	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)

Source: DPMH Consult Review dated April 29, 2025.
* Deliveries include live births and non-live births.
Definitions: PTB: estimated gestational age (EGA) of <37 weeks; SB: fetal death occurring at ≥20 EGA; SGA: ≤10th percentile birth weight; CA: Not defined by the Applicant in the protocol; SAB: pregnancy loss at <20 weeks EGA.
Abbreviations: DPMH, Division of Pediatrics and Maternal Health; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; RBP, Randomized Blinded Phase; TTN, transient tachypnea of the newborn; VSD, ventricular septal defect.

For the full DPMH assessment, please see the DPMH review. In summary, the DPMH review team agreed with the Applicant that pregnancy safety outcomes were similar in the LEN and F/TDF groups. DPMH also concluded that the prevalence of adverse pregnancy outcomes in LEN recipients was not conclusively different from the background prevalence rates. The DPMH recommendations were incorporated into Sections 8.1 and 8.2 of the USPI for LEN.

Maternal Outcomes

Overall safety in pregnant participants was assessed and displayed in Table 62 (this analysis is limited to the RBP data in the original NDA submission as the SUR did not include datasets). There were no maternal deaths in any treatment group. Overall, there is a similar percentage of SAEs and any AEs between treatment groups. The higher rates of SAEs among the pregnant population versus the overall population across treatment groups is accounted for by SAEs in the pregnancy, puerperium, and perinatal conditions SOC (reported by 15.2%, 17.6%, and 17.7% of LEN, F/TAF, and F/TDF pregnancy recipients, respectively). Further details can be found in Section 17.5. Imbalances of general AEs between groups for pregnant participants are consistent with those in overall participants, with higher incidence of ISRs in the LEN group, and lower

incidence of nausea and vomiting in the LEN group. There are no major imbalances of TEAEs for pregnancy-associated PTs between groups of pregnant participants which do not favor LEN; for example, morning sickness rates are higher in the F/TDF group (6.1%) compared to LEN (1%). DPMH also assessed maternal pregnancy outcomes (e.g., gestational hypertension, pre-eclampsia) and found these outcomes to be infrequent with lower prevalence rates in the LEN group than the background prevalence rate.

Table 62. Overview of Adverse Events, Safety Population Reporting Pregnancy, PURPOSE 1

Event Category	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (pregnancy) N=191 n (%)	F/TAF (pregnancy) N=210 n (%)	F/TDF (pregnancy) N=96 n (%)
SAE	59 (2.8)	85 (4.0)	35 (3.3)	34 (17.8)	43 (20.5)	20 (20.8)
SAEs with fatal outcome	0	6 (0.3)	0	0	0	0
Life-threatening SAEs	8 (0.4)	11 (0.5)	4 (0.4)	3 (1.6)	4 (1.9)	4 (4.2)
SAEs requiring hospitalization	45 (2.1)	56 (2.6)	27 (2.5)	23 (12.0)	23 (11.0)	14 (14.6)
SAEs resulting in substantial disruption of normal life functions	6 (0.3)	7 (0.3)	1 (0.1)	2 (1.0)	2 (1.0)	1 (1.0)
AE leading to permanent discontinuation of study drug	9 (0.4)	2 (0.1)	0	2 (1.0)	0	0
AE leading to dose modification of study drug	21 (1.0)	25 (1.2)	12 (1.1)	1 (0.5)	1 (0.5)	2 (2.1)
AE leading to interruption of study drug	21 (1.0)	25 (1.2)	12 (1.1)	1 (0.5)	1 (0.5)	2 (2.1)
AE leading to reduction of study drug	0	0	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0	0	0

Event Category	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (pregnancy) N=191 n (%)	F/TAF (pregnancy) N=210 n (%)	F/TDF (pregnancy) N=96 n (%)
Any AE	1893 (88.5)	1779 (83.3)	881 (82.3)	176 (92.1)	181 (86.2)	84 (87.5)
Severe and worse	92 (4.3)	97 (4.5)	52 (4.9)	33 (17.3)	33 (15.7)	22 (22.9)
Moderate	1137 (53.1)	1045 (48.9)	500 (46.7)	108 (56.5)	100 (47.6)	48 (50.0)
Mild	664 (31.0)	637 (29.8)	329 (30.7)	35 (18.3)	48 (22.9)	14 (14.6)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Duration is 52 weeks.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event; SC, subcutaneous.

There were no pregnancies in PURPOSE 2, which enrolled primarily persons of non-childbearing potential.

Lactation

LEN Concentrations in Breast Milk and Infant Plasma

Participants who became pregnant and consented to remain on study drug and breast fed 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.

The ratio of LEN concentration in breast milk (M) to that in maternal plasma (P) (i.e., M:P ratio) was calculated for the available matched pairs (range of time since delivery: 28 to 120 days) irrespective of time since last injection. Median milk-to-plasma (M:P) ratio for LEN was 0.63 (range: 0.29-1.90) for 8 matched pairs. Of note, there was one participant who had significantly higher concentrations than other participants of LEN levels in breast milk of 104 ng/mL which contributed to the wide range in M:P ratio as well as the infant to mother plasma ratio (discussed below). When reviewing the data without this participant's breast milk data, the median M:P ratio was 0.53 (range: 0.29-0.83) for 7 matched pairs. The review team discussed the data with DPMH who acknowledged the wide range in ratios was primarily driven by outlier data (n=1) and agreed that the M:P ratio of less than 1.0 generally indicates limited distribution to milk.

The review team agrees with the Applicant that LEN was detected in breast milk and that it is unknown whether LEN affects breast milk production.

Transfer of LEN from the mother to the infant was described as the ratio of observed LEN concentrations in infant plasma to that in maternal plasma (i.e., infant-to-mother plasma ratio) for the available matched mother-infant pairs (range of time since delivery: 10 to 115 days) irrespective of time since last injection. 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). The review team discussed the data with DPMH. Similar to the M:P ratio, a wide range in infant to mother plasma ratio was observed. The one participant who had the significantly higher LEN levels in breast milk, had a corresponding plasma level of 54.8 ng/ml. This participant's breastfed infant had a LEN plasma level of 10.7 ng/ml, which was the highest concentration observed in an infant. It

should be noted that this infant's plasma level, while higher than the rest of the infant cohort, was several fold lower than both the C_{max} and C_{trough} levels reported in adults who received LEN.

Data for ten out of the 11 matched pairs were from infant samples drawn between 0 to <13 weeks post-delivery, while the one infant plasma sample where LEN was below the limit of assay quantitation (BLQ, 0.5 ng/ml) was drawn between 13 and 28 weeks post-delivery. The review team considered the following when interpreting the plasma data from breast fed infants: (1) when removing the BLQ concentration data point from 13-28 weeks post-delivery, the median infant to mother plasma at 0 to 13 weeks post-delivery was 0.06 (range: 0.01-0.2, n=10) and (2) inherent variability that is to be expected in infant plasma as the transfer of LEN into infant plasma may largely be characterized by the amount of breastmilk an infant consumes.

The review team agrees with the Applicant that the infant-to-mother plasma ratio indicates that the amount of LEN that enters infant plasma after exposure via breast milk is very low and that observed concentrations do not pose known concerns.

Females/Males of Reproductive Potential

Other than the pregnancy data reported above, 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.

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDAs 220018 and 22020 with respect to chemistry, manufacturing, and controls (CMC) and has determined that they meet all applicable standards to support the identity, strength, quality, and purity that they purport. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

Lenacapavir injection was originally approved under NDA 215973 for the treatment of HIV-1 infection in adults (b) (4) Gilead submitted NDA 220018 to seek approval for lenacapavir injection for the new indication of pre-exposure prophylaxis (PrEP) of HIV-1. The Applicant cross-references the entirety of Module 3 in NDA 215973 for the CMC information to support approval of NDA 220018; no new CMC information has been submitted under NDA 220018.

Lenacapavir injection will be supplied as a sterile, preservative-free, yellow solution with a strength of 309 mg/mL for subcutaneous injection. The drug product will be packaged in a vial kit, containing two vials of the drug product, two withdrawal needles, two syringes, and two safety injection needles. Lenacapavir injection proposed for PrEP for HIV-1 under NDA 220018 has the same active ingredient and formulation as lenacapavir injection for HIV-1 treatment approved under NDA 215973. The product quality information (i.e., drug substance, drug product, manufacturing, and quality microbiology) has already been assessed and found adequate under NDA 215973; there are no changes proposed for NDA 220018. Therefore, the application is acceptable from a product quality perspective. Based on the stability data provided, the

expiration of lenacapavir injection is 36 months when stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), protect from light.

Lenacapavir tablets were originally approved under NDA 215974 for the treatment of HIV-1 infection in adults (b) (4) Gilead submitted NDA 220020 to seek approval for lenacapavir tablets for the new indication of pre-exposure prophylaxis (PrEP) of HIV-1. The Applicant cross-references the entirety of Module 3 in NDA 215974 for the CMC information to support approval of NDA 220020; no new CMC information has been submitted under NDA 220020.

Lenacapavir tablets will be supplied as beige, capsule-shaped, film-coated, debossed with "GSI" on one side and "62L" on the other side in counts of 4 packaged in HDPE bottles. Lenacapavir tablets proposed for PrEP for HIV-1 under NDA 220020 have the same active ingredient and formulation as lenacapavir tablets for HIV-1 treatment approved under NDA 215974. The product quality information (i.e., drug substance, drug product, manufacturing, and biopharmaceutics) has already been assessed and found adequate under NDA 215974; there are no changes proposed for NDA 220020. Therefore, the application is acceptable from a drug product quality perspective. Based on the stability data provided, the expiration of lenacapavir tablets is 24 months when stored at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

9.1. Device or Combination Product Considerations

Lenacapavir injection will be supplied as a kit containing two vials of the drug product, two syringes, two 18G, 1½ inch withdrawal needles, and two 22G, ½ inch injection needles. All the device components of the kit are 510(k)-cleared devices.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Clinical Site Inspection

The clinical sites chosen for inspection from the PURPOSE 1 and PURPOSE 2 studies were selected based primarily on numbers of enrolled participants, site efficacy, and prior inspectional history.

Sites chosen for PURPOSE 1 include:

- Site 11413, investigator Dr Khatija Ahmed in South Africa, with 352 randomized participants, for which records for 102 randomized participants were evaluated.
- Site 22455, investigator Dr Philisiwe Makhoba in South Africa with 258 randomized participants, for which records for 50 randomized participants were evaluated.

Sites chosen for PURPOSE 2 include:

- Site 1000, investigator Dr Jose Valdez Ramalho Madruga in Brazil with 217 randomized participants, for which records from all 216 randomized and dosed participants were evaluated (one randomized participant was never dosed).
- Site 366, investigator Dr Ian Frank in the US with 17 randomized participants, for which records for all 17 randomized participants were evaluated.

No evidence of unreported HIV-1 seroconversions was found at any site. While a total of nine participants were given SC injections outside of the protocol-specified injection window period at Site 11413 (four participants in the LEN group, five participants in the comparator groups receiving placebo injections), no incident HIV-1 infections occurred in those participants.

In total, four AEs (folliculitis, upper respiratory infection, dizziness and Dengue fever) were not reported to the FDA from site 1000 and one AE of urinary tract infection was not reported from site 22455. No other underreporting of adverse events was detected. These five unreported AEs are considered unimpactful to the safety conclusions.

The results of the clinical site inspections support the conclusion that the studies were conducted adequately, and the data generated by these inspected sites and reported by the Applicant appear to be acceptable in support of this NDA.

Good Clinical Practice

On April 16, 2025, DAV was informed of findings of good clinical practice non-compliance in an inspection conducted by the South African Health Products Regulatory Authority (SAHPRA) for site 24838 under investigator Dr. MA Makwela. After a thorough review, we do not believe these findings impact the overall efficacy conclusions. Please see Section 16.3, Sensitivity Analysis of the Primary and Key Secondary Analyses for details. This same study site was selected for inspection under PURPOSE 1, as clinical site 11413 under Dr Khatija Ahmed and the data generated by this site and reported by the Applicant appeared to be acceptable in support of this NDA (see above).

Financial Disclosure

Please see Section 25 for the Financial Disclosure Summary.

11. Advisory Committee Summary

Not applicable; this application was not discussed at an advisory committee meeting.

III. Additional Analyses and Information

12. Summary of Regulatory History

U.S. Regulatory Actions and Marketing History

Lenacapavir (LEN), formerly known as GS-6207, is a human immunodeficiency virus-1 (HIV-1) capsid inhibitor, that was initially developed for treatment of HIV-1 infection under investigational new drug (IND) 136260 for the injectable dosage form and IND 138311 for the tablet dosage form.

On December 22, 2022, NDA 215973 for SUNLENCA (lenacapavir) injection, 463.6 mg/1.5mL (309 mg/mL) and NDA 215974 for SUNLENCA (lenacapavir) tablet, 300 mg were approved for the treatment of HIV-1 infection in heavily treatment experienced adults with multi-drug resistant HIV-1 whose current antiretroviral regimen is failing. The approved dosing regimen contains an initiation Phase consisting of oral tablet and subcutaneous injection dosing, followed by a maintenance Phase consisting of once every 6-month injections. For the full regulatory history of NDA 215973 and NDA 215974 to initial approval, see the Office Director Review (dated February 28, 2022) and Integrated Review (dated December 20, 2022) (FDA 2022a).

On November 25, 2024, efficacy supplements for NDA 215973/S-006 and NDA 215974/S-008 were approved to add an alternative 300 mg once weekly, oral bridging dosing regimen for SUNLENCA tablet, for planned and unplanned missed subcutaneous doses.

Summary of Submission/Presubmission Regulatory Activity

Development of LEN for HIV-1 pre-exposure prophylaxis (PrEP) was initiated under IND 136260 on May 29, 2020, via the submission of a Type B, end-of-Phase 2 (EOP), meeting request. The purpose of the meeting was to obtain agreement on the design of two proposed Phase 3 PrEP studies that would support the registration of GS-6207 for the HIV-1, PrEP indication. This meeting was cancelled by Gilead following receipt of the Agency's September 5, 2020, Meeting Preliminary Comments correspondence. In the Preliminary Comments, the Agency provided feedback on the design of the Phase 3 PrEP trials. One trial would enroll men who have sex with men (MSM) and transgender women (TGW), and the other trial would enroll cisgender adolescent girls and young women (AGYW). The Agency generally agreed with the proposed approach for these studies but recommended against proceeding with the proposed trials until additional long-term pharmacokinetic (PK) and safety experience became available from ongoing treatment studies GS-US-200-4625, GS-US-200-4334, and others.

On November 18, 2020, Gilead established preIND 153858 for GS-6207 (LEN) for pre-exposure prophylaxis (PrEP) of HIV-1 infection, with a submission that provided responses to the Agency's September 5, 2020, EOP-2, Preliminary Comments correspondence (IND (b) (4) and a request for feedback on their safety review strategy for both studies. The Agency provided their recommendations and comments on December 20, 2020.

On December 23, 2020, the Agency received a request for Breakthrough Therapy (BT) designation for PrEP of HIV-1 infection. The request was withdrawn on January 19, 2021, because the request was premature.

On March 12, 2021, the Agency received IND 153858, which contained two Phase 3 studies: GS-US-412-5624 (PURPOSE 1), "A 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," and GS-US-528-9023 (PURPOSE 2), "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 Non-binary People ≥16 Years of Age who Have Sex with Male Partners and are at Risk for HIV Infection." The Agency issued a Study May Proceed communication on April 12, 2021.

On April 13, 2021, a request for BT designation for PrEP of HIV-1 infection was received. The request was denied on June 9, 2021, (b) (4)

Gilead submitted an Initial Pediatric Study Plan (iPSP) on May 13, 2021, and a revised iPSP on August 18, 2021. An Agreed iPSP was issued by the Agency on September 14, 2021. The iPSP outlined a plan to request a waiver for pediatric patients from birth to less than 16 years of age because studies are impossible or highly impracticable. Gilead planned to include a pediatric assessment for pediatric patients 16 years to less than 18 years of age. Gilead submitted an Amended iPSP on November 27, 2023, and a revised Amended iPSP on March 1, 2024. An Amended Agreed iPSP was issued on March 22, 2024. Changes were made to the dates the pediatric studies would be completed and the dates the final study reports would be submitted.

Gilead submitted a Fast Track designation request for LEN for pre-exposure prophylaxis of HIV-1 infection on June 30, 2021, and this request was granted on August 17, 2021.

A December 20, 2021, a teleconference was held wherein Gilead was informed that INDs 136260 and 153858 were being placed on Full Clinical Hold per 21 CFR 312.42(b)(2)(iv) for insufficient information to assess risks to human subjects and 21 CFR 312.42(b)(2)(i) for unreasonable and significant risk of illness or injury to human subjects. The hold was based upon issues related to the container closure system that was being used for LEN injection product and the extent to which these issues are associated with injection site reaction reports.

On February 9, 2022, Gilead submitted a Clinical Hold Complete Response together with PURPOSE 1 and PURPOSE 2 protocol amendments containing updated injection site reaction safety monitoring plans and implementation of oral weekly bridging for LEN tablets. In response, the Agency issued a Remove Full Hold/Impose Partial Hold letter on March 16, 2022, allowing Gilead to proceed with PURPOSE 1 and PURPOSE 2 only with the proposed weekly dosing of 300 mg LEN orally as an alternative to Q6M injection.

On April 15, 2022, Gilead submitted a Complete Response to the Partial Clinical Hold, which included data to support the use of a new container closure system for the LEN injection. On May 13, 2022, the Agency issued a Remove Partial Clinical Hold letter following review of the Sponsor's Complete Response.

On May 04, 2022, Gilead submitted a Type C meeting request to [redacted]. On August 3, 2022, the Agency issued a Final Written Response correspondence that recommended that Gilead consider development of more rigorous research methodologies than the approaches presented in the briefing package.

On September 22, 2023, Gilead submitted a Type C meeting request (IND 153858) to discuss the use of an HIV recency assay, estimation of HIV background incidence rates, and efficacy analysis for PURPOSE 1 and PURPOSE 2 studies. The teleconference was held November 28, 2023, during which the Agency provided guidance on the draft statistical analysis plan and interim analysis plan.

On November 27, 2023, Gilead submitted to IND 153858 a request for comments and advice regarding their proposal to submit a unique trade name for two new original NDAs for lenacapavir injection and lenacapavir tablet for HIV PrEP. On December 13, 2023, the Agency's informed Gilead that their proposal was acceptable.

On June 14, 2024, Gilead submitted a Request for Proprietary Name Review for LEN tablets and injection. On November 12, 2024, the Agency conditionally approved the proposed name of YEZTUGO.

On July 23, 2024, Gilead submitted a Type B, Pre-NDA virtual face-to-face meeting request to discuss their plans to submit new original NDAs for LEN tablets, 300 mg and LEN injection 463.5 mg/1.5 mL (309 mg/mL) for HIV-1 PrEP in adults and adolescents weighing at least 35 kg and the content and format of the NDAs. In addition, Gilead requested feedback on the proposed rolling review plan and plan to submit a request for BT designation. During the September 19, 2024, meeting the Agency agreed with the content and format of the future NDA submissions. In addition, the Agency conditionally agreed with the proposed two stage Rolling Review schedule for the proposed original NDAs.

On August 23, 2024, Gilead submitted a request for BT designation that included the results from the interim analysis from PURPOSE 1 and PURPOSE 2. Breakthrough Therapy Designation was granted on October 16, 2024, for pre-exposure prophylaxis of HIV-1 infection.

On October 11, 2024, Gilead submitted a request for rolling submission and review of portions of the NDAs for LEN for PrEP. This request was granted on October 30, 2024, on the basis of LEN receiving FT designation for PrEP of HIV-1 infection.

On November 16, 2024, Gilead submitted tier 1 of the Rolling Review submission for original NDA 220018 and NDA 220020, for lenacapavir for HIV-1 PrEP injection and tablet, respectively. On December 19, 2024, Gilead submitted the final submissions to NDA 220018 and NDA 220020 marking submission of complete NDA packages. These applications include an oral bridging dosing regimen for planned and unplanned missed injections in addition to the primary dosing regimen of initiation with injection and tablet followed by once every 6 month maintenance doses. The applications were filed on February 17, 2025, received priority review, and have a PDUFA goal date of June 19, 2025.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The nonclinical studies to support the safety of LEN were submitted and reviewed under investigational new drug applications 136260 and 138311 and NDAs 215973 and 215974 for the treatment of HIV-1 in heavily treatment-experienced adults with multidrug resistance HIV-1. Additional studies submitted to support LEN in the present NDA are reviewed in the following sections. LEN is also referred to as GS-6207 in these studies.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Juvenile Toxicity

An Oral (Gavage) Juvenile Toxicity Study of GS-6207 in Wistar Han Rats With a 4-Week Recovery Phase (Study No. TX-200-2084)

The effects of LEN were evaluated in a juvenile toxicity study in rats. The rats were dosed orally with 0, 3, 10, or 30 mg/kg/day from postnatal Day 7 through 55 followed by a 4-week recovery period.

There were 9 deaths in the main study animals that were either due to gavage procedure or unrelated to LEN. Statistically significant increases in cholesterol were detected in males at 30 mg/kg when compared to the controls at the end of the dosing period. Although, not statistically significant, there was a trend of increased cholesterol levels in females at 10 and 30 mg/kg when compared with controls. At the end of the recovery Phase, the increased cholesterol levels either fully or partially resolved in males and females.

There were no LEN-related effects on growth or development.

13.2.2. Local Tolerance

A Single Dose Slow Bolus Subcutaneous Injection or Slow Bolus Intramuscular Injection Local Tolerance Study With Lenacapavir in Female New Zealand White Rabbits With a 91-Day Observation Period (Study No. TX-200-2085)

This study examined the local effect of a single dose of lenacapavir (LEN, 500 mg/ml) and its vehicle (polyethylene glycol 300, water injection (b) (4) when administered to female rabbits through slow bolus injection via the subcutaneous (SC) or intramuscular (IM) routes. The animals were observed for 91 days post dose and necropsied on Day 92 post dose.

Dosing with LEN via the SC route resulted in clinical observations of a palpable mass and/or scabbing at the dosing sites. Additional observations at this dosing site included atonia,

desquamation, and increase observations of erythema and eschar, and increases in observations and severity of edema when compared with the control dosing site via SC administration.

Two out of 6 animals in the vehicle dosing group via the SC route had observations of edema, erythema, and/or eschar noted which correlated with scabbing, dry sores, and/or a small palpable mass at the dosing site.

Dosing with LEN via the IM route resulted in desquamation, edema, and erythema at the dosing site. Two out of 6 vehicle control animals had observations of erythema on Day 92, which the Applicant attributed to shaving.

At the end of the dosing period on Day 92 (terminal necropsy), macroscopic observations included gelatinous, mass, and/or scab at the dosing site for LEN via the SC route (Table 63).

Table 63. Summary of LEN-Related Macroscopic Findings (92 Days Postdosing, Terminal Necropsy)

Tissue/finding	Sex	Females	
	Dose Site[a]	A	B
	LEN Dose (mg)	0	500
	Number examined	6	
Subcutaneous Injection Site, A			
Gelatinous		1[a]	
Subcutaneous Injection Site, B			
Gelatinous		2	
Mass		1	
Scab		2	

Source: Table 4.1 of Sponsor's study report no. TX-200-2085.
[a] Vehicle control article was administered to Dose Site A, and the test article was administered to Dose Site B. Based on macroscopic/microscopic observations at Dose site A in animal B0007, this single incidence of gelatinous material at Dose Site A was likely due to dosing error or compound migration and not vehicle related.
Abbreviation: LEN, lenacapavir.

There were no macroscopic findings for the IM dosing site noted.

A summary of the histopathology findings is presented in Table 64. A single animal dosed with the vehicle control via the SC route had a finding of granulomatous inflammation. Considering this occurred in a single animal and there were no findings in control animals dosed with the vehicle via the IM route, the Applicant attributed this finding related to the dosing procedure. LEN-related findings of granulomatous inflammation were noted at the dosing sites when LEN was administered via the SC and IM routes. Additionally, infiltration of macrophages was noted when LEN was dosed via the SC route.

Table 64. LEN-Related Histopathology Findings (92 Days Postdosing, Terminal Necropsy)

Tissue/finding	Sex	Females			
	Dose Route	Subcutaneous[a]		Intramuscular[a]	
	Dose Site[a]	A	B	C	D
	LEN Dose (mg)	0	500	0	500
	Number examined	6		6	
Subcutaneous Injection Site A					
Inflammation, granulomatous, subcutaneous					
	Total number affected	1[b]		NA	
	Moderate	1		NA	
Subcutaneous Injection Site, B					
Inflammation, granulomatous, subcutaneous					
	Total number affected	5		NA	
	Minimal	3		NA	
	Moderate	2		NA	
Infiltrate, macrophage, subcutaneous					
	Total number affected	1		NA	
	Minimal	1		NA	
Intramuscular Injection Site, D					
Inflammation, granulomatous, intramuscular					
	Total number affected	NA		3	
	Minimal	NA		2	
	Moderate	NA		1	

Source: Table 4.2 of Sponsor's study report no. TX-200-2085.
[a] Vehicle control article was administered to Dose Sites A and C. Test article was administered to Dose Sites B and D.
[b] Based on macroscopic/microscopic observations at Dose site A in animal B0007, this single incidence of gelatinous material at Dose Site A was likely due to dosing error or compound migration and not vehicle related.
Abbreviations: LEN, lenacapavir; NA, not applicable.

14. Clinical Pharmacology

14.1. In Vitro Studies

No new *in vitro* studies were conducted under this NDA. Please refer to the SUNLENCA NDA 215973/215974 for *in vitro* studies conducted with LEN (FDA 2022a).

14.2. In Vivo Studies

14.2.1. GS-US-200-4540: Phase 1 Study To Evaluate the Effect of SC Injection Sites on the Pharmacokinetics of LEN

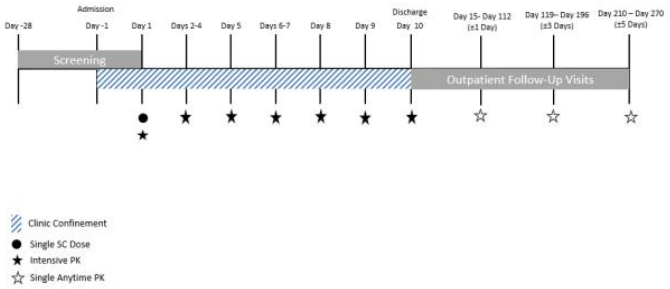
Study Design

This was a Phase 1 single-center, open-label, parallel-design, single-dose, multicohort study in 40 healthy adult participants and consisted of 4 cohorts (n=10 each). Primary PK endpoints included AUC_{last}, AUC_{inf}, and C_{max} of LEN. Additional PK parameters assessed included

$\%AUC_{exp}$, T_{max}, C_{last}, T_{last}, apparent clearance (CL/F), apparent volume of distribution (Vz/F), $t_{1/2}$, and the terminal elimination rate constant (λz) of LEN, as applicable. An overview of the study design is in Figure 26.

- Thigh (Cohort 1): Single SC LEN (927 mg; 2 x 1.5 mL of LEN injection, 309 mg/mL) administered bilaterally in the thigh
- Upper arm (Cohort 2): Single SC LEN (927 mg; 2 x 1.5 mL of LEN injection, 309 mg/mL) administered bilaterally in the upper arms
- Abdomen (Cohort 3): Single SC LEN (927 mg; 2 x 1.5 mL of LEN injection, 309 mg/mL) administered in different quadrants of the abdomen
- Gluteal region (Cohort 4): Single SC LEN (927 mg; 2 x 1.5 mL of LEN injection, 309 mg/mL) administered bilaterally in the gluteal regions

Figure 26. Study Schema, GS-US-200-4540



PK = pharmacokinetic(s); SC = subcutaneous

Source: Final Clinical Study report US-GS- 200-4540, Figure 1.

PK Sampling

Intensive PK sampling occurred relative to LEN administration at the following time points: Day 1: 0 (predose; 5 minutes before dose), 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours postdose. Single PK samples were collected any time on the following days postdose: Days 15, 21, 35, 49, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 140, 154, 168, 182, 196, 210, 240, and 270 and at early termination visit.

Results

Demographics:

The 40 participants received LEN and were included in the PK analysis. An equal number of males and females enrolled in each injection site cohort. The median age of enrolled participants was 46 years (range 21-54), 80% of whom were White, and all were Hispanic or Latino. The median BMI across all cohorts was 26.8 (range 21.3-31.1).

PK Results

LEN PK by injection site in comparison to abdomen were summarized in Section 7.7.2 in Table 53, Table 54, and Table 55.

Overall, LEN concentrations were detectable up to Day 270 after a single SC injection into each respective site.

- Following single SC dose administration into the thigh, LEN AUC_{last}, AUC_{inf}, and C_{max} was 12% lower, 20% higher, and 8% lower, respectively, compared with the abdomen.
- Following single SC dose administration into the upper arm, LEN AUC_{last}, AUC_{inf}, and C_{max} was 4% higher, 7% lower, and 33% higher, respectively, compared with the abdomen.
- Following single SC dose administration into the gluteal region, LEN AUC_{last}, AUC_{inf}, and C_{max} was 18%, 11%, and 26% higher, respectively, compared with the abdomen.
- The PK from the reference abdominal cohort were similar to PK from a similar healthy volunteer study population administered the same dose and LEN formulation US-GS-200-4538 (reviewed under SUNLENCA NDA 215973/215974).

Applicant's Conclusion

(b) (4)

The Applicant proposes the thigh, (b) (4) to be acceptable alternate sites of injection.

FDA's Conclusion

Based on the available PK data, the review team concluded that available PK data support the recommendation for the thigh to be an acceptable alternate site of injection, (b) (4) . Please refer to Section 7.7.2 for discussion on the review team's assessment and conclusion.

14.2.2. PURPOSE 1 (GS-US-412-5624): Phase 3, Randomized, Double-Blind, Multicenter Study To Evaluate the Safety and Efficacy of LEN and F/TAF for PrEP in Cisgender Adolescent Girls and Young Women ≥16 to ≤25 Years of Age Who Have Sex With Partners Assigned Male at Birth

PURPOSE 1 was a Phase 3 double blinded, multicenter, randomized study to evaluate safety and efficacy of twice yearly long-acting subcutaneous LEN, and daily oral emtricitabine/tenofovir alafenamide for pre-exposure prophylaxis in AGYW at risk for HIV-1 infection. Refer to Sections 6.2.1 for trial design, objectives, and key efficacy results of PURPOSE 1. In this section of the review, only clinical pharmacology data collected for the following exploratory endpoints are assessed: (1) LEN plasma concentrations (2) adherence rates of F/TAF and F/TDF using intracellular tenofovir-diphosphate (TFV-DP) levels in DBS, (3) LEN levels in pregnant, postpartum women, breast milk and in breastfed infant plasma, and (4) plasma levels of hormonal contraceptives while receiving LEN.

PK Sampling and Analysis Sets

During the randomized blinded Phase, samples for plasma LEN quantitation and TFV-DP levels in DBS were collected on study Weeks 4, 8, 13, and every 13 weeks thereafter.

To describe LEN and TFV-DP DBS PK, an approximate 10% random sampling of PK study samples was deemed sufficient to be representative of the overall PK of LEN and oral daily PrEP with F/TAF or F/TDF.

LEN PK and DBS analysis sets included all randomized participants who received at least one dose of study drug, were selected in the random sampling of approximately 10% of the randomized participants, and had at least 1 non-missing LEN plasma or DBS concentration value.

Pharmacokinetic Results

Adults

Mean (lower bound of 90% CI) LEN C_{trough} at Weeks 26 and 52 were 34.1 (31.5) and 44.7 (39.8) ng/mL, respectively, in the preselected random 10% subset of adult participants (excluding adolescents, participants who became pregnant, participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection, as applicable) in the randomized blinded Phase. Summary statistics of LEN plasma concentrations are presented in Table 65 below.

Table 65. Summary Statistics of LEN Plasma Concentrations by Study Visit in the Randomized Blinded Phase, LEN PK Analysis Set[a], PURPOSE 1

Parameter	Week 4 (N = 165)	Week 8 (N = 158)	Week 13 (N = 163)	Week 26 (N = 156)	Week 39 (N = 129)	Week 52 (N = 73)	Week 65 (N = 23)	Week 78 (N = 9)
Mean (ng/mL)	34.7	59.9	68.3	34.1	85.0	44.7	91.0	52.2
90% CI (lower) (ng/mL)	31.8	53.7	63.1	31.5	78.8	39.8	69.5	41.3
90% CI (upper) (ng/mL)	37.7	66.1	73.5	36.6	91.2	49.7	112.5	63.0

CI = confidence interval; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s)
a Excluding adolescents, participants who became pregnant, participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection, as applicable.
Values were rounded to 3 significant figures, except for N.
Lower limit of quantitation was 0.5 ng/mL for LEN.
For injection visits, records with on-time injection (both injections administered in full dose within ± 2 weeks of targeted day relative to previous injection) were summarized.
For other visits, records collected per protocol-specified visit windows were summarized.
Values below the limit of quantitation were treated as 0 for summary statistics.
Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Table 22.

No incident HIV-1 infections were reported at the 52-week interim analysis. The LEN C_{trough} (lower bound of the 90% CI) remained above the IQ4 at both Weeks 26 and 52.

Adolescents

Please refer to Section 8.3 for discussion on LEN plasma concentrations in adolescents.

Pregnant Women and Postpartum Period

Please refer to Section 8.4 for discussion on LEN plasma concentrations in pregnant women and during postpartum period.

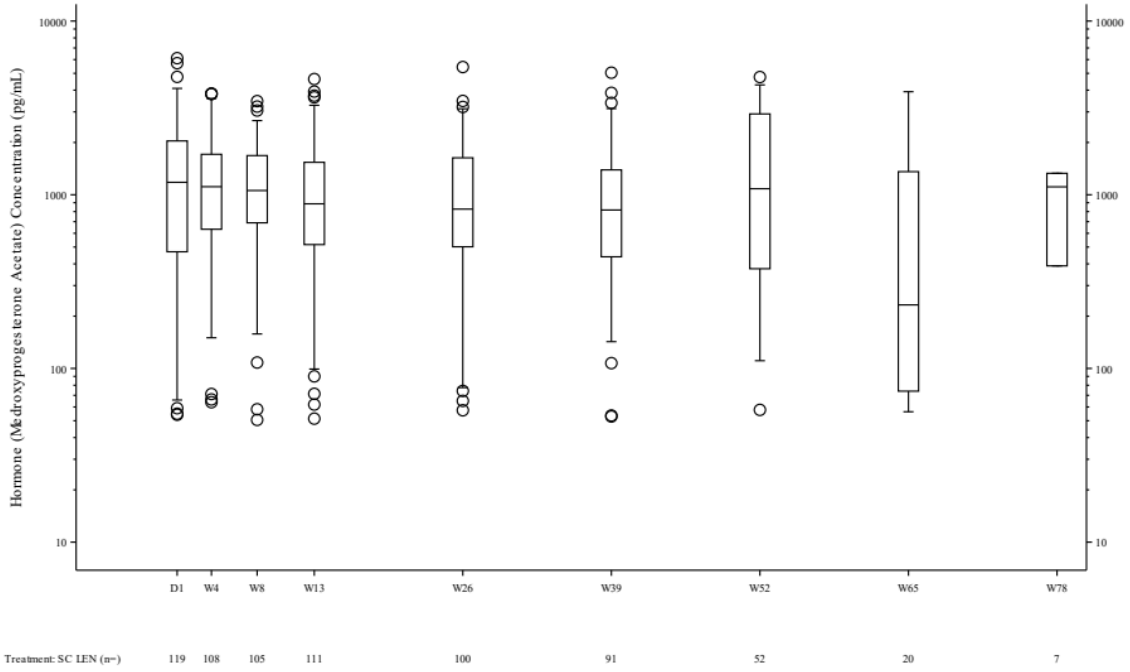
Breast Milk and Infant Plasma

Please refer to Section 8.4 for discussion on LEN concentrations in breast milk and infant plasma.

Drug-Drug Interaction: LEN Impact on Hormonal Contraceptives

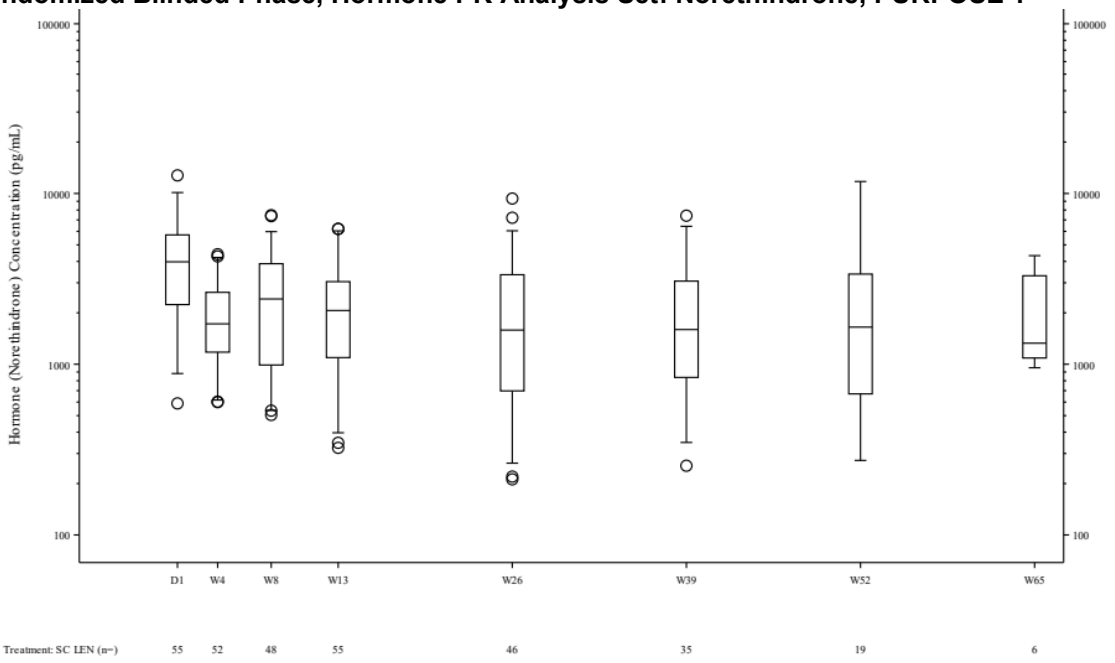
To characterize the impact of LEN on the concentrations of certain common long-acting hormonal contraceptives, available concentrations were evaluated in a subset of participants in the LEN group who received medroxyprogesterone acetate, norethindrone enanthate, or etonogestrel; please see Section 8.2 for a summary assessment. Hormonal contraceptive concentrations were collected prior to LEN dosing and at available time points starting at week 4 after LEN dosing. Figure 27, Figure 28, and Figure 29 describe long-acting hormonal contraceptives concentrations in participants receiving LEN. All doses, frequencies, form, and changes in dosing of hormonal contraceptives were allowed per protocol. LEN does not appear to have a significant impact on long-acting contraceptives.

Figure 27. Boxplots of Medroxyprogesterone Acetate Plasma Concentrations by Study Visit, Semilogarithmic Scale, for Participants in the LEN Group Who Received Medroxyprogesterone Acetate in the Randomized Blinded Phase, Hormone PK Analysis Set: Medroxyprogesterone Acetate, PURPOSE 1



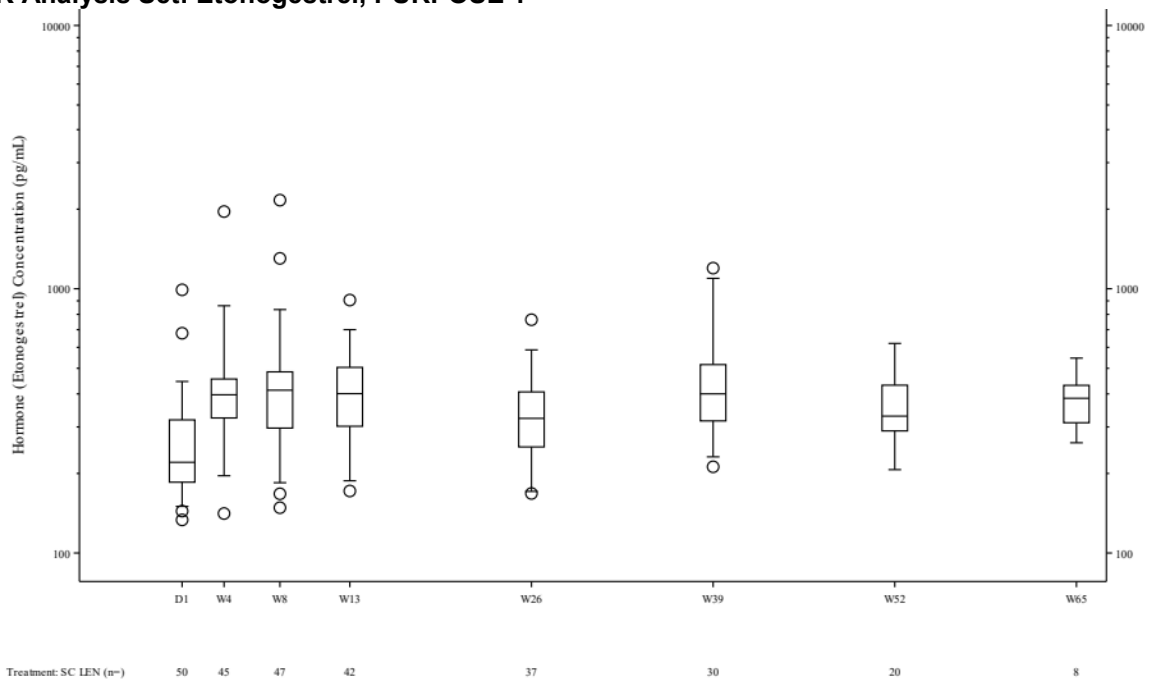
LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (50 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Figure 12.

Figure 28. Boxplots of Norethindrone Plasma Concentrations by Study Visit, Semilogarithmic Scale, for Participants in the LEN Group Who Received Norethindrone Enanthate in the Randomized Blinded Phase, Hormone PK Analysis Set: Norethindrone, PURPOSE 1



LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (200 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Figure 13.

Figure 29. Boxplots of Etonogestrel Plasma Concentrations by Study Visit, Semilogarithmic Scale, for Participants in the LEN Group With Etonogestrel in the Randomized Blinded Phase, Hormone PK Analysis Set: Etonogestrel, PURPOSE 1



LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (25 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Figure 14.

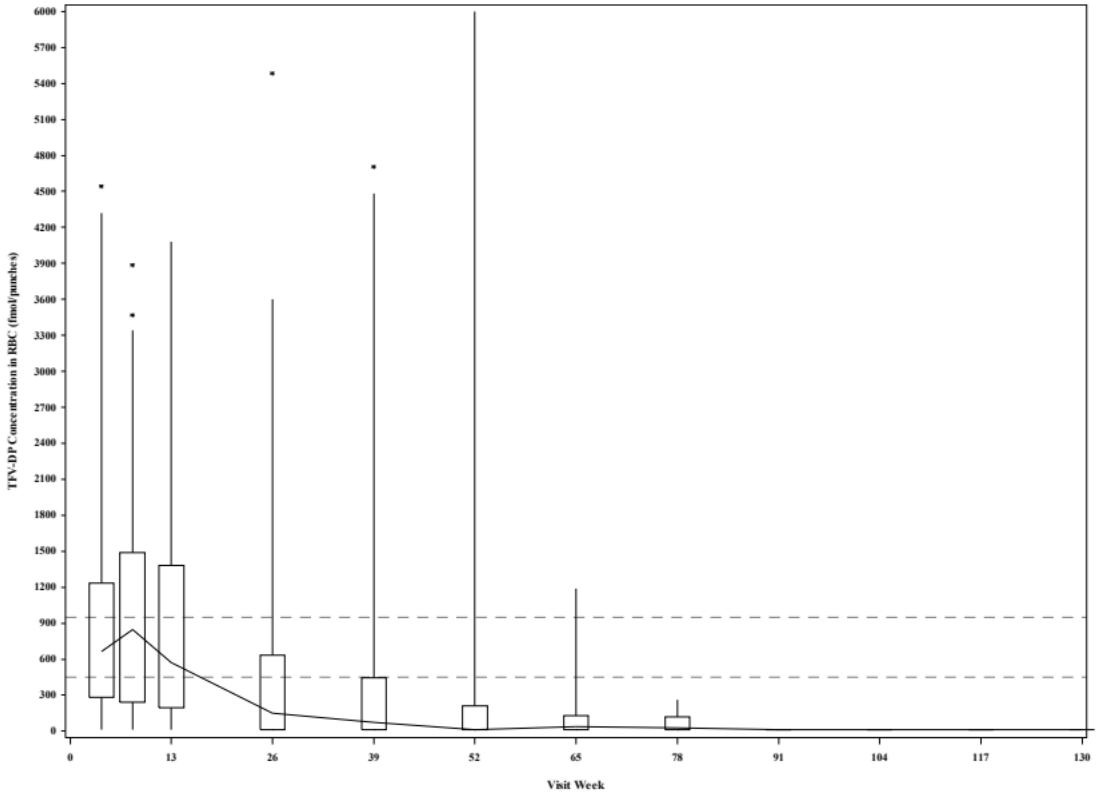
Adherence Assessment

Adherence to F/TAF and F/TDF was assessed objectively by measuring the concentrations of TFV-DP in DBS. DBS testing were performed in a random 10% subset of study participants and in all participants who were diagnosed with HIV-1. The correlation between adherence and TFV-DP concentrations from F/TAF and F/TDF in red blood cells (RBCs) by DBS has been evaluated in several publications (Grant et al. 2014; Anderson et al. 2018; Yager et al. 2020). The review team considers that TFV-DP concentration in DBS is a reasonable tool to assess the adherence in the comparator arms in PURPOSE-1.

Among the preselected 10% random sampling of participants, the majority in both the F/TAF (71.9%) and F/TDF (78.1%) groups had low adherence at 26 weeks (concentrations consistent with dosing <2 days per week). High adherence (concentrations consistent with ≥4 doses per week) largely declined from Week 8: F/TAF (37.1%) and F/TDF (17.9%) to Week 26 in F/TAF (19%) and F/TDF (10.9%) (Figure 30 and Figure 31). Table 66 below describes results of an exploratory case-control analysis of adherence based on DBS TFV-DP concentrations at HIV-1 diagnosis. It should be noted, the decline in participant adherence captured by low DBS levels was discordant with other measures of study adherence, namely pill count and questionnaire data. By pill count, 74.3% of the F/TAF group and 74.4% of the F/TDF group were ≥95% adherent to study drug. Self-reported adherence as measured by ePRO questionnaire indicated most participants reported "good", "very good", or "excellent" in their ability to take oral study medications every day as recommended for all the visits. Despite these reported adherence

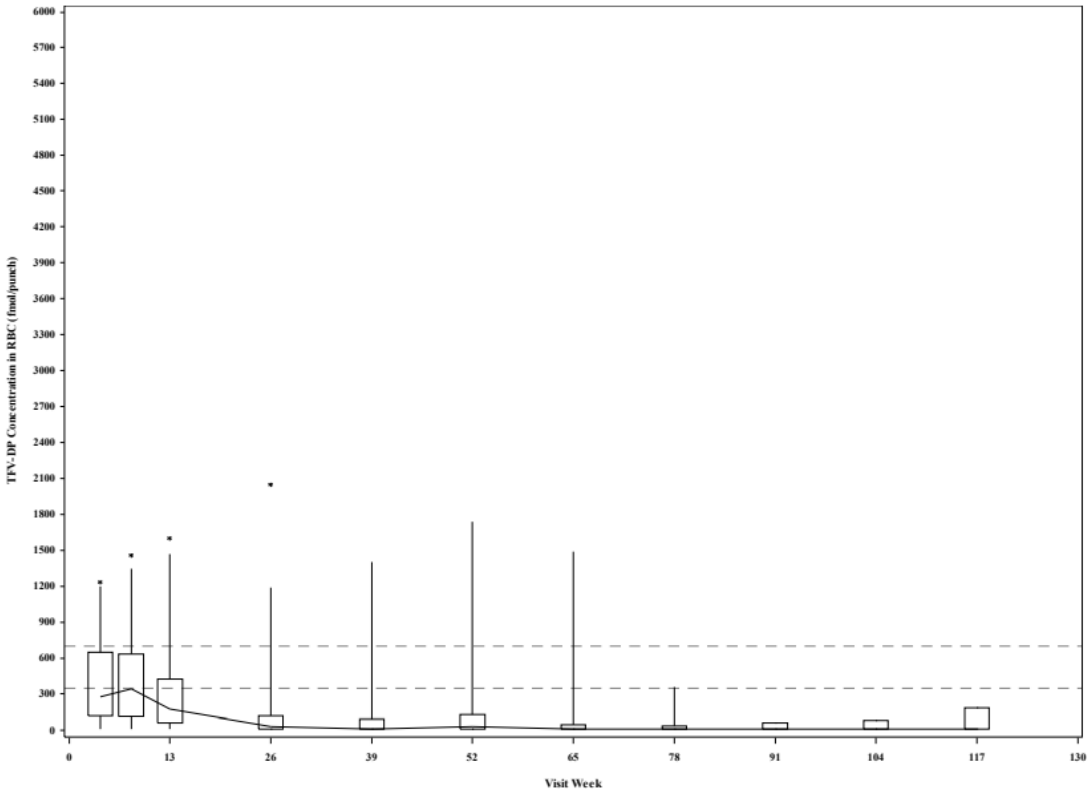
measures that suggest participants were taking their prescribed daily oral F/TAF and F/TDF, the objective DBS levels provide insight into the true adherence patterns of participants. These observations reflect "real life" usage patterns of daily oral pills for HIV-1 PrEP and likely reflect the adherence challenges in this study population of adolescent girls and young women. This is an important determination as injectable LEN demonstrated superiority over oral daily options for HIV-1 PrEP and suggests that the success of LEN may be largely attributed to the varying degrees of non-adherence observed in the oral daily F/TAF and F/TDF groups.

Figure 30. DBS TFV-DP Concentrations in Red Blood Cells From F/TAF (fmol/punch) by Visit While at Risk of HIV, Randomized Blinded Phase, DBS Cohort Analysis Set, PURPOSE 1



Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Figure 6.
Week 4 value was prior to DBS TFV-DP concentration reaching steady state and may therefore underestimate adherence. Below the limit of quantitation treated as one-half the LLOQ for summary, defined for DBS TFV-DP as 25 fmol/punches. Values >6000 not displayed. Black box indicates Q1 and Q3 with lines connecting medians; whiskers indicate first and 99th percentiles. Grey dash = Adherence to F/TAF: Low <450, Medium ≥450 to <950, High ≥950 fmol/punches.
Abbreviations: DBS, dried blood spot; F/TAF, emtricitabine/tenofovir alafenamide; HIV, human immunodeficiency virus; LLOQ, lower limit of quantitation; Q1, first quartile; Q3, third quartile; RBC, red blood cell; TFV-DP, tenofovir diphosphate.

Figure 31. DBS TFV-DP Concentrations in Red Blood Cells From F/TDF (fmol/punch) by Visit While at Risk of HIV, Randomized Blinded Phase, DBS Cohort Analysis Set, PURPOSE 1



Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Figure 7.
Week 4 value was prior to DBS TFV-DP concentration reaching steady state and may therefore underestimate adherence. Below the limit of quantitation treated as one-half the LLOQ for summary, defined for DBS TFV-DP as 25 fmol/punch. Values >6000 not displayed. Black box indicates Q1 and Q3 with lines connecting medians; whiskers indicate first and 99th percentiles. Grey dash = Adherence to F/TDF: Low <350, Medium ≥350 to <700, High ≥700 fmol/punch.
Abbreviations: DBS, dried blood spot; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; LLOQ, lower limit of quantitation; Q1, first quartile; Q3, third quartile; RBC, red blood cell; TFV-DP, tenofovir diphosphate.

Table 66. Adherence Based on DBS TFV-DP Concentrations in RBC (fmol/punch[es]) at HIV-1 Diagnosis Visit, DBS Case-Control Analysis Set, PURPOSE 1

	F/TAF (N=196)		F/TDF (N=89)	
Adherence at HIV Diagnosis	Cases (HIV Diagnosis) (N=37)	Matched Controls (Diagnosis of No HIV) (N=159)	Cases (HIV Diagnosis) (N=14)	Matched Controls (Diagnosis of No HIV) (N=69)
Low (< 2 days/Week)	34 (91.9%)	116 (65.9%)	13 (92.9%)	60 (85.7%)
Medium (2 - 3 days/Week)	1 (2.7%)	26 (14.8%)	0	3 (4.3%)
High (>= 4 days/Week)	2 (5.4%)	34 (19.3%)	1 (7.1%)	7 (10.0%)
- Missing -	0	1	0	0
Low (< 2 days/Week)	34 (91.9%)	116 (65.9%)	13 (92.9%)	60 (85.7%)
Not Low (>= 2 days/Week)	3 (8.1%)	60 (34.1%)	1 (7.1%)	10 (14.3%)
- Missing -	0	1	0	0
Exact Odds Ratio	9.00		2.19	
(95% CI)	(2.06, 83.36)		(0.26, 106.37)	
p-value	0.0006		0.8261	
High (>= 4 days/Week)	2 (5.4%)	34 (19.3%)	1 (7.1%)	7 (10.0%)
Not High (< 4 days/Week)	35 (94.6%)	142 (80.7%)	13 (92.9%)	63 (90.0%)
- Missing -	0	1	0	0
Exact Odds Ratio	0.23		0.66	
(95% CI)	(0.03, 1.02)		(0.01, 7.68)	
p-value	0.0542		1.0000	

Source: Study GS-US-412-5624 (PURPOSE 1) Interim Week 52 Clinical Study Report, Table 15.9.2.8.2.
Adherence cutoffs for F/TAF: Low <450, Medium >=450 to <950, High >=950 fmol/punches and F/TDF: Low <350, Medium >=350 to <700, High >=700 fmol/punch.
Abbreviations: DBS, dried blood spot; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; RBC, red blood cell(s); TFV-DP, tenofovir diphosphate.

The acceptability of the results of the statistical analysis comparing cases and matched controls has not been reviewed by the FDA. This table is included for illustrative purposes only to show the trend of association between adherence and HIV diagnosis among participants diagnosed with HIV in PURPOSE-1 comparator arms.

14.2.3. PURPOSE 2 (GS-US-528-9023): Phase 3, Randomized, Double-Blind, Multicenter Study To Evaluate the Efficacy and Safety of LEN for 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

PURPOSE 2 is 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. Refer to Sections 6.2.2 for trial design, objectives, and key efficacy results of PURPOSE 2. In this section of the review, only clinical pharmacology data collected for the following exploratory endpoints are assessed: LEN plasma levels (2) concentrations of hormones in participants receiving LEN (3) adherence rates to F/TDF using TFV-DP in DBS.

PK Sampling and Analysis Sets

During the randomized blinded Phase, samples for plasma LEN quantitation and TFV-DP levels in DBS were collected on study Weeks 4, 8, 13, and every 13 weeks thereafter.

To describe LEN and TFV-DP DBS PK, an approximate 10% random sampling of PK study samples was deemed sufficient to be representative of the overall PK of LEN and oral daily PrEP with F/TAF or F/TDF.

LEN PK and DBS analysis sets included all randomized participants who received at least one dose of study drug, were selected in the random sampling of approximately 10% of the randomized participants and had at least 1 non-missing LEN plasma or DBS concentration value.

Pharmacokinetic Results

Adults

Mean (lower bound of 90% CI) LEN C_{trough} at Weeks 26 and 52 were 22.8 (21.6) and 27.8 (25.2) ng/mL, respectively, in the preselected random 10% subset of adult participants (excluding adolescents, participants who became pregnant [if any], participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection) in the randomized blinded Phase. Summary statistics are described in Table 67.

Table 67. Summary Statistics of LEN Plasma Concentrations by Study Visit, Randomized Blinded Phase, LEN PK Analysis Set[a], GS-US-528-9023

Parameter	Week 4 (N = 374)	Week 8 (N = 340)	Week 13 (N = 362)	Week 26 (N = 267)	Week 39 (N = 154)	Week 52 (N = 111)	Week 65 (N = 50)	Week 78 (N = 23)	Week 91 (N = 12)
Mean (ng/mL)	34.8	52.9	52.4	22.8	64.1	27.8	64.0	37.4	109
90% CI (lower) (ng/mL)	32.7	49.6	50.1	21.6	60.2	25.2	57.2	20.4	65.1
90% CI (upper) (ng/mL)	36.9	56.1	54.7	24.1	68.1	30.4	70.9	54.4	153

CI = confidence interval; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s)
a Excluding adolescents, participants who became pregnant (if any), participants who received oral LEN bridging, and participants diagnosed with HIV-1 infection.
Values were rounded to 3 significant figures, except for N.
Lower limit of quantitation was 0.5 ng/mL for LEN.
For injection visits, records with on-time injection (both injections administered in full dose within ± 2 weeks of targeted day relative to previous injection) were summarized.
For other visits, records within protocol-specified windows (with targeted date relative to previous injection) were summarized.
Values below the limit of quantitation were treated as 0 for summary statistics.
Source: Study GS-US-528-9023 (PURPOSE 2) Interim Week 52 Clinical Study Report, Table 15.

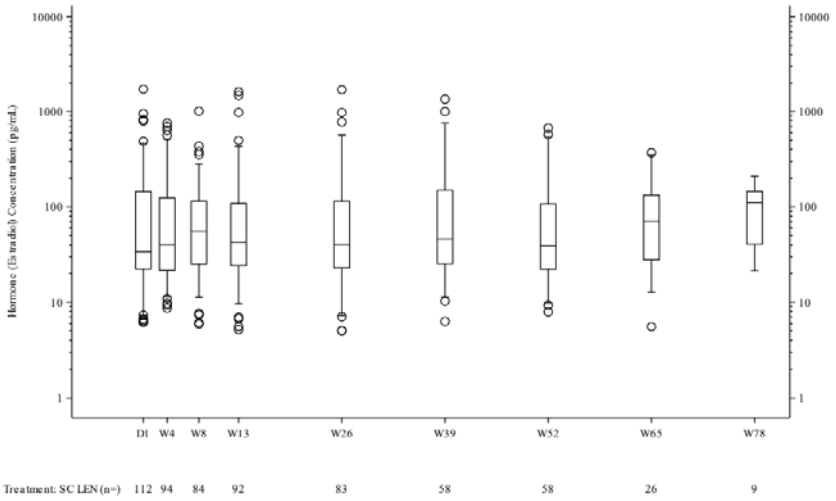
Adolescents

Please refer to Section 8.3 on discussion of LEN plasma concentrations in adolescents.

Drug Interaction With Hormone Therapies

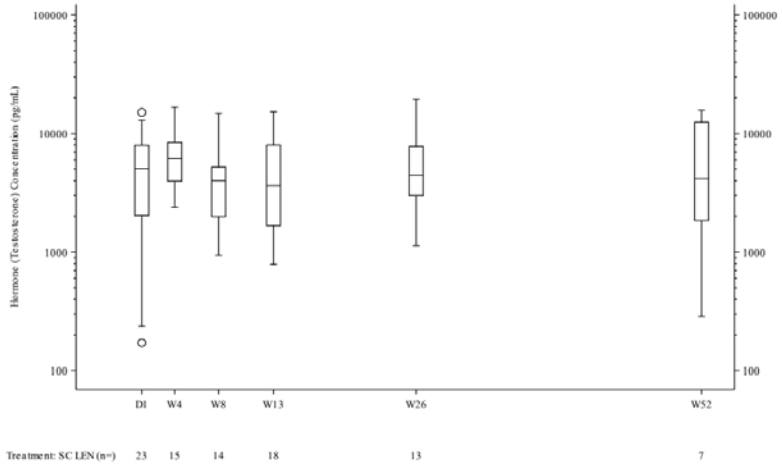
The concentrations of gender-affirming hormones were evaluated in a subset of participants in the LEN group who were assigned as male at birth and received estradiol or were assigned as female at birth and received testosterone to assess the impact of LEN on the concentrations of these gender-affirming hormones; please see Section 8.2 for a summary assessment. Hormone concentrations were collected prior to initiating LEN dosing and at available time points starting at Week 4 after LEN dosing. Figure 32, Figure 33, and Figure 34 describe hormone concentrations (estradiol, testosterone, dihydrotestosterone) in participants receiving LEN. All doses, frequencies, form, and changes in dosing of hormone therapies were allowed per protocol. LEN does not appear to have a significant impact on estradiol, testosterone, and dihydrotestosterone.

Figure 32. Boxplots for Estradiol Serum Concentrations by Study Visit, Semilogarithmic Scale, for Participants Assigned Male at Birth in the LEN Group Who Received Estradiol in the Randomized Blinded Phase, Hormone PK Analysis Set: Estradiol, PURPOSE 2



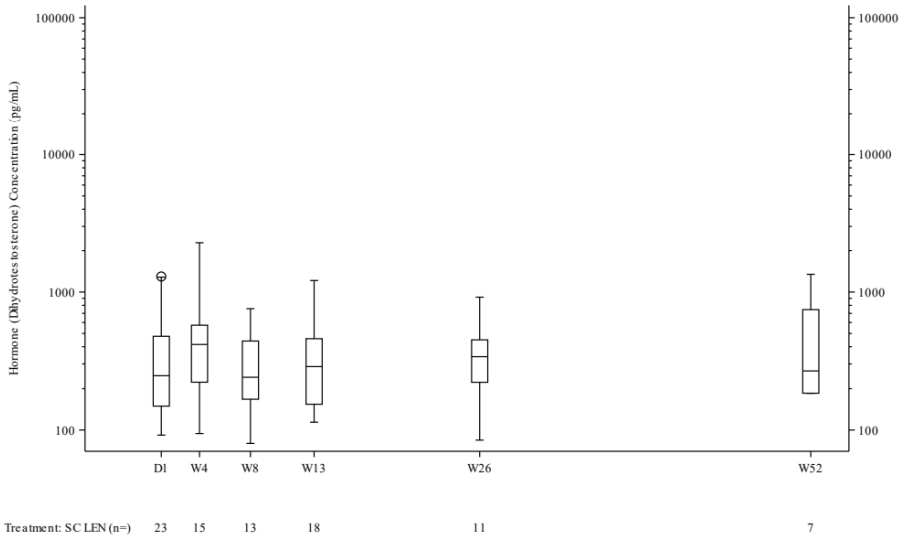
LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (5 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-528-9023 (PURPOSE 2) Interim Week 52 Clinical Study Report, Figure 6.

Figure 33. Boxplots for Testosterone Plasma Concentrations by Study Visit, Semilogarithmic Scale, for Participants Assigned Female at Birth in the LEN Group Who Received Testosterone in the Randomized Blinded Phase, Hormone PK Analysis Set: Testosterone, PURPOSE 2



LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (100 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-528-9023 (PURPOSE 2) Interim Week 52 Clinical Study Report, Figure 7.

Figure 34. Boxplots for Dihydrotestosterone Plasma Concentrations by Study Visit, Semilogarithmic Scale, for Participants Assigned Female at Birth in the LEN Group Who Received Testosterone in the Randomized Blinded Phase, Hormone PK Analysis Set: Dihydrotestosterone, PURPOSE 2



LEN = lenacapavir; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Values below the limit of quantitation (50 pg/mL) were treated as 0 for summary statistics.
Summary statistics for a given time point displayed if sample size ≥ 5.
Black box indicates Q1 and Q3 with the median as a horizonal line inside the box; whiskers indicate fifth and 95th percentiles.
Source: Study GS-US-528-9023 (PURPOSE 2) Interim Week 52 Clinical Study Report, Figure 8.

Adherence Assessment

As in PURPOSE 1, adherence to F/TDF were assessed objectively by measuring the concentrations of TFV-DP in DBS. DBS were performed in a random 10% subset of study participants and in all participants who were diagnosed with HIV-1.

In contrast to PURPOSE 1, adherence as measured by TFV-DP in DBS was higher in PURPOSE 2. The majority of participants in the F/TDF group had high adherence (consistent with dosing ≥4 days per week): 82.4% at Week 8 to 62.2% at Week 52. Adherence as measured by DBS was consistent with what was reported by pill count (≥95% adherent) and ePRO questionnaire where most participants reported "good," "very good," or "excellent" in their ability to take oral study drugs every day in the past month at Week 26 (LEN 76.5%; F/TDF 73.8%) and Week 52 (LEN 76.1%; F/TDF 75.0%). Though a decline in adherence was observed between Weeks 8 and 52, overall adherence to a daily oral pill as measured by TFV-DP concentrations was higher in men in PURPOSE 2 versus women in PURPOSE 1. This observation is largely consistent with literature describing the overall decreased uptake and adherence in women with a daily oral pill for HIV-1 PrEP compared to men.

14.3. Bioanalytical Method Validation and Performance

LEN in Plasma

Concentrations of LEN in plasma samples were determined using fully validated high performance liquid chromatography-tandem mass spectrometry bioanalytical methods

(calibrated range 0.5-500 ng/ml). The validated bioanalytical method (Method ID: GS07HPP, Study Report # 8359841) was previously reviewed and supported the approval of SUNLENCA (NDA 215973/215974). The same validated method was used to support LEN quantitation in human plasma samples collected from PURPOSE 1 (Study GS-US-412-5624) and PURPOSE 2 (Study GS-US-528-9023) trials. All samples were analyzed in the timeframe supported by frozen stability storage data.

Pre-specified criteria for incurred sample reproducibility analyses were in accordance with the acceptance criteria as outlined in the ICH guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) where at least two-thirds of the incurred sample reproducibility results are to be within +/- 20% of the initial concentrations. Incurred sample reproducibility assessment for PURPOSE 1 was performed by reanalysis of 7.7% of study samples, and 100% of incurred sample reproducibility samples (185 of 185) met the prespecified criteria. Incurred sample reproducibility assessment for PURPOSE 2 was performed by reanalysis of 6.9% of study samples, and 100% of samples (177 of 177) met the prespecified criteria.

LEN in Human Milk

The milk bioanalytical method was validated at the calibrated range of 0.5 to 500 ng/mL (Study Report# 8468191) and was used to support LEN quantitation in human milk samples collected from PURPOSE 1 (Study GS-US-412-5624). The method involved liquid extraction of LEN and its deuterated internal standard (GS-833737) from human milk, followed by quantitation using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Bioanalytical method validation parameters for LEN in human milk are summarized in Table 68.

Incurred sample reproducibility assessment was performed by reanalysis of 9.1% of study samples, and [100%] of samples ([1 of 1]) met the prespecified criteria.

Table 68. Bioanalytical Method Validation Parameters for LEN in Human Milk

Parameter	Result
Calibrated range (ng/mL)	0.5-500ng/ml
Interday precision range (%CV)	2.9%-9.8%
Interday accuracy range (%RE)	-5.8%-2.4%
Stability in frozen matrix (day)	746 days at −10 to −30°C 746 days at −60 to −80°C

Source: Reviewer's summary of the Applicant's bioanalytical method validation report.
Abbreviations: CV, coefficient of variation; LEN, lenacapavir; RE, relative error.

TFV-DP and FTC-TP in Dried Blood Spots

An indirect reversed-Phase LC-MS/MS bioanalytical method was developed and validated after dephosphorylation of intracellular TFV-DP (emtricitabine-diphosphate) and FTC-TP (emtricitabine-triphosphate). This method was used to support TFV-DP and FTC-TP quantitation in blood samples collected from PURPOSE 1 (Study GS-US-412-5624) and PURPOSE 2 (Study GS-US-528-9023) trials. Bioanalytical method validation parameters are summarized in Table 69.

Table 69. Bioanalytical Method Validation Parameters for Intracellular TFV-DP and FTC-TP Concentration in Lysed Cellular Matrix Obtained From DBS

Parameter	TFV-DP	FTC-TP
Calibrated range (fmol/sample)	25 to 6000	100 to 200,000
Inter-extraction precision range (%CV)[a]	3.5 to 11.6	4.2 to 10.8
Intra-assay precision range (%CV)[a] for F/TDF[b]	0.2 to 10.5	1.1 to 12.9
Interassay precision (%CV)[a] 2 ×7 mm punches for F/TAF[b]	3.9 to 6.5	4.1 to 4.2
Interassay precision (%CV)[a] 1 ×3 mm punch for F/TAF[b]	7.7 to 8.0	5.7 to 10.7
Stability in frozen matrix (days)	1835 at −80 °C	1835 at −80 °C

%CV = percentage coefficient of variation; DBS = dried blood spot; F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); F/TDF = emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®); FTC-TP = emtricitabine triphosphate; TFV-DP = tenofovir diphosphate

a Precision is expressed as %CV (relative standard deviation) using human clinical specimens.

b Accuracy is not presented, as human clinical specimens were used to assess precision.

Source: 2.7.1 Summary of Biopharmaceutic Studies, Table 1.

Hormone Therapies in Plasma

Validated bioanalytical methods were used to quantify plasma concentrations of the following hormone therapies from samples collected from PURPOSE 1 (Study GS-US-412-5624) and PURPOSE 2 (Study GS-US-528-9023) trials: estradiol (calibrated range: 5-500 pg/ml), testosterone and dihydrotestosterone (calibrated range: 100-30,000pg/ml and 50-5000 pg/ml), etonorgestrel (calibrated range: 25-5000 pg/ml), medroxyprogesterone acetate (calibrated range: 50-10,000 pg/ml), norethindrone (calibrated range: 100-20,000 pg/ml).

FDA Assessment

Method validation and sample analysis were all acceptable.

14.4. Immunogenicity Assessment—Impact of Pharmacokinetics/Pharmacodynamics, Efficacy, and Safety

Immunogenicity data were not submitted to this application, and therefore not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Physiologically Based Pharmacokinetics

Model Objective

- Evaluate the impact of 6-month rifampin treatment (600 mg PO once daily [QD]) and 6-month rifabutin treatment (300 mg PO QD) on the PK of LEN after subcutaneous (SC) injection of every 6 months (Q6M) formulation and proposed dosing recommendations for LEN in combination with rifamycins (rifampin [RIF] and rifabutin [RIFAB])

- Evaluate the feasibility of extending the DDI dosing recommendation proposed for rifabutin to other moderate CYP3A inducers such as bosentan, and modafinil.
- Evaluate the feasibility of extending the DDI dosing recommendation proposed for rifampin to other strong CYP3A inducers such as carbamazepine and phenytoin.

Background

Lenacapavir was approved in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection (NDA 215973/215974). In this application (NDA 220018/220020), the Applicant seeks for approval of HIV-1 pre-exposure prophylaxis (PrEP) in adults and adolescents. The proposed dosing regimen is an initiation dosing, Day 1 972 mg subcutaneous injection and 600 mg tablet; Day 2 600 mg tablet, followed by once every 6-months continuation injection dosing (927 mg).

Lenacapavir exhibits low clearance, low solubility, and low permeability. The oral absolute bioavailability is 6-10%. Following a single IV dose of LEN 20 mg, unchanged LEN accounts for 68.8% of total radioactivity in plasma and 32.9% in feces. Median $t_{1/2}$ ranged from approximately 10 to 12 days for 300 to 900 mg oral doses, with mean CL/F of 55 L/h. For LEN SC, median $t_{1/2}$ ranged from 8 to 12 Weeks, with mean CL/F was approximately 4.2 L/h (Study GS-US-200-4538). Lenacapavir is a substrate of CYP3A, P-gp, and UGT1A1. Lenacapavir is a moderate inhibitor of CYP3A. Lenacapavir is an inhibitor of P-gp and BCRP but does not inhibit OATP. Table 70 presents the clinical DDI studies results reported in NDA 215973 (FDA 2022a).

Table 70. Summary of Clinical DDI Studies

Co-Administered Drug	Dose of Co-Administered Drug	Mean Ratio of LEN W/Without Co-Administered Drug	
		AUC	C_{max}
Cobicistat (strong CYP3A and P-gp inhibitor)	150 mg QD	2.3	2.1
ATV/COBI (strong CYP3A, P-gp, and UGT1A1 inhibitor)	300/150 mg QD	4.2	6.6
Voriconazole (strong CYP3A inhibitor)	400 mg BID (Day 1) +200 mg BID (Day 2 and later)	1.4	1.1
Rifampin (strong CYP3A inducer)	600 mg QD	0.15	0.44
Efavirenz (moderate CYP3A inducer)	600 mg QD	0.43	0.64

Source: SUNLENCA USPI (Gilead Sciences 2022).
Abbreviations: AUC, area under the concentration-time curve; ATV/COBI, atazanavir/cobicistat; BID, twice daily; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, drug-drug interaction; LEN, lenacapavir; P-gp, P-glycoprotein; QD, once daily; UGT, UGT, uridine 5'-diphospho-glucuronosyltransferase; USPI, United States Prescribing Information.

All clinical DDI studies for LEN were conducted following oral administration. According to the USPI for NDA 215973/215974 (Gilead Sciences 2022), LEN is contraindicated with strong CYP3A inducers, and coadministration with combined P-gp, UGT, and strong CYP3A inhibitors is not recommended.

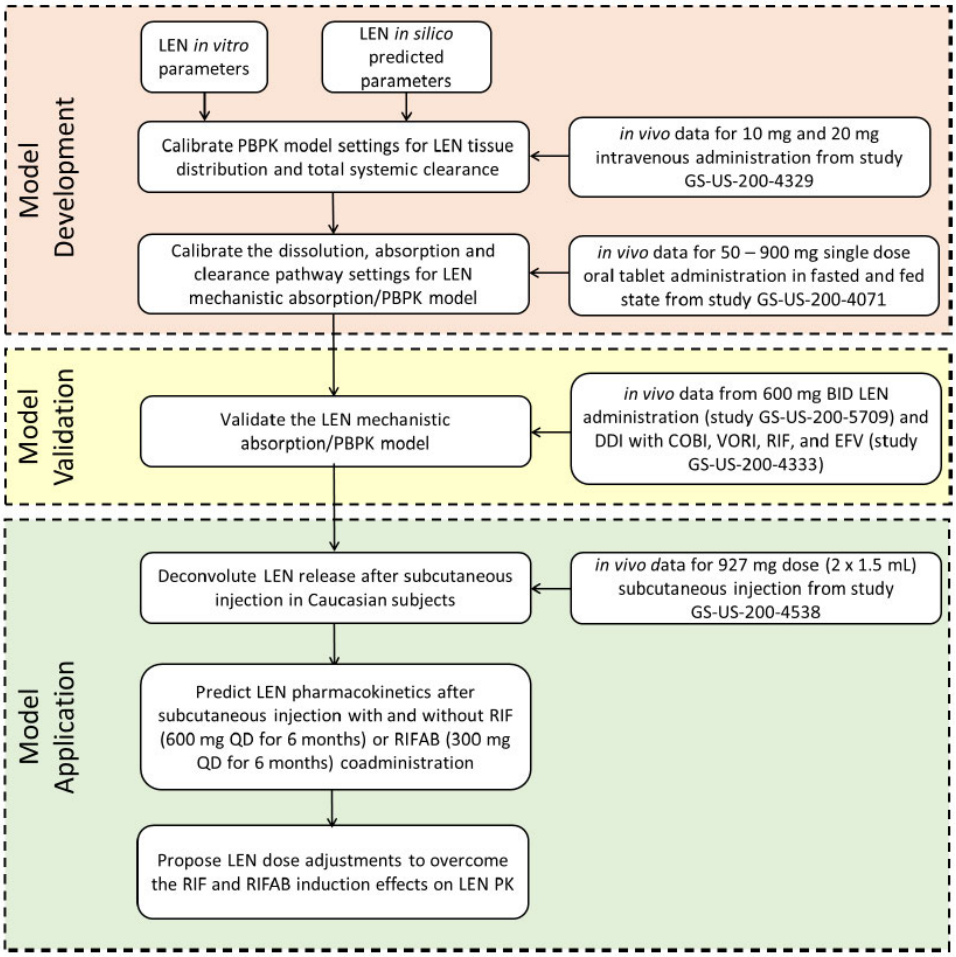
In the current submission, the Applicant proposed using PBPK analysis to assess the impact of rifampin (600 mg PO QD) and rifabutin (300 mg PO QD) on the pharmacokinetics of subcutaneously administered LEN (every-6-month formulation) and to support dosing recommendations for LEN when co-administered with rifamycins. This review evaluates the adequacy of the submitted PBPK report (SPI-2024-1099), title *"Development of a PBPK Model for Lenacapavir (GS-6207) in GastroPlus®: Application to Evaluate the DDI Between*

Lenacapavir and Rifamycins" and the Applicant's responses to FDA information requests (March 4, 2025, and April 17, 2025) in support of the proposed clinical recommendation for the management of DDI. Please see Section 7.7.3 for a summary of the assessment of the recommended dosing adjustments when LEN is co-administered with rifampin or rifabutin.

PBPK Models

The PBPK analyses were performed using GastroPlus® version 9.8.3 (Simulations Plus, Inc.). The LEN PBPK model consists of a full PBPK model and a mechanistic oral model (ACAT™). Figure 35 presents the diagram for overall model development.

Figure 35. Model Development Diagram



Source: SPI-2024-1099 LEN PBPK report Figure 1.
Abbreviations: BID, twice daily; COBI, cobicistat; EFV, efavirenz; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; QD, once daily; RIF, rifampin; RIFAB, rifabutin; VORI, voriconazole.

The LEN PBPK model was developed using in vitro data; physicochemical properties; human absorption, distribution, metabolism, and excretion studies; and clinical PK data. Systemic clearance of LEN was assumed to be mainly through P-gp-mediated clearance, metabolism by CYP3A and UGT1A1. The Km value for CYP3A4 was predicted by ADMET Predictor and maximum rate of metabolism (V_{max}) values fitted against in vivo data. The contribution of CYP3A and P-gp pathway was assigned and/or validated using clinical DDI data with cobicistat

(COBI), voriconazole, RIF, and efavirenz (EFV). P-gp mediated clearance was fitted to reach approximately 40% of dose secreted in feces as unchanged LEN after IV administration. Default voriconazole, rifampin and efavirenz PBPK models from GastroPlus were used. Cobicistat PBPK model was updated with Applicant's in-house in-vitro inhibition data. Table 71 presents the key LEN PBPK model parameters.

Table 71. Key PBPK Model Parameters

Parameter	Value	Reference
Exp logP	5.1	NDA 215973, Module 3.2.S.1.3
Diffusion Coefficient	0.42 x 10^{-5} cm/s[a]	ADMET Predictor Version 11.0
Exp pKas	3.9 (base); 6.8 (acid)	NDA 215973, Module 3.2.S.1.3
pKas	1.775 (base); 6.407 (acid)	Fitted to solubility vs. pH profile
Aqueous LEN Solubilities[a]	0.11 µg/mL @ pH=1.8 0.1 µg/mL @ pH=3.9 0.31 µg/mL @ pH=6.9 12 µg/mL @ pH=8.9 310 µg/mL @ pH=10.4 610 µg/mL @ pH=10.7 1300 µg/mL @ pH=11.1	NDA 215973, Module 3.2.S.1.3
FaSSIF LEN Solubility	3.9 µg/mL	NDA 215973, Module 3.2.S.1.3
FeSSIF LEN Solubility	4.1 µg/mL	NDA 215973, Module 3.2.S.1.3
Aqueous tablet Solubilities[b]	4.33 µg/mL @ pH=4.5 10 µg/mL @ pH=6 14.3 µg/mL @ pH=6.8	NDA 215974, Module 3.2.P.5.2 (REP-22545)
FaSSIF Tablet Solubility[b]	13.9 µg/mL	NDA 215974, Module 3.2.P.5.2 (REP-22545)
FeSSIF Tablet Solubility[b]	3.9 µg/mL	NDA 215974, Module 3.2.P.5.2 (REP-22545)
Bile Salt Solubilization Ratio	2000	Fitted to *in vivo* data[c]
z-factor[d]	7.6 × 10^{-3} mL/mg/s	NDA 215974, Module 3.2.P.5.2 (REP-22545)
Precipitation Time	800,000 s (50 mg PO dose) 80,000 s (all other PO doses)	Fitted to *in vivo* data[c]
Human Effective Permeability (P_{eff})	3.709 x 10^{-4} cm/s	Fitted to *in vivo* data[c]
Percent Unbound in Enterocytes	0.7 % unbound	Fitted to *in vivo* data[c]
Blood:Plasma Concentration Ratio (R_{bp})	0.64	NDA 215973, Module 2.6.4 (Study AD-200-2021)
Percent Unbound in Plasma (Fup)	0.385[e] % unbound	NDA 215973, Module 5, Study GS-US-200-4330
Adjusted Fup	0.302 % unbound	GastroPlus algorithm[f]
Kidney Apical PStc	5 mL/s	Fitted to *in vivo* data[c]
Liver CLint	500 L/h	Fitted to *in vivo* data[c]
Adipose and Muscle Kp[g]	36.23 and 20.37	Fitted to *in vivo* data[c]

Parameter	Value	Reference
Metabolism		
CYP3A4 $K_{m,u}$	0.427[h] µM	ADMET Predictor Version 11.0
CYP3A4 V_{max}	80 pmol/min/mg prot	Fitted to *in vivo* data[c]
UGT1A1 $K_{m,u}$	0.591 µM	Fitted to *in vivo* data[c]
UGT1A1 V_{max}	4 x 10^{-3} pmol/min/mg prot	Fitted to *in vivo* data[c]
Carrier-Mediated Transport		
P-gp K_m	0.0104 µM	Fitted to *in vivo* data[c]
P-gp $V_{max,PBPK}$[i]	0.0008 mg/s/mg transp	Fitted to *in vivo* data[c]
P-gp $V_{max,gut}$	0.0003 mg/s	Fitted to *in vivo* data[c]

Abbreviations: CLint, intrinsic clearance; FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated intestinal fluid; Fup, fraction unbound in plasma; Kp, tissue-plasma partition coefficient; K_m, Michaelis constant, the drug concentration at which the reaction rate is at half-maximum; $K_{m,u}$, unbound K_m; Kp, tissue-plasma partition coefficient; LEN, lenacapavir; logP, logarithm of the octanol-water partition coefficient; NDA, new drug application; pKa, negative base-10 logarithm of the acid dissociation constant; PO, oral; PStc, permeability surface area product; V_{max}, maximum rate of metabolism or transport; $V_{max,PBPK}$, maximum rate of transport for physiologically based pharmacokinetic location; $V_{max,gut}$, maximum rate of transport for gut location.

[a] The solubility 0.31 µg/mL @ pH=6.9 was used as reference solubility; remaining solubilities were used to calibrate the built-in pKa-based model for calculation of pH-dependent aqueous solubility of LEN.

[b] Solubilities estimated from *in vitro* dissolution data in aqueous buffers (without surfactant), FaSSIF, and FeSSIF media. Aqueous solubilities were used to estimate reference solubility for LEN tablet of 18 µg/mL @ pH=6.9.

[c] Parameters fitted to *in vivo* data from Studies GS-US-200-4329, GS-US-200-4071, and GS-US-200-4333 (NDAs 215973/SN 0001 and 215974/SN 0001, Module 5).

[d] Single value of z-factor [5] was fitted across all dissolution data of LEN tablet in aqueous buffers (without surfactant), FaSSIF, and FeSSIF media.

[e] Average of LEN unbound percents measured on Day 1 at LEN concentrations of 100 ng/mL and 500 ng/mL.

[f] Adjusted Fup was calculated from experimental Fup and logP using the default GastroPlus equation [6].

[g] Kps for all other tissues were calculated using default (Lukacova) method [7].

[h] Predicted from CYP3A4_HLM_Km model.

[i] The V_{max} value applicable to LEN interaction with P-gp in liver and kidney. During simulation, the value was multiplied by P-gp expression in each tissue and the tissue size.

Source: Table 1, SPI-2024-1099 LEN PBPK report.

Biotransformation of LEN is limited in vitro. Although LEN was metabolized via CYP3A and UGT1A1 in preclinical in-vitro assays, limited metabolism and minimal UGT1A1 metabolism was observed in human hepatocyte and microsomal studies (NDA 215973, PK summary, Study AD-200-2008). Thus, metabolism parameters (Vmax and Km) were predicted using in silico model, then optimized with in vivo data. In vitro studies show that LEN is a substrate of P-gp but not BCRP and OATP1Bs.

Both CYP3A and UGT1A1 were proposed as clearance pathways for LEN based on preclinical in-vitro data, human mass-balance, and a DDI study with ATV/COBI. However, minimal contribution of UGT1A1 was assigned in the final PBPK model. In response to FDA's information request, the Applicant acknowledged that there are uncertainties in the contributions of UGT1A1 and CYP3A4 to LEN elimination in vivo but stated that the contribution of CYP3A was calibrated to capture the observed DDIs with several CYP3A precipitant drugs (voriconazole, cobicistat, rifampin and efavirenz). Additionally, incorporating UGT contribution made minimal difference in the predicted DDI effect of rifampin (a dual CYP3A and UGT inducer). Validation of the PBPK model with ATV/COBI DDI studies was not conducted. The reviewer considers that the involvement of CYP3A pathway is evidential based clinical data and P-gp meditated clearance is supported by IV mass balance data. Therefore, the involvement of UGT1A1 could be less than CYP3A and P-gp based on the overall in-vitro and in-vivo data.

PK Validation-PK Simulation

The Applicant's PBPK model for LEN was verified with clinical PK set following 1) a single dose of 20 mg intravenous administration, 2) single oral doses 50-900 mg; 3) multiple oral doses of 600 mg twice daily (BID) over 10 days; and 4) a single SC dose of 927 mg. Since SC injections are not enabled for DDI predictions in GastroPlus, the SC LEN injections were replaced with a schedule of IV infusions of the same dose. Table 72 presents the comparison of simulated and observed LEN PK following single oral doses of 50, 300, and 900 mg.

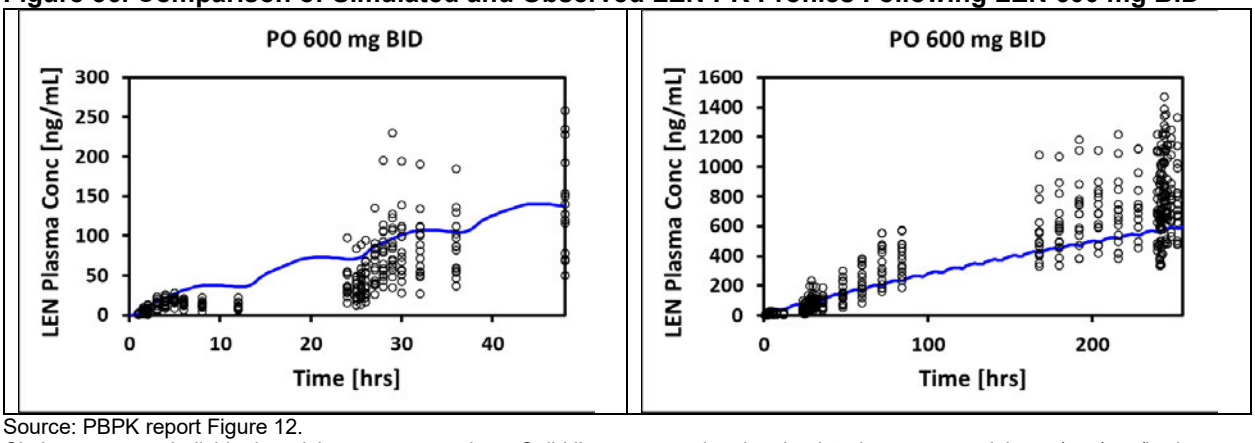
Table 72. Comparison of Simulated and Observed LEN PK Following Single Oral Dose of LEN

	Observed[a]		Simulated		Sim/Obs	
Dose	C_{max} **[ng/mL]**	**AUC$_{inf}$ [ng.h/mL]**	C_{max} **[ng/mL]**	**AUC$_{inf}$ [ng.h/mL]**	C_{max}	**AUC$_{inf}$**
50 mg, SD	7.4	2296.4	6.7	1655	0.91	0.72
300 mg, SD	22.8	6513.7	27.8	5970.7	1.22	0.92
900 mg, SD	33.7	8882.3	34.3	9921.2	1.02	1.12

Source: SPI-2024-1099 LEN PBPK report, Table 4 (study GS-US-200-4071).
[a] Observed data are geometric means of individual values.
[b] A PBPK model representing an average participant (sex/age/body weight) in study GS-US-200-4071.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; LEN, lenacapavir; obs, observed; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; sim, simulated; SD, single dose.

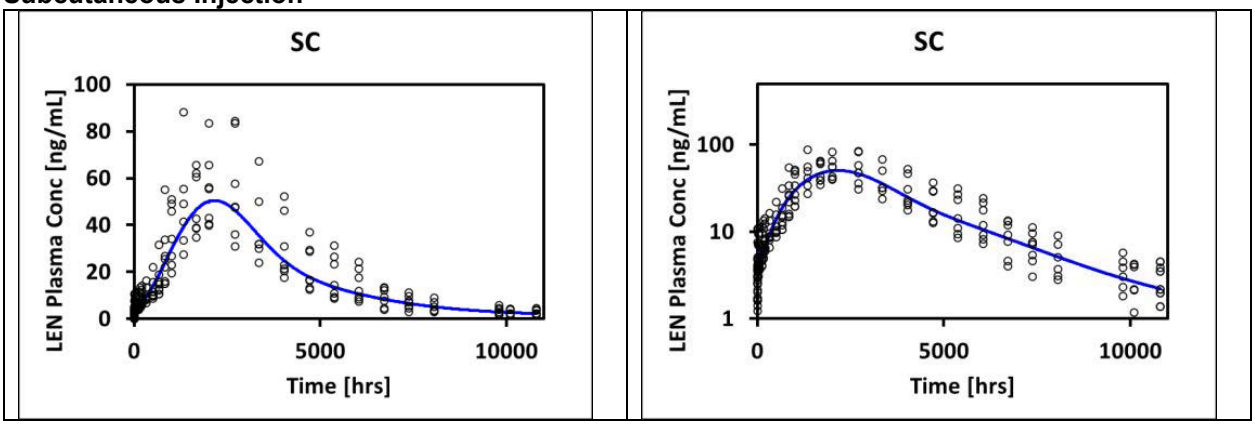
Figure 36 presents the Comparison of simulated and observed LEN PK profiles following LEN 600 mg BID reported in study GS-US-200-5709. Figure 37 presents the comparison of simulated and observed LEN PK profiles following a single dose 927 mg subcutaneous injection.

Figure 36. Comparison of Simulated and Observed LEN PK Profiles Following LEN 600 mg BID



Source: PBPK report Figure 12.
Circles represent individual participant concentrations. Solid line representing the simulated average participant (sex/age/body weight) in study GS-US-200-5709. Plot on the left shows details of the first 50 hours after administration, and the plot on the right shows entire profile on log-linear scale.
Abbreviations: BID, twice daily; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral.

Figure 37. Comparison of Simulated and Observed LEN PK Profiles Following 927 mg Subcutaneous Injection



Source: PBPK report Figure 8.
Circles represent individual participant concentrations. Solid lines represent the simulated average participant (sex/age/body weight) in study GS-US-200- 4538 in linear (left) and log scale (right). The subcutaneous injection was modelled as a series of IV infusions.
Abbreviations: LEN, lenacapavir; IV, intravenous; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; SC, subcutaneous.

PK Validation-DDI Simulation

The contribution of P-gp (P-gp efflux) were fitted to reach approximately 40% of dose secreted in feces as unchanged LEN after IV administration as observed in Study GS-US-200-4329. Hepatic P-gp efflux was then optimized to approximate the differences in physiological P-gp expressions in the intestine. The contribution of CYP3A and P-gp to total LEN elimination was optimized/verified with clinical DDI study results with voriconazole, RIF, COBI, and EFV which represent different effects on CYP3A4 and P-gp activity. Table 73 presents the comparison of simulated and observed DDI effects of CYP3A inhibitors and inducers on a single dose of LEN in the presence of multiple doses of inhibitors or inducers.

Table 73. Comparison of Simulated and Observed DDI Effects of CYP3A Inhibitors and Inducers on LEN PK

	Observed[a] DDI Ratio		Simulated DDI Ratio		Sim/Obs	
DDI	C_{max} [ng/mL]	AUC_{inf} [ng.h/mL]	C_{max} [ng/mL]	AUC_{inf} [ng.h/mL]	C_{max}	AUC_{inf}
LEN+COBI (P-gp and strong CYP3A4 inhibitor)	2.1	2.28	1.48	1.79	0.7	0.79
LEN+VORI (strong CYP3A inhibitor)	1.1	1.41	1.47	1.91	1.34	1.35
LEN+RIF (P-gp and strong CYP3A4 inducer)	0.45	0.15	0.25	0.11	0.56	0.73
LEN+EFV (moderate CYP3A inducer)	0.64	0.44	0.41	0.2	0.64	0.45

Source: PBPK report Table 5.
[a] Study GS-US-200-4333.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; COBI, cobicistat; CYP, cytochrome P450; DDI, drug-drug interaction; EFV, efavirenz; LEN, lenacapavir; obs, observed; PBPK, physiologically-based pharmacokinetics; P-gp, P-glycoprotein; PK, pharmacokinetics; sim, simulated; RIF, rifampin; VORI, voriconazole.

The objective of PBPK modeling is to propose dosing regimens to manage DDI when LEN is co-administrated with rifampin and rifabutin. The initial focus would be the DDI potential of rifamycins as CYP3A inducers and their interactions with LEN as a CYP3A substrate. However, P-gp-mediated clearance would be a major clearance pathway evidence by IV mass-balance study and clinical DDI data. As shown in Table 73, clinical DDI effects (AUC ratio) with strong

CYP3A inhibitors voriconazole and cobicistat are 1.4 and 2.3 respectively, while 85% reduction was observed with rifampin. Based on in-vitro data, LEN is metabolically stable and is a substrate of P-gp but not BCRP and OATP1Bs. Although it is possible that other clearance pathways were involved, CYP3A and P-gp would be two major DDI mechanism for LEN based on the available in-vitro and clinical data. As presented in Table 74 and Table 75 turning off gut or liver P-gp resulted in 2.08-fold or 1.81-fold (Table 74), respectively, increase in AUC and turning off gut or liver CYP3A resulted in 1.6-fold or 1.28-fold (Table 75), respectively, increase in AUC after PO administration. Thus, LEN PBPK analysis suggested that P-gp mediated clearance is the dominant pathway after PO administration. For SC administration, the impact of intestinal P-gp elimination would be less.

Table 74. Contribution of P-gp-Specific Clearance for LEN

LEN Dosing	P-gp setting	C_{max} (ng/mL)	AUC_{inf} (ng.h/mL)	C_{max} Ratio*	AUC_{inf} Ratio*
600 mg PO single dose	GI ON / hepa ON	31.62	7960		
	GI OFF / hepa ON	46.72	16518	1.48	2.08
	GI ON / hepa OFF	33.87	14427	1.07	1.81
	GI OFF / hepa OFF	49.87	28433	1.58	3.57
927 mg SC single dose	GI ON / hepa ON	50.45	204900		
	GI OFF / hepa ON	53.77	220300	1.07	1.08
	GI ON / hepa OFF	83.86	367500	1.66	1.79
	GI OFF / hepa OFF	83.91	367800	1.66	1.80

Source: Applicant's response to FDA IR (dated April 17, 2025).
GI ON: Keep P-gp efflux in GI tract. GI OFF: Turn off P-gp efflux activity in GI tract. hepa ON: Keep P-gp efflux in liver. hepa OFF: Turn off P-gp efflux activity in liver.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; GI, gastrointestinal; LEN, lenacapavir; hepa, hepatic; P-gp, P-glycoprotein; PO, oral; SC, subcutaneous.

Table 75. Contribution of CYP3A-Specific Clearance for LEN

LEN Dosing	CYP3A setting	C_{max} (ng/mL)	AUC_{inf} (ng.h/mL)	C_{max} Ratio*	AUC_{inf} Ratio*
600 mg PO single dose	GI ON / hepa ON	31.62	7960		
	GI OFF / hepa ON	43.06	12724	1.36	1.60
	GI ON / hepa OFF	32.74	10163	1.04	1.28
	GI OFF / hepa OFF	44.63	16293	1.41	2.05
927 mg SC single dose	GI ON / hepa ON	50.45	204900		
	GI OFF / hepa ON	50.99	206300	1.01	1.01
	GI ON / hepa OFF	62.37	258100	1.24	1.26
	GI OFF / hepa OFF	64.55	263300	1.28	1.29

Source: Applicant's response to FDA IR (dated April 17, 2025).
GI ON: Keep CYP3A clearance in GI tract. GI OFF: Turn off CYP3A clearance in GI tract. hepa ON: Keep CYP3A clearance in liver. hepa OFF: Turn off CYP3A clearance activity in liver.
Abbreviations: AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome P450; GI, gastrointestinal; LEN, lenacapavir; hepa, hepatic; PO, oral; SC, subcutaneous.

In general, the limitation of using PBPK analysis to support DDI assessment for P-gp and CYP3A is to distinguish the contributions of each pathway. In this submission, IV mass-balance data provided critical insight into hepatic P-gp–mediated clearance. When combined with the low absolute bioavailability and in vitro absorption data, the evidence further supports the identifiability of P-gp–mediated clearance. In addition, the model can generally describe the clinical DDI results (Table 73). The reviewer considers the LEN PBPK model (both oral and SC) to be adequately validated for DDI assessment.

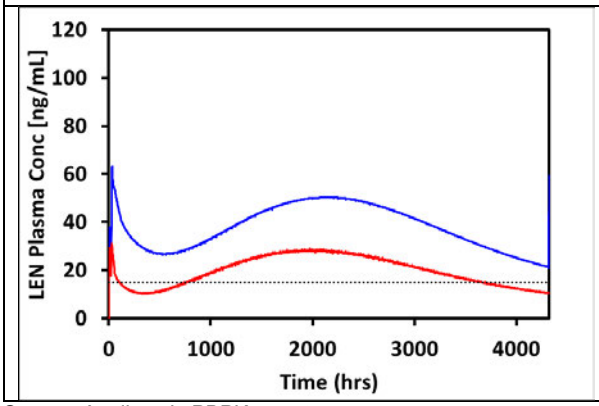
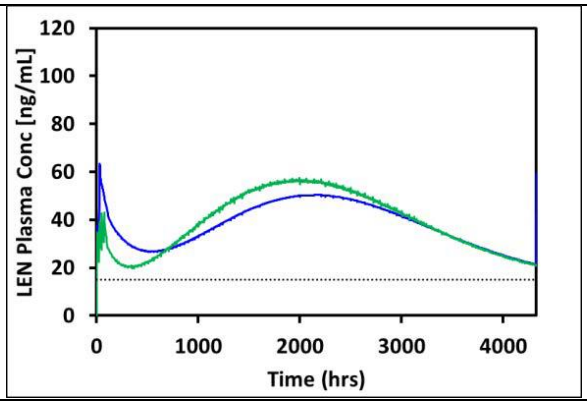
The reviewer also evaluated the PBPK models for cobicistat, voriconazole, rifampin and efavirenz submitted with this application. Based on the validation files submitted, the reviewer considered that the rifampin PBPK model was adequately verified for CYP and P-gp pathways as the model was extensively validated with clinical DDI studies covering a wide range of scenarios: single, multiple dosing of rifampin on CYP3A (mainly midazolam) and P-gp substrates (digoxin and fexofenadine) where the substrates were administered via both PO and IV. In comparison, less clinical validations were available for cobicistat, voriconazole, and efavirenz.

PBPK Application

For DDI dosing regimen, a standard PK match strategy was used to ensure the LEN exposure can be adequately maintained for the duration of rifamycin treatment. The Applicant tested different dosing scenarios by varying the timing of rifamycin treatments. Figure 38, Figure 39, and Figure 40 present the impact of a 6-month RIF treatment initiated at different time points—Day 1, C_{max}, and C_{min}—relative to LEN administration. The effect of additional simplified regimen (LEN SC dose +600 mg PO daily on Days 1 and 2 of SC injection) starting on Day 1 of RIF treatment is also shown in the corresponding figures. As shown in these figures, the proposed additional doses of LEN when co-administered with rifabutin would provide adequate LEN plasma concentrations. An additional half dose SC injection (1 x 1.5 mL of Q6M formulation) on the day of rifabutin treatment was proposed when co-administrated with RIFAB.

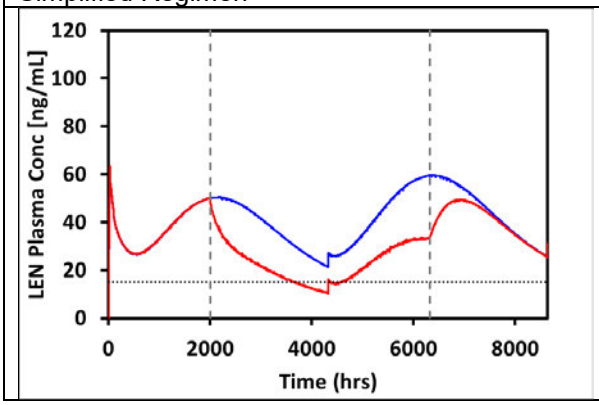
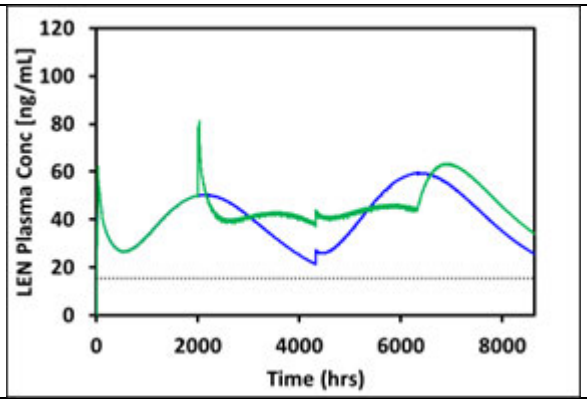
The proposed additional LEN simplified regimen would maintain the LEN plasma concentration similar to those after the proposed LEN dosing without inducers.

Figure 38. Impact of RIF Treatment and Proposed Additional LEN Dosing, Day 1 Scenario

Impact of RIF 6-Month Treatment Regimen on Day 1 of the LEN Simplified Regimen	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

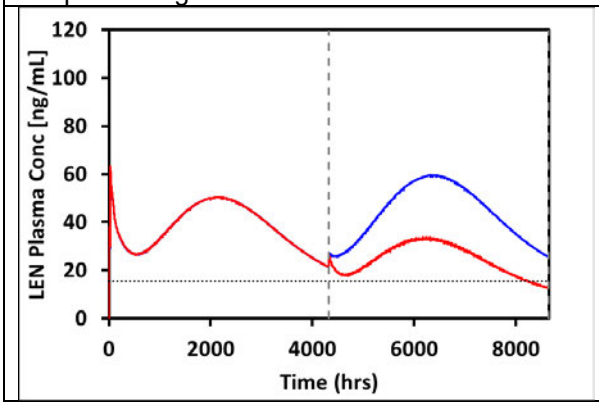
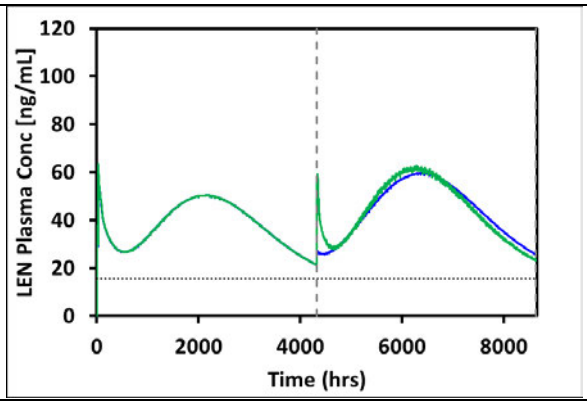
Source: Applicant's PBPK report.
Blue line represents LEN PK when administered alone, red lines represent LEN PK with 6-month RIF treatment (600 mg QD), green line represents LEN PK with RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration.
Abbreviations: LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Figure 39. Impact of RIF Treatment and Proposed Additional LEN Dosing, C_{max} Scenario

Impact of RIF 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{max} of the LEN Simplified Regimen	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

Source: Applicant's PBPK report.
Blue line represents LEN PK when administered alone, red line represents LEN PK with 6-month RIF treatment (600 mg QD) starting at 2000 hrs after the start of LEN treatment, green line represents LEN PK with RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration, 2 vertical dashed lines outline the RIF treatment period.
Abbreviations: C_{max}, maximum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Figure 40. Impact of RIF Treatment and Proposed Additional LEN Dosing, C_{min} Scenario

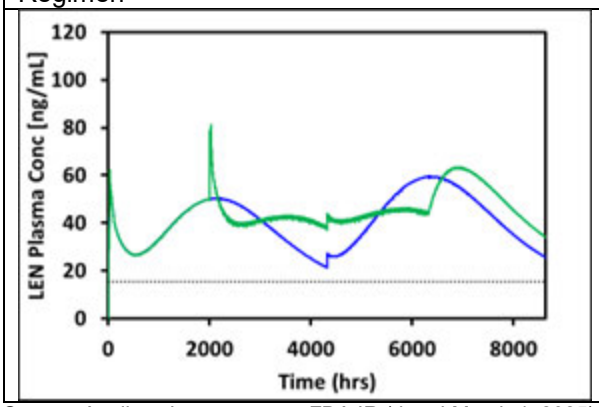
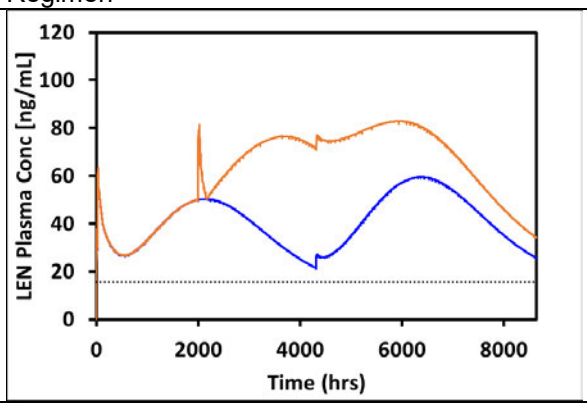
Impact of RIF 6-Month Treatment Regimen on PK of LEN When Initiated Near the C_{min} of the LEN Simplified Regimen	LEN PK with Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) at the Start of RIF Treatment
	

Source: Applicant's PBPK report.
Blue line represents LEN PK when administered alone, red line represents LEN PK with 6-month RIF treatment (600 mg QD) starting at 4320 hrs after the start of LEN treatment, green line represents LEN PK with RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration, 2 vertical dashed lines outline the RIF treatment period.
Abbreviations: C_{min}, minimum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Additional DDI Scenarios

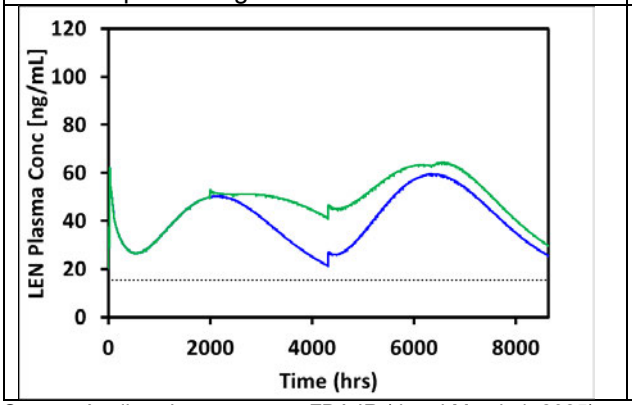
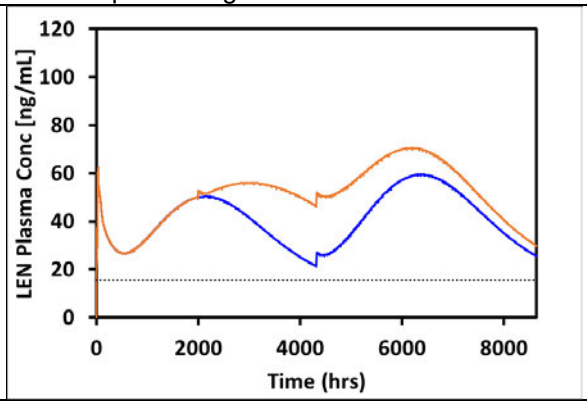
FDA issued an information request for conducting additional simulation scenario (e.g. prematurely discontinued rifamycins after received the additional LEN doses). The Applicant submitted simulations (Figure 41and Figure 42) to demonstrate the magnitude of LEN exposure when the rifamycin was terminated within one week.

Figure 41. Impact of 6-Month and 1-Week RIF Treatment on LEN PK After Receiving the Additional LEN Doses

Impact of RIF 6-Month + Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) When Initiated Near the C_{max} of the LEN Simplified Regimen	Impact of RIF 1-week + Additional LEN Doses (927 mg SC +600 mg PO Daily for 2 Days) When Initiated Near the C_{max} of the LEN Simplified Regimen
	

Source: Applicant's response to FDA IR (dated March 4, 2025).
Blue line represents LEN PK when administered alone, green line represents LEN PK with 6-month RIF treatment (600 mg QD) with additional LEN simplified regimen starting at 2000 hrs after the start of LEN treatment, Orange line represents LEN PK with 1-week RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration, 2 vertical dashed lines outline the RIF treatment period.
Abbreviations: C_{max}, maximum plasma concentration; IR, Information Request; LEN, lenacapavir; PK, pharmacokinetics; PO, oral; QD, once daily; RIF, rifampin; SC, subcutaneous.

Figure 42. Impact of 6-Month and 1-Week RIFAB Treatment on LEN PK After Receiving the Additional LEN Doses

Impact of RIFAB 6-Month + Additional LEN Doses (463.5 mg SC) When Initiated Near the C_{max} of the LEN Simplified Regimen	Impact of RIFAB 1-week + Additional LEN Doses (463.5 mg SC) When Initiated Near the C_{max} of the LEN Simplified Regimen
	

Source: Applicant's response to FDA IR (dated March 4, 2025).
Blue line represents LEN PK when administered alone, green line represents LEN PK with 6-month RIFAB treatment (300 mg QD) with additional LEN (463.5 mg SC) starting at 2000 hrs after the start of LEN treatment, Orange line represents LEN PK with 1-week RIF treatment + with additional LEN simplified regimen. Dotted horizontal line marks 15.5 ng/mL plasma concentration, 2 vertical dashed lines outline the RIFAB treatment period.
Abbreviations: C_{max}, maximum plasma concentration; LEN, lenacapavir; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PO, oral; QD, once daily; RIFAB, rifabutin; SC, subcutaneous.

For the safety margin, the Applicant selected a scenario where additional dose/s of LEN are administered, however no rifamycin is initiated. The exposures were compared with those observed in Studies GS-US-200-4332, GS-US-200-5717, and GS-US-200-5709 (Cohort 3). Table 76 presents the safety margin for LEN based on Study 4332. Refer to Section 7.7.3 for details regarding additional data that support the safety of LEN at higher exposures.

Table 76. Lenacapavir Safety Margin With Additional Dosing in the Absence of Rifamycin Treatment

	Supratherapeutic Exposure		Additional LEN dosing (Scenario 3)		Therapeutic Exposure
	Study 4332[a]	Study 5709 Cohort 3[b]	Additional LEN Dosing without RIF Administration	Additional LEN Dosing without RIFAB Administration	LEN Simplified Regimen alone
LEN dosing	Oral 600 mg BID for 8 days (N=47)	Oral 600 mg BID for 10 days, followed by QD for 1 day (N= 15)	LEN Simplified Regimen plus additional LEN SC 927 mg on Day 3 with loading doses of 600 mg on Day 3 and Day 4	LEN Simplified Regimen plus additional half dose LEN SC injection (463.5 mg, 1x 1.5 mL) on Day 1	927 mg SC Q6M + 600 mg oral on Day 1 and Day 2
Mean C_{max} (ng/mL)	1070.4	1012.1	157.6	105.1	88.50
C_{max} Safety Margin relative to study 4332			6.8-fold	10.2-fold	
Mean AUC_{tau} (ng*hr/mL)	10640.6	9706.9	958.0[c]	648.5[c]	455.9[c]
AUC_{tau} Safety Margin relative to Study 4332			11.1-fold	16.4-fold	

Source: Applicant's response to FDA IR (dated March 4, 2025).
Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; IR, Information Request; LEN, lenacapavir; Q6M, every 6 months; QD, once daily; RIFAB, rifabutin; SC, subcutaneous.

Extending the DDI Dosing Recommendation to Common CYP3A Inducers

Given the adequate safety margin and acceptable PBPK analysis for DDI simulation, the review team explored the option to extend the DDI dosing regimen for Rifampin (a P-gp inhibitor/inducer and a strong CYP3A inducer) and Rifabutin (a moderate CYP3A inducer) to other strong CYP3A inducers (such as carbamazepine and phenytoin) and other moderate inducers (such as bosentan and modafinil).

Moderate CYP3A Inducer

P-gp and CYP3A are both regulated by activators of the PXR and/or CAR receptors, but P-gp is usually less induced than CYP3A. For example, Lorlatinib and EFV is reported to reduce fexofenadine AUC (a P-gp substrate) by 60% and 23% while there is no DDI effects reported between P-gp substrate (digoxin, fexofenadine, dabigatran) with bosentan, modafinil and phenobarbital. In addition, there is sufficient safety margin for LEN even if additional LEN dosing (463.5 mg SC) is given in the absence of rifabutin. The Applicant concludes proposed LEN dose adjustment can be appropriately applied to the majority of moderate CYP3A inducers, with or without P-gp induction potential.

Strong CYP3A Inducer

The Applicant also considers it feasible to apply the DDI dosing regimen established for rifampin to other strong CYP3A inducers, without negatively impacting the safety or efficacy of LEN.

A similar line of discussion was included in the Applicant's 04/17 IR response. The Applicant provided a summary table showing that rifampin is among the most potent inducers of both CYP3A4 and P-gp among clinically used compounds. Therefore, the DDI dosing regimen established for rifampin is expected to be adequate for other strong CYP3A inducers without compromising efficacy. Table 77 shows their summary of clinical studies involving P-gp substrates co-administered with strong CYP3A4 inducers. Regarding safety, the Applicant referred to earlier discussions indicating that even with additional dosing in the absence of rifampin, LEN exposure remains within its established safety margin. The reviewer considers the proposal to extend the rifamycin-based DDI dosing regimen to other CYP3A/P-gp inducers to be mechanistically reasonable, particularly given the safety margin.

Table 77. Summary of P-gp Substrate Induction With Strong CYP3A4 Inducers

		% Decrease in Substrate's PK		
Substrate	**Inhibitor**	**AUC**	C_{max}	**Reference**
Digoxin	Avasimibe	~40%	~28%	PMID: 12766253
	Phenytoin	~23%	~30%	PubMed 1490820; PubMed 4054206
	Rifampin	~16%-30%	~23%-39%	PubMed 18214850; PubMed 10411543; PubMed 22190694; PubMed 17365992; PubMed 17079360; PubMed 16221754
Fexofenadine	Apalutamide	~30%	~10%	PubMed 32338345; NDA 210951
	Carbamazepine	~43%	~42%	PubMed 19855315
	Rifampin	~65%	~33%-56%	PubMed 11240975; PubMed 24722393

Source: Applicant's response to FDA IR (dated April 17, 2025).
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CYP, cytochrome P450; P-gp, P-glycoprotein; PK, pharmacokinetics; PMID, PubMed identifier.

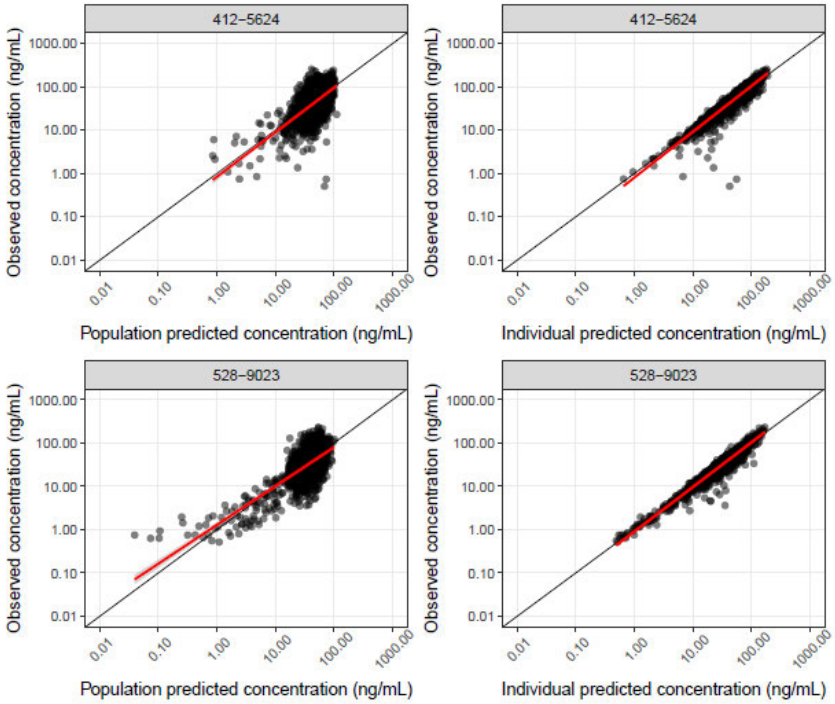
14.5.2. Population Pharmacokinetics

The following indicates the key supporting attributes of the Applicant's population PK analysis that make it acceptable for descriptive labeling, simulation of adolescents and supportive of describing plasma lenacapavir exposures in pregnancy.

- The model appears to capture the central tendency of both the population and individual PK data (Figure 43).
- The final parameter estimates were estimated with good precision (Table 78).
- The shrinkage for interindividual random effects on clearance (CL) and interindividual random effects on volume of distribution were reasonable at 18.5% and 36%.
- The final parameter estimate for CL is not meaningfully different from the Applicant's previously reviewed population PK analysis (Integrated Review of Lenacapavir Injection, NDA 215973 (FDA 2022a)).

- For adolescent predictions the allometric relationship (exponents of 0.75 and 1 for CL and volume of distribution applied is reasonable considering the goodness of fit achieved with the patients aged 16 years of age and older (Figure 43, Figure 44, and Figure 45).
- For the pregnancy population there were a sufficient number of participants who had PK data in each trimester and without PK to inform the population PK model regarding plasma concentrations in the mother (Table 79). Conclusions regarding distribution to the fetus cannot be made. Further the final model, without fixed effect parameters for pregnancy status, did not indicate trends for pregnancy status while the model appears to predict the data reasonably well (Figure 46).

Figure 43. Goodness-of-Fit Plots for the Applicant's Final Population PK Model by Clinical Trial[a]



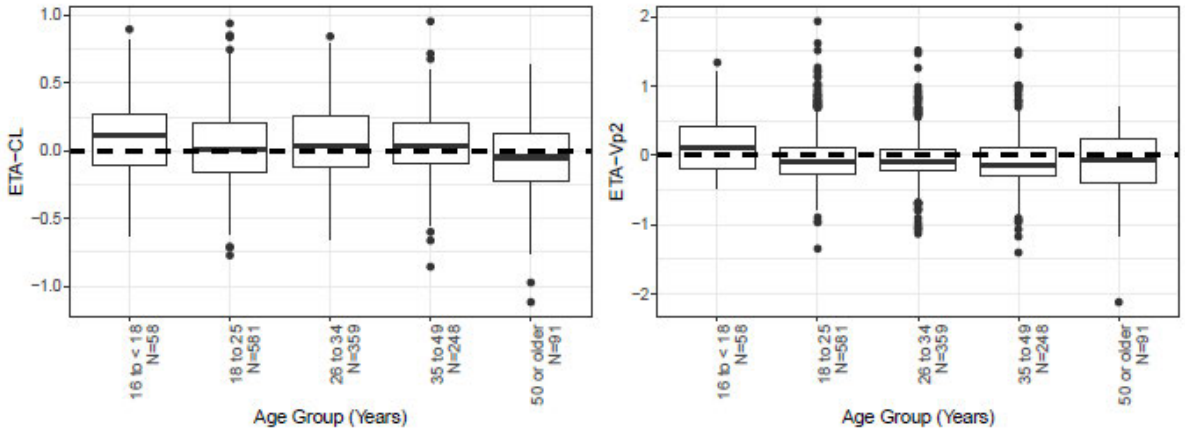
Source: Applicant's Population PK Report #1082, Figure 6.22.
[a] PURPOSE 1 on the top row and PURPOSE 2 on the bottom row.
Abbreviation: PK, pharmacokinetics.

Table 78. Clearance and Disposition Parameter Estimates for the Applicant's Final Model

			Final model	Non-parametric bootstrap
			Estimate (% RSE)	Median (95% CI)
Structural Parameters				
CL (L/h)	θ_1	Clearance	3.44 (1.38)	3.44 (3.33, 3.53)
Vp2 (L)	θ_2	Volume of distribution of compartment 2	1621 (5.55)	1638 (1519, 1767)
Q2 (L/h)	θ_3	Intercompartmental clearance to compartment 2	47.1 (2.05)	47.7 (44.6, 51.7)
Vc (L)	θ_4	Volume of distribution of central compartment	4.31 (7.55)	4.24 (4.08, 4.46)
Vp1 (L)	θ_5	Volume of distribution of compartment 1	31.9 (3.58)	31.8 (30.4, 34.2)
Q1 (L/h)	θ_6	Intercompartmental clearance to compartment 1	63.2 (5.99)	65.3 (61.7, 71.3)

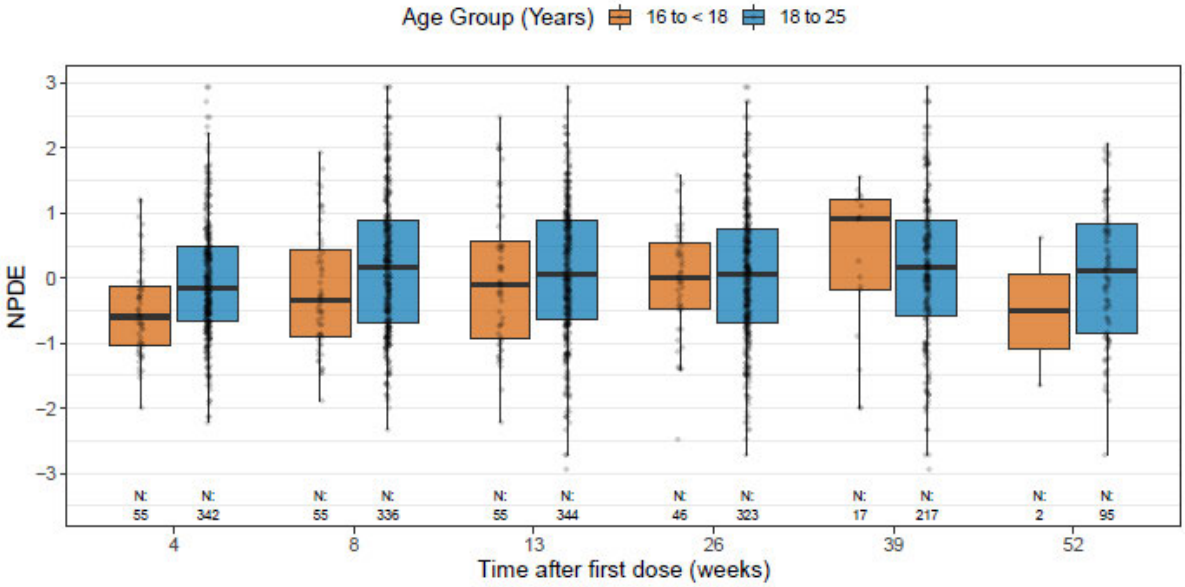
Source: Applicant's Population PK Report #1082, Table 6.10.
Abbreviations: CL, clearance; PK, pharmacokinetics; RSE, relative standard error; Q, intercompartmental clearance; Vc, volume of distribution of central compartment, Vp, volume of distribution of compartment.

Figure 44. ETA(CL) vs. Age Group for the Applicant's Final Population PK Model



Source: Applicant's Population PK Report #1082, Figure 10.76.
Abbreviations: ETA(CL), interindividual random effects on clearance; PK, pharmacokinetics.

Figure 45. Normalized Prediction Distribution Errors by Age Group and Time After First Dose



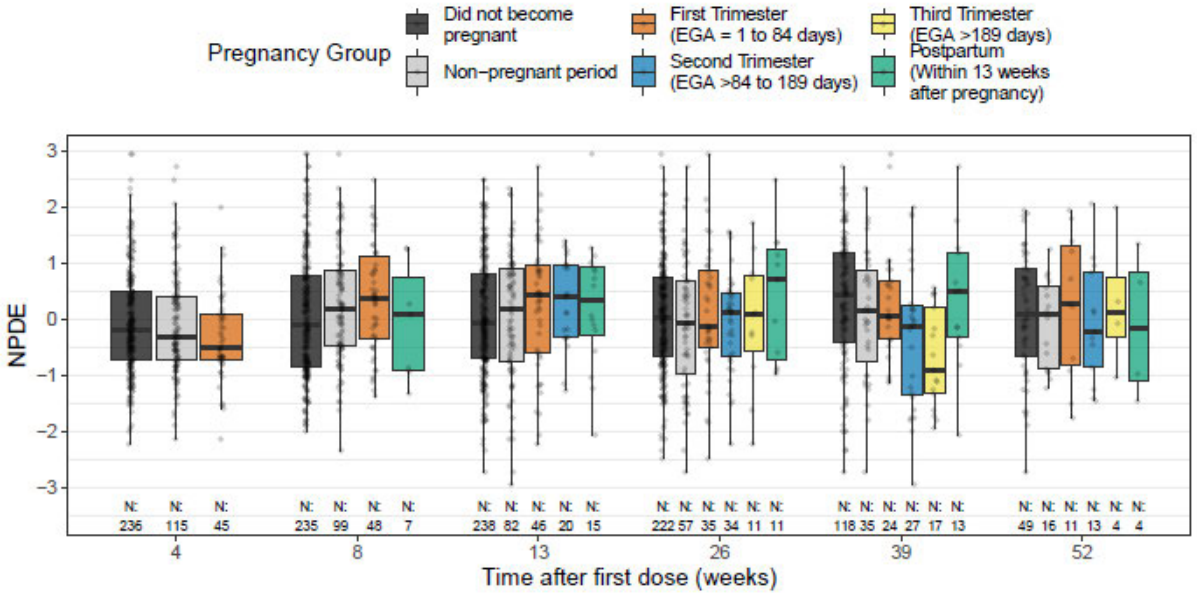
Source: Applicant's Population PK Report #1082, Figure 6.16.
Abbreviations: NPDE, normalized prediction distribution errors; PK, pharmacokinetics.

Table 79. Summary of Pregnancy Data by Study

	Study GS-US-			
	200-4334	200-4625	412-5624	528-9023
Pregnant during study?				
Yes	0 (0.0)	0 (0.0)	163 (40.0)	0 (0.0)
No	105 (100.0)	70 (100.0)	245 (60.0)	534 (100.0)
PK sample available during first trimester?				
Yes	0 (0.0)	0 (0.0)	149 (36.5)	0 (0.0)
No	105 (100.0)	70 (100.0)	259 (63.5)	534 (100.0)
PK sample available during second trimester?				
Yes	0 (0.0)	0 (0.0)	94 (23.0)	0 (0.0)
No	105 (100.0)	70 (100.0)	314 (77.0)	534 (100.0)
PK sample available during third trimester?				
Yes	0 (0.0)	0 (0.0)	39 (9.6)	0 (0.0)
No	105 (100.0)	70 (100.0)	369 (90.4)	534 (100.0)
PK sample available within 13 weeks after end of pregnancy?				
Yes	0 (0.0)	0 (0.0)	45 (11.0)	0 (0.0)
No	105 (100.0)	70 (100.0)	363 (89.0)	534 (100.0)

Source: Applicant's Population PK Report, Table 6.4.
First trimester is defined as gestational age of 1 to 84 days. Second trimester is defined as gestational age of 85 to 189 days. Third trimester defined as gestational age >189 days.
PURPOSE 1 = GS-US-412-5624 and PURPOSE 2 = GS-US-528-9023.
Abbreviation: PK, pharmacokinetics.

Figure 46. Normalized Prediction Distribution Errors by Pregnancy Status and Time After First Dose



Source: Applicant's Population PK Report #1082, Figure 6.17.
Abbreviations: EGA, estimated gestational age; NPDE, normalized prediction distribution errors; PK, pharmacokinetics.

14.6. Pharmacogenetics

Pharmacogenetics data were not submitted to this application, and therefore this section is not applicable.

15. Study/Trial Design

15.1. PURPOSE 1

15.1.1. Protocol Overview and Conduct

Title of Study

A 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

Study Centers

28 sites in South Africa and Uganda

Publications

- (Bekker et al. 2024)

Study Period

August 30, 2021 (first participant screened)

May 8, 2024 (last participant last visit for this report)

Phase of Development

Phase 3

Study Objectives and Endpoints

The primary objective of this study was to evaluate the efficacy of lenacapavir (LEN) and emtricitabine/tenofovir alafenamide (F/TAF; Descovy; DVY) in preventing the risk of HIV-1 infection relative to the background HIV-1 (bHIV) incidence.

Table 80. Study Objectives and Endpoints, PURPOSE 1

Objectives	Endpoints
Primary Objectives	
Incidence Phase • To estimate the bHIV incidence Randomized Blinded Phase • To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in adolescent girls and young women (AGYW) at risk of HIV-1 infection • To evaluate the efficacy of F/TAF for HIV-1 PrEP in AGYW at risk of HIV-1 infection	Incidence Phase • Diagnosis of recent HIV-1 infection Randomized Blinded Phase • Diagnosis of HIV-1 infection
Secondary Objectives	
Randomized Blinded Phase • To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the efficacy of LEN for HIV-1 PrEP in AGYW at risk of HIV-1 infection in participants adherent to LEN • To evaluate the efficacy of F/TAF for HIV-1 PrEP in AGYW at risk of HIV-1 infection in participants adherent to F/TAF • To compare the efficacy of F/TAF with F/TDF for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the safety and tolerability of LEN, F/TAF, and F/TDF for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To evaluate the safety and tolerability of LEN and F/TAF for HIV-1 PrEP in AGYW ≥16 to <18 years of age who have sex with male partners and are at risk for HIV-1 infection	• Diagnosis of HIV-1 infection, including among participants while adherent to study drug • Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN, F/TAF, and F/TDF for HIV-1 PrEP

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
Randomized Blinded Phase • To assess the adherence rate to LEN as assessed by on-time LEN injection • To assess LEN plasma levels • To assess the adherence rate to F/TAF and F/TDF using intracellular tenofovir-diphosphate (TFV-DP) levels in dried blood spot (DBS) • To evaluate the acceptability of a once every 6 months LEN injection for HIV-1 PrEP in AGYW at risk of HIV-1 infection • To assess study drug levels of interest in pregnant and postpartum women, in breast milk, and in infants • To explore concentrations of hormonal contraceptives in LEN participants	Randomized Blinded Phase • Adherence to LEN as assessed by on-time LEN injection • LEN plasma levels • Adherence to F/TAF or F/TDF assessed using the intracellular TFV-DP concentration in DBS • Study drug concentrations in maternal plasma, breast milk, and infant plasma • Concentrations of hormonal contraceptives in LEN participants • Self-reported questionnaire outcomes pertaining to acceptability, as follows: • Adherence to oral study product • Numeric pain rating scale (NPRS)– injection pain • Administration and dosing for PrEP medication (injection acceptability) • PrEP impacts and administration preference • Self-reported questionnaire outcomes pertaining to sexual risk and behavior

Source: Study synopsis of the CSR of PURPOSE 1.
Abbreviations: bHIV, background HIV-1; F/TAF, emtricitabine/tenofovir alafenamide; LEN, lenacapavir.

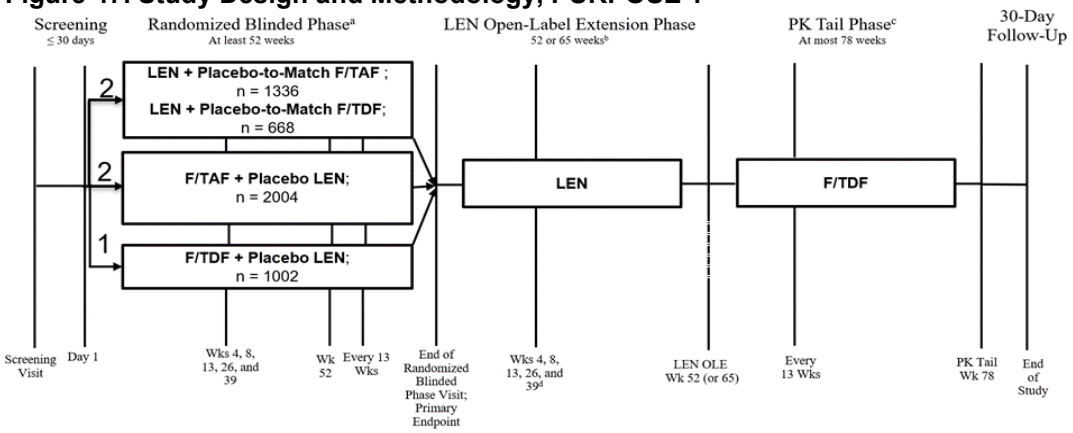
Study Design and Methodology

This is a Phase 3, randomized, double-blind, multicenter study to compare the HIV-1 incidence in each of the LEN and F/TAF groups with the counterfactual control of bHIV incidence, defined as the estimated HIV-1 incidence in the screened population. Truvada serves as the internal active control. This study includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a Pharmacokinetic (PK) Tail Phase.

The Incidence Phase estimated the bHIV incidence rate within the population screened for eligibility using recency assay results from samples that were positive for HIV-1 infection incorporated into a recent infection testing algorithm (RITA). Participants determined to be HIV-1 negative and who met eligibility criteria proceeded to the Randomized Blinded Phase, where they were randomized in a 2:2:1 ratio to receive either LEN, F/TAF, or F/TDF, respectively. After the completion of the Randomized Blinded Phase, participants were offered the opportunity to receive OL LEN in the LEN OLE Phase, which allows for further long-term efficacy and safety follow-up. Participants who discontinued study drug during the Randomized Blinded Phase entered the PK Tail Phase, which provides a known efficacious OL regimen to provide HIV prevention for participants during the time when LEN concentrations decline.

Enrollment of adolescents (participants ≥16 and <18 years of age) commenced following the DMC review of unblinded safety data from the first 300 adult participants through 8 weeks of follow-up and recommendation to continue the study. Gilead notified sites when they could begin enrollment of adolescents.

Figure 47. Study Design and Methodology, PURPOSE 1



Source: Figure 1 of the CSR of PURPOSE 1.
Abbreviations: F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; OL, open-label; OLE, open-label extension; PK, pharmacokinetic(s).

- Participants were to continue in the Randomized Blinded Phase until all randomized participants have completed at least 52 weeks of follow-up in the study and Gilead completed the primary analysis. In the case that the Randomized Blinded Phase was stopped early for an efficacy outcome, some participants may have less than 52 weeks of follow-up.
- The duration will be dependent on timing of the OL LEN injection
- Participants who prematurely discontinued study drug during the Randomized Blinded Phase or LEN OLE Phase, or those randomized to LEN in the Randomized Blinded Phase who declined to participate in the LEN OLE Phase upon unblinding, will transition to the PK Tail Phase.
- Week 4 and Week 8 visits are only required for participants who were randomized to oral F/TAF or F/TDF in the Randomized Blinded Phase.

Number of Participants Planned

Approximately 5010 participants in the Randomized Blinded Phase.

Diagnosis and Main Criteria for Inclusion

Eligible participants were cisgender AGYW who met the following criteria:

Incidence Phase (Cross-Sectional Study)

- Age ≥16 to ≤25 years at screening.
- HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months.
- Sexually active (had ≥2 vaginal intercourse encounters within the last 3 months) with cisgender male individuals.
- Prior use of HIV PrEP (including F/TDF) or HIV postexposure prophylaxis [PEP] in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir) was not allowed.

- Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) were not eligible. Individuals could be eligible if they participated in an HIV vaccine or bNAb study but had documentation that they did not receive active product (e.g., placebo recipients).

Randomized Blinded Phase

- Negative local rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag), central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT.
- No acute viral hepatitis A, B, or C or evidence of chronic hepatitis B or C infection.
- eGFR ≥60 mL/min at screening according to the
- Cockcroft-Gault formula for CL_{cr}.
- Body weight ≥35 kg.
- No severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (e.g., ascites, encephalopathy, variceal bleeding).
- Participation in any other clinical study (including observational and COVID-19 vaccine studies) without prior approval from the Applicant was prohibited while participating in this study. NOTE: Receipt of routine COVID-19 vaccine was not exclusionary. Participation in the qualitative study (GS-US-528-6365) did not require Applicant approval.

Duration of Study Drug Administration

Participants were given study drugs (LEN, F/TAF, or F/TDF) for a planned minimum duration of 52 weeks in the Randomized Blinded Phase. In the LEN OLE Phase, participants will receive SC LEN injections every 26 weeks and complete study visits for a planned duration of up to 65 weeks. In the PK Tail Phase, participants will receive F/TDF for up to 78 weeks.

Test Product, Dose, Mode of Administration, and Batch No.

Randomized Blinded Phase

- SC LEN 927 mg injection, 309 mg/mL (2 X 1.5 mL) administered every 26 weeks (starting on Day 1/Injection 1 visit) and oral LEN 600 mg (2 X 300 mg tablets) administered on Day 1/Injection 1 and Day 2.
- F/TAF (200/25 mg), administered orally once daily with or without food.

Lenacapavir Open-Label Extension Phase

SC LEN 927 mg injection, 309 mg/mL (2 X 1.5 mL) administered every 26 weeks. Participants randomized to F/TAF or F/TDF in the Randomized Blinded Phase also administered oral LEN 600 mg (2 X 300 mg tablets) on LEN OLE Days 1 and 2.

Batch Numbers for Randomized Blinded Phase

- LEN 300-mg tablets: GJ2004D1, GJ2102D2, GJ2202B1
- SC LEN 927-mg injection: GB2201B1, GB2202B1, GB2211B1, GB2210B1, P112410C

- F/TAF tablets: CR2004B1, CR2102B1

Reference Therapy, Dose, Mode of Administration, and Batch No.

Randomized Blinded Phase

- F/TDF (200/300 mg), administered orally once daily with or without food.
- Placebo-to-match (PTM) F/TDF, administered orally once daily.
- PTM F/TAF, administered orally once daily.
- Placebo for SC LEN injection, (2 X 1.5 mL) administered every 26 weeks and PTM oral LEN (2 tablets) administered on Day 1/Injection 1 and Day 2.

Pharmacokinetic Tail Phase

- F/TDF administered orally once daily

Batch Numbers

- F/TDF tablets: AX2001B1, AX2102B1, AX2106B1, AX2305B1
- PTM F/TDF tablets: AX2002B1, AX2107B1, AX2108B1
- PTM F/TAF: CR2005B1
- Placebo for SC LEN injection: GB2010B1, GB2103B1
- PTM LEN tablets: GJ2003B1

Criteria for Evaluation

Efficacy

In the Incidence Phase, HIV-1 infection was defined by 1 or more of the following criteria pertaining to HIV tests performed at the central laboratory during the screening visit (i.e., the first set of central laboratory HIV tests performed):

- Serologic evidence of seroconversion (positive instrumented fourth generation HIV-1/2 Ab/Ag test, confirmed by a HIV-1/2 Ab differentiation assay reactive for HIV-1)
- Virologic evidence of HIV-1 infection (HIV-1/2 RNA qualitative NAAT positive for
- HIV-1 or any positive HIV-1 RNA quantitative NAAT ≥200 copies/mL)

In the Randomized Blinded Phase, incident HIV-1 infection was determined by a blinded 3-physician panel who reviewed all available HIV test results and determined the participant's HIV-1 status and the earliest date with evidence of HIV-1 infection.

Pharmacokinetics

LEN plasma levels, LEN plasma levels during pregnancy, postpartum and in infants, LEN levels in breast milk, drug-drug interactions between LEN and long-acting hormonal contraceptives.

Safety

Occurrence of TEAEs and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN, F/TAF, and F/TDF for HIV-1 PrEP.

Other

Adherence

- On-time LEN injection administration (defined as ≤28 weeks of the previous injection)
- Adherence to F/TAF or F/TDF assessed using intracellular TFV-DP levels in DBS

Questionnaires

The following self-reported data were assessed by questionnaires:

- Sexual risk and behavior
- Adherence to oral study product
- NPRS–injection pain
- Administration and dosing for PrEP medication (injection acceptability)
- PrEP impacts and administration preference
- Experienced preference for PrEP medication (results not reported in this clinical study report [CSR])

Statistical Methods

Efficacy

The primary efficacy evaluations were comparisons of the observed HIV-1 incidence (per 100 PY) in the LEN or F/TAF group during the study versus the bHIV incidence (H_{01} to H_{04}). The bHIV incidence was calculated from the Incidence Phase based on a RITA using an incidence estimator similar to (Kassanjee et al. 2012). The incidence rate ratios of the LEN group versus the bHIV incidence and the F/TAF group versus the bHIV incidence were calculated. The associated 95% CIs and *P* values were estimated using the delta method by (Gao et al. 2021) or a likelihood-based method by (Shao and Gao 2024) if there were 0 infections.

As key secondary efficacy evaluations, the difference in HIV-1 incidence was used to evaluate the comparability of LEN or F/TAF relative to F/TDF (H_{05} and H_{07}, respectively), and the incidence rate ratio was used to evaluate the superiority of LEN or F/TAF versus F/TDF (H_{06} and H_{08}, respectively). The 95% CI for the difference in incidence was calculated using a hybrid approach with an additional modification to use the exact CI for a single Poisson rate parameter. The associated *P* value was obtained using the duality of hypothesis testing and CI. The incidence rate ratios of the LEN group versus the F/TDF group and the F/TAF group versus the F/TDF group were calculated. The associated 95% CIs and *P* values were estimated using a Poisson regression model or an exact conditional Poisson regression model if there was 0 infection.

The DMC formally evaluated efficacy and futility data, only once, after 50% of the planned number of participants completed at least 52 weeks of follow-up or prematurely discontinued

from the study. The prespecified efficacy hypotheses were tested using a gated sequential testing approach where the type I error level for the efficacy interim analysis was set at a 1-sided alpha level of α_1=0.0026.

The prespecified interim stopping criteria required the demonstration of superiority of LEN versus the bHIV incidence (H_{02}) with the point estimate of LEN/bHIV incidence ≤0.5 and superiority of LEN versus F/TDF (H_{06}), both at α_1=0.0026. If the stated criteria for LEN were met, the hypotheses H_{03}, H_{04}, H_{07}, and H_{08} for F/TAF were tested sequentially.

The DMC could recommend stopping the Randomized Blinded Phase early if the prespecified efficacy or futility evaluation criteria were met, in which case the interim analysis would serve as the primary analysis.

Pharmacokinetics

Individual participant concentration data were listed and summarized using descriptive statistics (number of participants, mean, SD, percentage coefficient of variation [%CV], median, minimum, maximum, first quartile [Q1], third quartile [Q3], and 90% CI). The geometric mean, 90% CI, and the mean and SD of the natural log-transformed values were also presented. In addition, figures were provided for analytes of interest and/or populations of interest (as appropriate), including boxplots of concentration data versus time.

Safety

Safety data were summarized separately for the Randomized Blinded Phase Safety Analysis Set and the Open-Label Oral PrEP Safety Analysis Set. The Randomized Blinded Phase Safety Analysis Set included all participants who received at least one dose of any study drug. The Open-Label Oral PrEP Safety Analysis Set included all participants who prematurely discontinued randomized study drug during the Randomized Blinded Phase for any reason, permanently transitioned to the PK Tail Phase, and received at least one dose of study OL oral PrEP. All safety data from both Phases of the study were included in data listings.

Treatment-emergent AEs were defined as any adverse events (AEs) that led to premature discontinuation of study drug or had an onset date on or after the study drug start date and no later than the last exposure date after permanent discontinuation of study drug. Last exposure date for the Randomized Blinded Phase was defined as the earlier of the last study date or the date of the first OL oral PrEP dose minus 1 day for participants in the LEN group, and the earlier of the last Randomized Blinded Phase dose date plus 30 days, the last study date, or the date of the first OL oral PrEP dose minus 1 day for participants in the F/TAF or F/TDF group. An exception to the treatment-emergent definition was for injection site reactions (ISRs) to study SC injection (with high-level term = ISRs and related to either study drug or study procedures), where treatment-emergent ISRs to study SC injection were defined as any ISR AEs to study SC injection with an onset date on or after the first SC LEN or placebo injection date through the last study date in the study. Unless otherwise specified, all AEs discussed in this CSR were treatment-emergent and are referred to as AEs for the purposes of this report.

Clinical and laboratory AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0. Adverse events were summarized by study Phase based on the Randomized Blinded Phase Safety Analysis Set and Open-Label Oral PrEP Safety Analysis Set

and included ISRs to study SC injection in the Randomized Blinded Phase, which were also summarized separately.

Additional analysis was performed for ISRs to study SC injection. Participant-level and event-level summaries were provided for each SC injection visit and overall visits by study drug group. Additional details for events of injection site nodules and indurations to study SC injection were collected and summarized separately, and with both participant-level and event-level summaries.

Laboratory data collected during the study were analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data were provided by study Phase for the Randomized Blinded Phase Safety Analysis Set and the Open-Label Oral PrEP Safety Analysis Set. Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline visit, up to and including the last exposure date for participants who permanently discontinued study drug, or the last available date in the database snapshot for participants who were still on study drug at the time of analysis. If the relevant baseline laboratory value was missing, any abnormality of at least Grade 1 observed at any postbaseline visit was considered treatment emergent. Unless otherwise specified, all laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as laboratory abnormalities for the purposes of this report.

Laboratory abnormalities were graded using DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017) (NIH 2017).

Other

Sexual behaviors, sexual partner characteristics, and clinical outcomes of sexual behavior (sexually transmitted infections [STIs]) while at risk of HIV-1 infection during the study were summarized for participants in the Full Analysis Set.

Participant assessments of PrEP impacts and administration preference, administration and dosing (pertaining to injection acceptability), NPRS, and self-reported adherence to oral study product were collected using questionnaires and summarized by study drug group, overall, and visit for the Randomized Blinded Phase Safety Analysis Set. Categorical responses were summarized with the number and percentage of participants in each category.

15.1.2. Sample Size and Power

A total sample size of 5010 was considered for this study. More than 95% power would be achieved with 2000 participants in the LEN study drug group to show at least a 20% reduction compared with the bHIV (powered for both H_{01} and H_{02}). In this sample size analysis, the following assumptions were made:

- bHIV of 3.00/100 PY
- LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 incidence compared with the nonrandomized control of bHIV
- Mean duration of recent infections (MDRI) of 173 days, with rSE of 6.5%
- FRR of 1.5%, with rSE of 70%
- Average follow-up of 1 year

- 2:2:1 allocation for LEN: F/TAF: F/TDF
- Alpha level of 0.025 (1-sided)

The bHIV assumption was based on recent longitudinal clinical trial data (ECHO Trial Consortium 2019). The LEN incidence corresponds to an 80% risk reduction and was consistent with the incidences observed in a large randomized controlled trial of long-acting cabotegravir for PrEP conducted in a similar study population (Delany-Moretlwe et al. 2021).

The MDRI and FRR were based on the Sedia Lag-EIA (Kassanjee et al. 2016), assuming T =2 years and virologic cutoff of 75 copies/mL. Under the assumption of T =1 year, the power dropped to 94%. The power calculation was based on the formula in (Gao et al. 2021)) using the test statistics for rate ratio.

The statistical power to compare the randomized study drug groups was not assessed.

15.1.3. Analysis Sets

The analysis sets that apply to both PURPOSE 1 and PURPOSE 2 studies are shown in Table 7.

15.1.4. Multiple Alpha-Controlled Hypotheses

There were eight alpha-controlled efficacy evaluations planned for PURPOSE 1 study and the null hypothesis for each one is listed in Table 8.

If the study was not stopped at the efficacy IA, the planned final efficacy analyses included the multiple testing procedure shown in Figure 1 in Section 6.2.1.3.4.

15.1.5. Analysis of the Primary Efficacy Endpoint

Estimation of HIV-1 Incidence

Figure 48 shows the testing process at the Incidence Phase. For the Incidence Phase of this study, the bHIV was reported per 100 PY for the All Screened Set based on a RITA (as described in Table 81) using an HIV-1 incidence formula similar to (Kassanjee et al. 2012), adjusting for participants with HIV-1 who may not have recency results.

The bHIV was estimated by the formula:

Equation 1. Estimation of HIV-1 Incidence

$$\hat{\lambda}_0 = \frac{N_{rec}/(N_{+,test}/N_+) - \beta N_+}{N_-(\Omega - \beta T)}$$

T: cutoff time (eg, 2 years) for the definition of true recent infections
Ω: MDRI
β: FRR

The variance of $\hat{\lambda}_0$ in the log scale $\hat{\sigma}^2_{\log(\hat{\lambda}_0)}$ will be estimated by the delta method,

$$\hat{\sigma}^2_{\log(\hat{\lambda}_0)} = \frac{N_{rec}(N_{+,test} - N_{rec})}{N_{+,test}(N_{rec} - N_{+,test}\beta)^2} + \frac{N}{N_+ N_-} + \sigma^2_\beta \frac{N_{+,test}(N - N_{+,test})}{N(N_{rec} - N_{+,test}\beta)^2} + \frac{\sigma^2_\Omega}{(\Omega - \beta T)^2} + \sigma^2_\beta \left[\frac{N_{+,test}\Omega - N_{rec}T}{(N_{rec} - N_{+,test}\beta)(\Omega - \beta T)}\right]^2$$

Source: Section 6.1.2 of the SAP of PURPOSE 1.

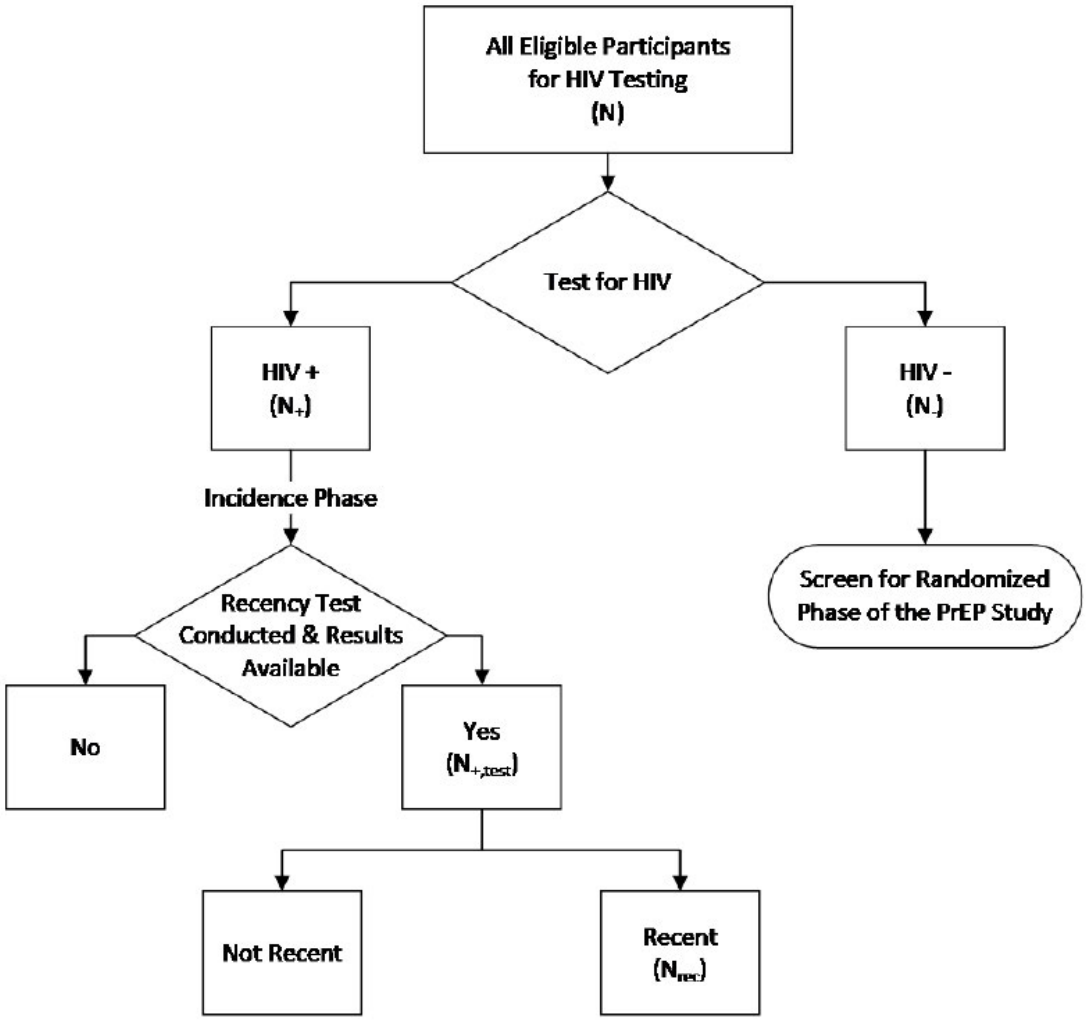
Table 81. Recency Outcome From the RITA

	HIV-1 Recency Test ODn		
HIV-1 RNA	≤ 1.50	>1.50	Missing ODn
> 75 copies/mL	Recent	Not Recent	Undeterminable
≤ 75 copies/mL	Not Recent	Not Recent	Not Recent

For the RITA , if a participant's HIV-1 RNA is missing or recency outcome is undeterminable, it will be excluded from $N_{+,test}$, but will still be included in N_+.

Source: Table 6-2 of the SAP of PURPOSE 1.
Abbreviations: ODn, normalized optical density; RITA, recent infection testing algorithm; SAP, statistical analysis plan.

Figure 48. Screening Schema and Contribution of Participants to the Estimation of the bHIV



The following are the notations.
N: Total number of participants screened
N_-: number of participants who test negative
N_+: number of participants who test positive
$N_{+,test}$: number of positive participants who have recency outcomes available
N_{rec}: number of recent infections as classified by the RITA
Source: Figure 6-1 of the SAP of PURPOSE 1.
Abbreviations: bHIV, background HIV-1 incidence; PrEP, pre-exposure prophylaxis; RITA, recent infection testing algorithm; SAP, statistical analysis plan.

Choice of Recency Assay, Assay Parameters, and Algorithm Parameters

The Sedia LAg-EIA was the primary recency assay as it is the most widely used and has been field validated. The number of recent infections was classified based on the RITA (Kassanjee et al. 2016). A participant, diagnosed with HIV-1, was counted as a recent infection if the normalized optical density was below the 1.5 threshold, provided that the HIV-1 RNA viral load was above the cutoff of 75 copies/mL.

For the primary analysis, the assay parameters given by (Kassanjee et al. 2016) were used for bHIV estimation. Table 25 in Section 6.3.1 gives the assay parameters and their rSEs for T =2

years. The sample size calculation in the protocol was also based on (Kassanjee et al. 2016) with T =2 years for pooled samples.

Since subtype data were not available for analysis, country, as a correlate, was used to estimate the percentage of each subtype instead. Based on a literature review for the geographical distribution of the study sites, the Applicant assumed all HIV-1 infections from South Africa to be subtype C, and infections from Uganda to be 56% subtype A, 41% subtype D, and 3% subtype C.

The MDRI used in estimating the bHIV for this study was calculated as the weighted average of the MDRIs for the subtypes included in the study. More specifically, let w_1, w_2 be the proportion of HIV-1 infections from South Africa and Uganda, respectively. The distribution of the three subtypes was:

- Subtype A: 0.56w2
- Subtype C: w1+0.03w2
- Subtype D: 0.41w2

Let Ω_A, Ω_C, Ω_D be the MDRI for the subtypes A/C/D, and $\sigma_{\Omega,A}$, $\sigma_{\Omega,C}$, $\sigma_{\Omega,D}$ be the corresponding standard errors, which was computed as the product of MDRI and the rSE of the MDRI. The overall MDRI was estimated by:

$$\Omega = 0.56w_2\Omega_A + (w_1+0.03w_2)\Omega_C + 0.41w_2\Omega_D$$

And the standard error of the overall MDRI was estimated by:

$$\sigma_\Omega = \mathrm{Sqrt}((0.56w_2)^2\,\sigma_{\Omega,A}{}^2 + (w_1+0.03w_2)^2\,\sigma_{\Omega,C}{}^2 + (0.41w_2)^2\,\sigma_{\Omega,D}{}^2)$$

The rSE of the overall MDRI was calculated as σ_Ω/Ω, reported as a percentage (%).

The overall FRR was estimated by the weighted average of the FRR for the subtypes. Let β_A, β_C, and β_D be the FRR for the subtypes A/C/D, and $\sigma_{\beta,A}$, $\sigma_{\beta,C}$, and $\sigma_{\beta,D}$ be the corresponding standard errors, which was computed as the product of the FRR and the rSE of the FRR. The overall FRR was estimated by:

$$\beta = 0.56w_2\beta_A + (w_1+0.03w_2)\beta_C + 0.41w_2\beta_D.$$

And the standard error of the overall FRR was estimated by:

$$\sigma_\beta = \mathrm{Sqrt}((0.56w_2)^2\,\sigma_{\beta,A}{}^2 + (w_1+0.03w_2)^2\,\sigma_{\beta,C}{}^2 + (0.41w_2)^2\,\sigma_{\beta,D}{}^2)$$

HIV-1 Infection in Study

The HIV-1 incidence rates in LEN, F/TAF and F/TDF study drug groups were estimated using a method appropriate for a single Poisson rate based on the FAS. The HIV-1 incidence λ_1 was estimated by the number of HIV-1 infections in study divided by the total follow-up time in study for each group. Here "in study" included postbaseline time in study [including the RBP and follow-up time of participants who discontinue the randomized blinded study drug early (regardless of reason) and may receive OL oral PrEP administered via the PK Tail Phase or stop taking any PrEP during the study].

The exact $(1-\alpha)\times 100\%$ CI for λ_1 was constructed as follows (Ulm 1990):

Equation 2. Confidence Interval Estimation of HIV-1 Incidence

$$(L_l, L_u) = \left(\frac{\chi^2_{2Y,\frac{\alpha}{2}}}{2D}, \frac{\chi^2_{2(Y+1),1-\frac{\alpha}{2}}}{2D} \right)$$

Here (L_l, L_u) were the lower and upper bound of the exact CI. Y was the observed number of infections, D was the total follow-up time, and $\chi^2_{\nu,\alpha}$ was the chi-square quantile for lower tail probability α on ν degrees of freedom. In the case where Y =0, the lower bound L_l would be set to 0. The standard error of the incidence estimate λ_1 in the log scale was estimated by $1/\sqrt{Y}$ based on the Poisson assumption (Gao et al. 2021).

Intercurrent Events

On December 20, 2021, the administration of LEN SC injection was put on clinical hold, pausing the screening, and enrollment of new participants and continued dosing of injectable LEN for ongoing participants. Ongoing participants in the study, treated on or prior to December 21, 2021, whose next SC injection visit occurred during the clinical hold were either:

- Switched to open-label F/TDF or open-label F/TAF prior to Protocol Amendment 2, or
- Switched to blinded oral weekly LEN/PTM bridging study drug (instead of LEN SC or placebo injections every 6 months)

This clinical hold and early discontinuation of study drug were considered intercurrent events during the RBP. However, consistent with the intent-to-treat approach, these intercurrent events were ignored (i.e., a treatment policy strategy) for the primary efficacy evaluations.

Primary Efficacy Analyses

The primary efficacy analysis was the comparison of the observed HIV-1 incidence in the LEN group during the RBP to the bHIV. The statistical hypotheses were:

Null hypothesis: H_{01}: LEN/bHIV $\geq$1.0

Alternative hypothesis: H_{11}**:** LEN/bHIV $<$1.0

It would be concluded that HIV-1 incidence in the LEN group is significantly lower compared to the bHIV if the null hypothesis was rejected in favor of the alternative hypothesis, at an overall 1-sided significance level of 0.025.

Additionally for the primary analysis, the success criteria were defined as the HIV-1 incidence rate ratio of at least 20% reduction in the LEN study drug group compared with the bHIV estimated in the Incidence Phase, formulated as the key alpha-controlled H_{02} (gated on rejection of H_{01}) with a point estimate of LEN/bHIV $\leq$0.5 and comparability to F/TDF formulated as the key alpha-controlled H_{05}.

Methods for the Primary Efficacy Evaluations

The incidence rate ratio of the LEN group (λ_1) over the bHIV (λ_0) was calculated, and the associated CI was estimated using the delta method as provided by (Gao et al. 2021) (see below):

Let R denote the incidence rate ratio λ_1/λ_0. In log scale, $\log R$ (i.e., $\log(\lambda_1) - \log(\lambda_0)$) can be estimated by $\log \hat{R} = \log\hat{\lambda}_1 - \log\hat{\lambda}_0$. $\log R$ has an asymptotic normal distribution (Gao et al. 2021):

Equation 3. Confidence Interval Estimation of Incidence Rate Ratio

$$\log \hat{R} \sim N\left(\log R, \hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}\right)$$

In the case that the number of HIV-1 infections diagnosed in the LEN (or F/TAF) group is zero, the estimated HIV-1 incidence λ_1 will be zero, and the methods specified above would fail. The CI and the 1-sided p-value was then estimated using a likelihood-based method proposed by (Shao and Gao 2024).

15.1.6. Secondary Efficacy Analysis (Comparison With F/TDF)

Difference in HIV-1 incidence rates evaluated comparability of LEN relative to F/TDF, that is, null hypothesis H_{05}. Rejection of this hypothesis would support the conclusion that the HIV-1 incidence in the LEN group is comparable to F/TDF. To test this hypothesis, a CI was constructed using a hybrid approach recommended by (Li et al. 2011) with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI recommended by (Li et al. 2011).

Let $\hat{\lambda}_1, \hat{\lambda}_2$ be the estimates of the HIV-1 incidence rates in the two study drug groups, and let (l_1, u_1), (l_2, u_2) be the exact $(1-\alpha) \times 100\%$ CIs for single Poisson rates (Ulm 1990):

Equation 4. CIs for Single Poisson Rates

$$(l_i, u_i) = \left(\frac{\chi^2_{2Y_i,\alpha/2}}{2D_i}, \frac{\chi^2_{2(Y_i+1),1-\alpha/2}}{2D_i}\right), i = 1,2$$

where Y_i's were the observed numbers of infections and D_i's were the total follow-up times for each of the study drug groups, respectively, and $\chi^2_{\nu,\alpha}$ was the chi-square quantile for lower tail probability α on ν degrees of freedom. In the case where $Y_i = 0$, the lower bound l_i would be set to 0.

Then, the hybrid $(1-\alpha) \times 100\%$ CI for the incidence rate difference $\lambda_1 - \lambda_2$ was given by:

Equation 5. CI for the Incidence Rate Difference

$$L = \hat{\lambda}_1 - \hat{\lambda}_2 - \sqrt{(\hat{\lambda}_1 - l_1)^2 + (u_2 - \hat{\lambda}_2)^2}$$

$$U = \hat{\lambda}_1 - \hat{\lambda}_2 + \sqrt{(u_1 - \hat{\lambda}_1)^2 + (\hat{\lambda}_2 - l_2)^2}$$

It was concluded that LEN was comparable to F/TDF if U, the upper bound of the CI of the incidence rate difference (LEN – F/TDF), was less than 0.8 per 100 PY.

The corresponding p-value was calculated by using the duality of hypothesis testing and CI (Rohatgi 1984). For any specified α, the upper bound of the $(1 - \alpha)\times 100\%$, U, could be viewed as a decreasing function of α, i.e., view it as $U(\alpha)$. Solve the equation $U(\alpha)$ =0.8/100PY for α, then $\alpha/2$ would be the 1-sided p-value.

Ratio of HIV-1 incidence rates evaluated the relative statistical difference between LEN (or F/TAF) and F/TDF. The rate ratios of HIV-1 incidence between LEN and F/TDF and between F/TAF and F/TDF were calculated, and the associated CI was estimated using a generalized model associated with a Poisson distribution and logarithmic link with the study drug group being the main effect.

If the number of infections was zero in any of the experimental groups (LEN (or F/TAF) or F/TDF), the Poisson model would fail. Therefore, an exact conditional Poisson regression model would be used as the prespecified alternate to the generalized Poisson model specified above.

As specified earlier, H_{06} and H_{08} would each be tested sequentially after H_{05} and H_{07} have been rejected, respectively.

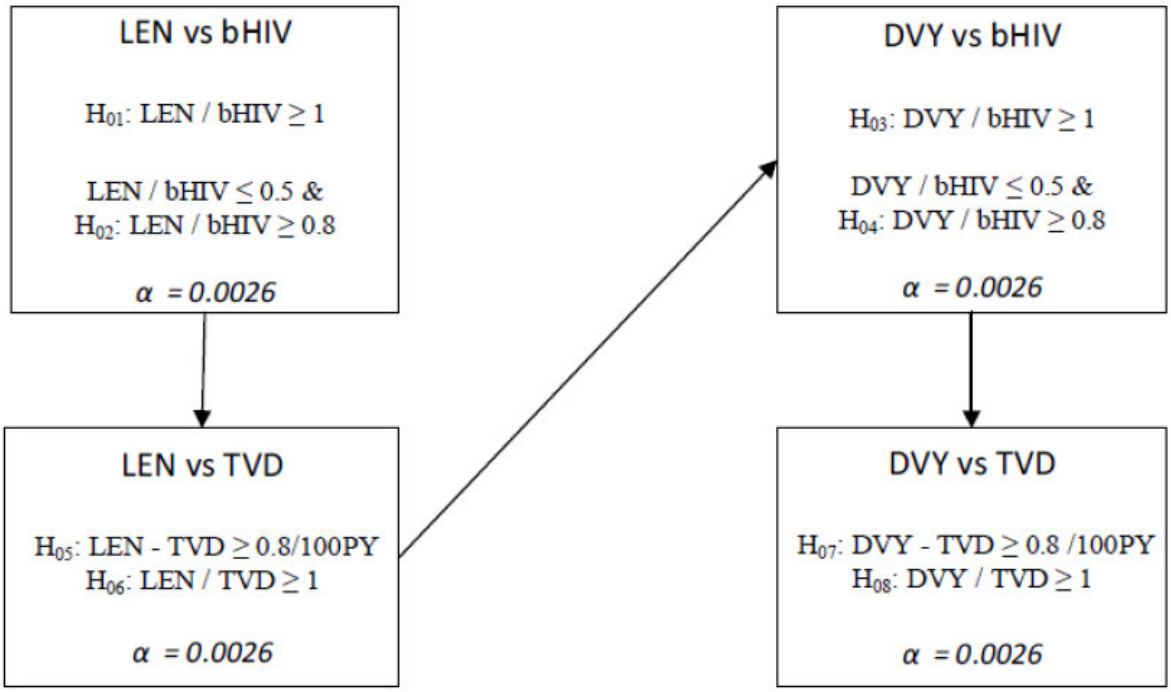
15.1.7. Interim Analyses

An external independent multidisciplinary DMC reviewed the progress of the study and performed interim reviews of the data (both interim efficacy and periodic safety) to protect participant welfare and preserve study integrity.

The DMC formally evaluated efficacy and futility data, only once, after 50% of participants enrolled had completed Week 52 of the study or prematurely discontinued from the study. The DMC recommended stopping the study early because the prespecified efficacy or futility evaluation criteria were met. Therefore, the interim analysis served as the primary analysis. The criteria for interim decisions and DMC recommendations as well as alpha-spending procedures are outlined below. Figure 49 presents the testing procedure at the interim analysis. The prespecified interim stopping criteria requires LEN superiority over bHIV (H_{01} and H_{02}) followed by LEN superiority over F/TDF (H_{05} and H_{06}), and the overall testing procedure follows a gated sequential testing approach where the nominal alpha levels for the interim analysis was set at $\alpha 1$=0.0026.

The original plan was if the RBP continues to the final primary analysis, the null hypotheses H_{01}, H_{02}, …, H_{08} would be tested according to the overall testing procedure.

Figure 49. Testing Procedure at the Interim Analysis, PURPOSE 1



Note: Alpha levels are one-sided. Testing within each block is sequential.
Source: Figure 3-2 of the SAP of PURPOSE 1.
Abbreviations: bHIV, background HIV-1 incidence; DVY, emtricitabine/tenofovir alafenamide; H_0, null hypothesis; LEN, lenacapavir; SAP, statistical analysis plan; TVD, emtricitabine/tenofovir disoproxil fumarate.

15.2. PURPOSE 2

15.2.1. Protocol Overview and Conduct

Title of Study

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

Study Centers

96 sites globally in Argentina, Brazil, Mexico, Peru, South Africa, Thailand, and the United States (U.S.)

Publications

- (Kelley et al. 2024)
- (Kelley et al. 2025)

Study Period

June 28, 2021 (first participant screened)

August 5, 2024 (last participant last visit for this report)

Phase of Development

Phase 3

Study Objectives and Endpoints:

The primary objective of this study is to evaluate the efficacy of lenacapavir (LEN) in preventing the risk of HIV-1 infection relative to the background HIV-1 (bHIV) incidence.

Table 82. Protocol Overview and Conduct, PURPOSE 2

Objectives	Endpoints
Primary Objectives	
Incidence Phase • To estimate the bHIV incidence Randomized Blinded Phase • To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection	Incidence Phase • Diagnosis of recent HIV-1 infection Randomized Blinded Phase • Diagnosis of HIV-1 infection
Secondary Objectives	
Randomized Blinded Phase • To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada; TVD) for HIV-1 PrEP in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection • To evaluate the safety and tolerability of LEN and F/TDF for HIV-1 PrEP in participants ≥16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection • To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥16 to <18 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection	Randomized Blinded Phase • Diagnosis of HIV-1 infection, including among participants while adherent to study drug • Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
Randomized Blinded Phase • To assess the adherence rate to LEN as assessed by on-time LEN injection • To assess LEN plasma levels • To assess the adherence rate to F/TDF using intracellular tenofovir-diphosphate (TFV-DP) levels in dried blood spot (DBS) • To evaluate the acceptability of a once every 6 months LEN injection for HIV-1 PrEP in participants at risk of HIV-1 infection • To explore concentrations of LEN in participants on exogenous hormones • To explore concentrations of estradiol and testosterone in LEN participants on exogenous hormones	Randomized Blinded Phase • Adherence to LEN as assessed by on-time LEN injection • LEN plasma levels • Adherence to F/TDF assessed using the intracellular TFV-DP concentration in DBS • LEN plasma levels in participants on exogenous hormones • Estradiol and/or testosterone levels in LEN participants on gender-affirming hormone therapy (GAHT) • Self-reported questionnaire outcomes pertaining to acceptability, as follows: • Adherence to oral study product • Numeric pain rating scale (NPRS)–injection pain • Administration and dosing for PrEP medication • PrEP impacts and administration preference • Self-reported questionnaire outcomes pertaining to integrated sexual behaviors and alcohol and substance use

Source: Study synopsis of the CSR of PURPOSE 2.
Abbreviations: bHIV, background HIV; LEN, lenacapavir.

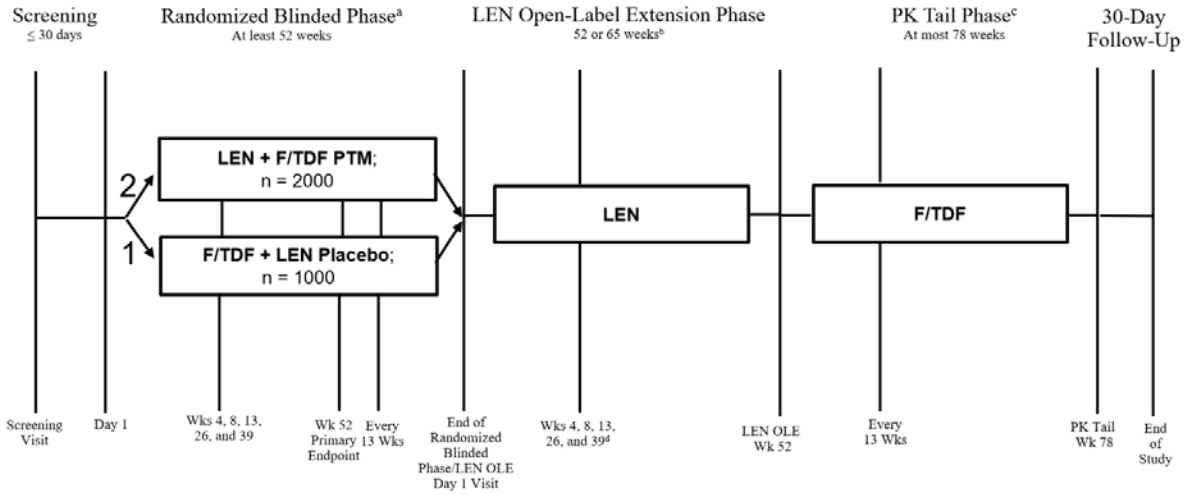
Study Design and Methodology

This is a Phase 3, randomized, double-blind, multicenter study to compare HIV-1 incidence in the LEN group with the counterfactual control of bHIV incidence, defined as the estimated HIV-1 incidence in the screened population. TRUVADA (F/TDF) is the internal active control. This study includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a Pharmacokinetic (PK) Tail Phase.

The Incidence Phase estimated the bHIV incidence within the population screened for eligibility using recency assay results from samples that were positive for HIV-1 infection incorporated into a RITA. Participants determined to be HIV-1 negative and who met eligibility criteria proceeded to the Randomized Blinded Phase, in which they were randomized in a 2:1 ratio to receive LEN or F/TDF, respectively. After completion of the Randomized Blinded Phase, participants were offered the opportunity to receive open-label LEN in the LEN OLE Phase, which allows for further long-term efficacy and safety follow-up. Participants who discontinued study drug during the Randomized Blinded Phase entered the PK Tail Phase, which provides a known efficacious open-label regimen to provide HIV prevention for participants during the time when LEN concentrations decline.

Enrollment of adolescents (participants ≥16 and <18 years of age) commenced following the DMC review of unblinded safety data from the first 300 adult participants through 8 weeks of follow-up and recommendation to continue the study. Gilead Sciences (Gilead) notified sites when they could begin enrollment of adolescents.

Figure 50. Study Methodology, PURPOSE 2



Source: Figure 1 of the CSR of PURPOSE 2.
Abbreviations: F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; OL, open label; OLE, open-label extension; PK, pharmacokinetic; PTM, placebo-to-match; SC, subcutaneous; wk, week.

- Participants were to continue in the Randomized Blinded Phase until all enrolled participants completed at least 52 weeks of follow-up in the study and Gilead completed the primary analysis. In the case that the Randomized Blinded Phase was stopped early for an efficacy outcome, some participants may have less than 52 weeks of follow-up.
- The duration will be dependent on timing of the OL LEN injection.
- Participants who prematurely discontinued study drug during the Randomized Blinded Phase or LEN OLE Phase, or those randomized to LEN in the Randomized Blinded Phase who declined to participate in the LEN OLE Phase upon unblinding, will transition to the PK Tail Phase. Participants in the United States could receive either OL oral F/TDF or F/TAF in the PK Tail Phase.
- Week 4 and 8 visits were only required for participants who were randomized to oral F/TDF in the Randomized Blinded Phase.

Number of Participants Planned

Approximately 3000 participants in the Randomized Blinded Phase.

Diagnosis and Main Criteria for Inclusion

Eligible participants were CGM, TGW, TGM, and GNB who met the following criteria:

Incidence Phase (Cross-Sectional Study)

- Age ≥16 years at screening.
- HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months.
- Sexually active with ≥1 partner assigned male at birth (condomless receptive anal sex) in
- the last 12 months and 1 of the following:
  - Condomless receptive anal sex with ≥2 partners in the last 12 weeks

  - History of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks
  - Self-reported use of stimulants with sex in the last 12 weeks

- Willing and able to comply with study procedures.
- Prior use of HIV PrEP (including F/TDF or F/TAF) or HIV postexposure prophylaxis in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir) was not allowed.
- Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) were not eligible. Individuals could be eligible if they participated in an HIV vaccine or bNAb study but had documentation that they did not receive active product (e.g., placebo recipients).

Randomized Blinded Phase

- Negative local rapid fourth generation HIV-1/2 antibody (Ab)/antigen (Ag), central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT.
- eGFR ≥60 mL/min at screening according to the Cockcroft-Gault formula for creatinine clearance.
- Body weight ≥35 kg.
- Participants of childbearing potential who engaged in frontal (vaginal) intercourse must have not intended to become pregnant during the study and agreed to utilize protocol-specified method(s) of contraception.
- Participation in any other clinical study (including observational and COVID-19 vaccine studies) without prior approval from the Applicant was prohibited while participating in this study. An exception was made for participation in the Applicant-approved ancillary qualitative participant interview study, which was allowed and did not require medical monitor approval.
- No acute viral hepatitis A, B, or C infection or evidence of chronic hepatitis B or C infection.
- No severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (e.g., ascites, encephalopathy, variceal bleeding).

Duration of Study Drug Administration

Participants in the Randomized Blinded Phase received study drug for a planned minimum duration of 52 weeks. In the LEN OLE Phase, participants will receive SC LEN injections every 26 weeks and complete study visits for a planned duration of up to 65 weeks. In the PK Tail Phase, participants will receive F/TDF for up to 78 weeks; participants in the US will have the option to receive F/TAF up to 78 weeks.

Test Product, Dose, Mode of Administration, and Batch No.

Randomized Blinded Phase

- SC LEN 927 mg injection, 309 mg/mL (2 X 1.5 mL) administered every 26 weeks (starting on Day 1/Injection 1 visit) and oral LEN 600 mg (2 X300 mg tablets) administered on Day 1/Injection 1 and Day 2.

Lenacapavir Open-Label Extension Phase

- SC LEN 927 mg injection, 309 mg/mL (2 X 1.5 mL) administered every 26 weeks. Participants randomized to F/TDF in the Randomized Blinded Phase also administered oral LEN 600 mg (2 X 300 mg tablets) on LEN OLE Days 1 and 2.

Batch Numbers for Randomized Blinded Phase

- LEN 300 mg tablets: GJ2004D1, GJ2102D2, GJ2103D2, GJ2203B1, and GJ2205B1
- SC LEN 927 mg injection: GB1906B1, GB2001B1, GB2002B1, GB2201B1, GB2202B1, GB2210B1, and GB2212B1

Reference Therapy, Dose, Mode of Administration, and Batch No.

Randomized Blinded Phase

- F/TDF fixed-dose combination (200 mg emtricitabine/300 mg tenofovir disoproxil fumarate), administered orally once daily with or without food.
- PTM F/TDF, administered orally once daily
- Placebo for SC LEN injection (2 X1.5 mL) administered every 26 weeks and PTM oral LEN (2 tablets) administered on Day 1/Injection 1 and Day 2.

Pharmacokinetic Tail Phase

- F/TDF, administered orally once daily
- F/TAF, administered orally once daily (US only)

Batch Numbers

- F/TDF tablets: AX2001B1, AX2101B1, AX2105B1, AX2203B1, AX2204B1, and AX2305B1
- PTM F/TDF tablets: AX2002B1, AX2103B1, AX2104B1, AX2107B1, AZ2108B1, AX2201B1, and AX2202B1
- Placebo for SC LEN injection: GB2010B1, GB2103B1, GB2208B1, and GB2403B1
- PTM LEN tablets: GJ2003B1
- F/TAF tablets (US only): CFHKZ, 6664901, and CR2102B1

Safety

Occurrence of TEAEs and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP.

Other

Adherence

- On-time LEN injection administration (defined as ≤28 weeks of the previous injection)
- Adherence to F/TDF assessed using intracellular TFV-DP levels in DBS

Questionnaires

The following self-reported data were assessed by questionnaires:

- Integrated sexual behaviors and alcohol and substance use questionnaire
- Adherence to oral study product questionnaire
- NPRS–injection pain questionnaire
- Administration and dosing questionnaire for PrEP medication
- PrEP impacts and administration preference questionnaire
- Experienced preference for PrEP medication questionnaire (results to be collected in the OLE and therefore not reported in this CSR)

Statistical Methods

Efficacy

The primary efficacy evaluation was a comparison of the observed HIV-1 incidence (per 100 PY) in the LEN group during the study versus the bHIV incidence (H_{01} and H_{02}). The bHIV incidence was calculated from the Incidence Phase based on a RITA using an incidence estimator similar to (Kassanjee et al. 2012). The incidence rate ratio of the LEN group over the bHIV incidence was calculated. The associated 95% CI and *P* value were estimated using the delta method by (Gao et al. 2021).

As key secondary efficacy evaluations, the difference in HIV-1 incidence was used to evaluate comparability of LEN relative to F/TDF (H_{03}), and the incidence rate ratio was used to evaluate superiority of LEN versus F/TDF (H_{04}). The 95% CI for the difference in incidence was calculated using a hybrid approach with an additional modification to use the exact CI for a single Poisson rate parameter. The associated *P* value was obtained using the duality of hypothesis testing and CI. The incidence rate ratio of the LEN group over the F/TDF group was calculated. The associated 95% CI and *P* value were estimated using a Poisson regression model.

The study's independent DMC formally evaluated efficacy and futility data, only once, after 50% of the planned number of participants completed at least 52 weeks of follow-up or prematurely discontinued from the study. The prespecified efficacy hypotheses were tested using a fixed-sequence approach where the type I error level for the interim analysis was set at a 1-sided alpha level of α_1=0.0026.

Prespecified interim stopping criteria required the demonstration of superiority of LEN versus the bHIV incidence (H_{02}) with the point estimate of LEN/bHIV incidence ≤0.5 and superiority of LEN versus F/TDF (H_{04}), both at α_1=0.0026.

The DMC could recommend stopping the Randomized Blinded Phase early if the prespecified efficacy or futility evaluation criteria were met, in which case the interim analysis would serve as the primary analysis.

Pharmacokinetics

Individual participant concentration data were listed and summarized using descriptive statistics (number of participants, mean, SD, percentage coefficient of variation [%CV], median, minimum, maximum, first quartile [Q1], third quartile [Q3], and 90% CI). The geometric mean, 90% CI, and the mean and SD of the natural log-transformed values were also presented. In addition, figures were provided for analytes of interest and/or populations of interest (as appropriate), including boxplots of concentration data versus time.

Safety

Data were summarized separately for the Randomized Blinded Phase Safety Analysis Set (RBP Safety Analysis Set) and the Open-Label Oral PrEP Safety Analysis Set. The RBP Safety Analysis Set included all participants who received at least 1 dose of any study drug. The Open-Label Oral PrEP Safety Analysis Set included all participants who prematurely discontinued randomized study drug during the Randomized Blinded Phase for any reason, and permanently transitioned to the PK Tail Phase, and received at least 1 dose of open-label oral PrEP. In the US, where participants had the choice of study drug in the PK Tail Phase (F/TDF or F/TAF), the open-label oral PrEP study drug groups and safety analyses will be based on the first open-label oral PrEP study drug received. All safety data from both Phases of the study were included in data listings.

The TEAEs were defined as any adverse events (AEs) that led to premature discontinuation of study drug or had an onset date on or after the study drug start date and no later than the last exposure date after permanent discontinuation of study drug. Last exposure date for the Randomized Blinded Phase was defined as the earlier of the last study date or the date of the first open-label oral PrEP dose minus 1 day for participants in the LEN group, and the earlier of the last Randomized Blinded Phase dose date plus 30 days, the last study date, or the date of the first open-label oral PrEP dose minus 1 day for participants in the F/TDF group. An exception to the treatment-emergent definition was for injection site reactions (ISRs) to study SC injection (with high-level term = ISRs and related to either study drug or study procedures), where treatment-emergent ISRs to study SC injection were defined as any ISR AEs to study SC injection with an onset date on or after the first SC LEN or placebo injection date through the last study date in the study. Unless otherwise specified, all AEs discussed in this CSR were treatment-emergent and are referred to as AEs for the purposes of this report.

Clinical and laboratory AEs were coded using MedDRA Version 27.0. Adverse events were summarized by study Phase based on the RBP Safety Analysis Set and Open-Label Oral PrEP Safety Analysis Set and included ISRs to study SC injection in the Randomized Blinded Phase, which were also summarized separately.

Additional analysis was performed for ISRs to study SC injection. Participant-level and event-level summaries were provided for each SC injection visit and overall visits by study drug group. Additional details for events of injection site nodules and indurations to study SC injection were collected and summarized separately, and with both participant-level and event-level summaries.

Laboratory data collected during the study were analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data were provided by study Phase for the RBP Safety Analysis Set and the Open-Label Oral PrEP Safety Analysis Set. Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline visit, up to and including the last exposure date for participants who permanently discontinued study drug, or the last available date in the database snapshot for participants who were still on study drug at the time of analysis. If the relevant baseline laboratory value was missing, any abnormality of at least Grade 1 observed at any postbaseline visit was considered treatment emergent. Unless otherwise specified, all laboratory abnormalities discussed in this CSR were treatment emergent and are referred to as laboratory abnormalities for the purposes of this report.

Laboratory abnormalities were graded using DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017) (NIH 2017).

Other

Sexual behaviors, sexual partner characteristics, and clinical outcomes of sexual behavior (sexually transmitted infections [STIs]) while at risk of HIV-1 infection during the study were summarized for participants in the FAS.

Participant assessments of PrEP impacts and administration preference, administration and dosing (pertaining to injection acceptability), NPRS, and self-reported adherence to oral study product were collected using questionnaires and summarized by study drug group, overall, and visit for the RBP Safety Analysis Set. Categorical responses were summarized with the number and percentage of participants in each category.

15.2.2. Sample Size and Power

A total sample size of 3000 was considered for this study.

More than 95% power would be achieved with 2000 participants in the LEN study drug group to show at least a 20% reduction compared with the bHIV (powered for both H_{01} and H_{02}). In this sample size analysis, the following assumptions were made:

- bHIV of 3.00/100 PY
- LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 incidence compared with the nonrandomized control of bHIV
- Mean duration of recent infections (MDRI) of 173 days, with rSE of 6.5%
- FRR of 1.5%, with rSE of 70%
- Average follow-up of 1.5 years in the study
- 2:1 allocation for LEN: F/TDF

- Alpha level of 0.025 (1-sided)

The bHIV assumption was estimated based on epidemiologic data (Mera et al.). The LEN incidence corresponds to an 80% risk reduction and was consistent with the incidences observed in a large randomized controlled trial of long-acting cabotegravir for PrEP conducted in a similar study population (Landovitz et al. 2021).

The MDRI and FRR were based on the Sedia Lag-EIA (Kassanjee et al. 2016), assuming T =2 years and virologic cutoff of 75 copies/mL. Under the assumption of T =1 year, the power remains at >95%. The power calculation is based on the formula in (Gao et al. 2021) using the test statistics for rate ratio.

The statistical power to compare the randomized study drug groups was not assessed.

15.2.3. Analysis Sets

Please refer to Table 7 for the description of the analysis sets.

15.2.4. Multiple Alpha-Controlled Hypotheses

There were 4 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed in Table 15. If the RBP continues to the final primary analysis, the null hypotheses $H01$, $H02$, $H03$ and $H04$ will be tested sequentially at level α_2=0.025 — α_1=0.025 — 0.0026=0.0224.

15.2.5. Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint, key secondary endpoint and their analyses for PURPOSE 2 were almost identical to those of PURPOSE 1. Please refer to Section 15.1 for details. The only difference was the countries enrolled in this study were different. Therefore, the subtype data distribution was different as well. Based on a literature review for the geographical distribution of our study sites, the Applicant assumed all HIV-1 infections from South Africa to be subtype C, all infections from Mexico, United States, Peru, and Argentina to be subtype B, infections from Thailand to be 12% subtype B and 88% subtype AE, and infections from Brazil to be 92% subtype B and 8% subtype C.

The MDRI used in estimating the bHIV for this study was calculated as the weighted average of the MDRI for the subtypes included in the study. Let w_1, w_2, w_3, w_4, w_5, w_6, w_7 be the proportion of HIV-1 infections from South Africa, Mexico, United States, Peru, Thailand, Argentina, and Brazil, respectively. The distribution of the three subtypes is:

- Subtype B: w2+w3+w4+0.12w5+w6+0.92w7
- Subtype C: w1+0.08w7
- Subtype AE: 0.88w5

Let Ω_A, Ω_C, Ω_{AE} be the MDRI for the subtypes B/C/AE, and $\sigma_{\Omega,A}$, $\sigma_{\Omega,C}$, $\sigma_{\Omega,AE}$ be the corresponding standard errors, which was computed as the product of MDRI and the rSE of the MDRI. The overall MDRI was estimated by

$\Omega = (w2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\Omega_B + (w_1 + 0.08w_7)\Omega_C + 0.88w_5\Omega_{AE}$.

And the standard error of the overall MDRI was estimated by

$\sigma_\Omega = Sqrt((w2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)^2 \sigma_{\Omega,B}^2 + (w_1 + 0.08w_7)^2 \sigma_{\Omega,C}^2 + (0.88w_5)^2 \sigma_{\Omega,AE}^2)$

The rSE of the overall MDRI was calculated as σ_Ω/Ω, reported as a percentage (%).

The overall FRR was estimated by the weighted average of the FRR for the subtypes. Let β_A, β_C, and β_{AE} be the FRR for the subtypes A/C/D, and $\sigma_{\beta,A}$, $\sigma_{\beta,C}$, and $\sigma_{\beta,AE}$ be the corresponding standard errors, which was computed as the product of the FRR and the rSE of the FRR. The overall FRR was estimated by

$\beta = (w2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\beta_B + (w_1 + 0.08w_7)\beta_C + 0.88w_5\beta_{AE}$.

And the standard error of the overall FRR was estimated by

$$\sigma_\beta = Sqrt((w2 + w3 + w4 + 0.12w5 + w6 + 0.92w7)^2 \sigma_{\beta,B}^2 + (w1 + 0.08w_7)^2 \sigma_{\beta,C}^2 + (0.88w_5)^2 \sigma_{\beta,AE}^2)$$

15.2.6. Interim Analyses

An external independent multidisciplinary DMC reviewed the progress of the study and performed interim reviews of the data (both interim efficacy and periodic safety) in order to protect participant welfare and preserve study integrity.

The DMC formally evaluated efficacy and futility data, only once, after 50% of participants enrolled had completed Week 52 of the study or prematurely discontinued from the study. The DMC recommended stopping the study early because the prespecified efficacy or futility evaluation criteria were met. Therefore, the interim analysis served as the primary analysis.

At the interim analysis, an alpha of 0.0026 (1-sided) would be spent and the remaining alpha at the primary analysis would be 0.025-0.0026=0.0224.

At the interim analysis, given the interim stopping criteria, the RBP of the trial would stop early if superiority of LEN over bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and over F/TDF, designated H_{04}, both at $\alpha 1 = 0.0026$ could be demonstrated.

16. Efficacy

16.1. Additional Subgroup Analyses for Primary and Key Secondary Efficacy Endpoint, PURPOSE 1

This section supplements the analyses and interpretation presented in Section 6.2.1.4.4. Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic factors and clinical characteristics at baseline. No participant in the LEN group had incident HIV-1 infection. The treatment effect was generally consistent across analyzed subgroups.

Table 83. HIV-1 Incidence by Subgroup in the LEN vs. F/TDF Groups and the bHIV Incidence, Full Analysis Set and All Screened Set, PURPOSE 1

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Age (years): 16 to <18			
N	56	23	154
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	41.88	18.28	
HIV-1 incidence per 100 Person-years	0.000	0.000	NA
95% CI	(0.000, 8.808)	(0.000, 20.185)	
Rate ratio (randomized study drug groups over bHIV incidence)	NA	NA	
95% CI	NA	NA	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		
Age (years): ≥18			
N	2078	1045	7940
Number of HIV-1 diagnoses in study	0	16	
Person-years of follow-up	1897.46	931.11	
HIV-1 incidence per 100 person-years	0.000	1.718	2.456
95% CI	(0.000, 0.194)	(0.982, 2.791)	(1.852, 3.257)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.700	
95% CI	(0.000, 0.042)	(0.397, 1.231)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.101)		

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Country: South Africa			
N	1807	908	6359
Number of HIV-1 diagnoses in study	0	14	
Person-years of follow-up	1626.87	797.04	
HIV-1 incidence per 100 person-years	0.000	1.757	1.894
95% CI	(0.000, 0.227)	(0.960, 2.947)	(1.350, 2.658)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.927	
95% CI	(0.000, 0.064)	(0.497, 1.730)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.117)		
Country: Uganda			
N	327	160	1735
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	312.47	152.34	
HIV-1 incidence per 100 person-years	0.000	1.313	4.721
95% CI	(0.000, 1.181)	(0.159, 4.742)	(3.001, 7.428)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.278	
95% CI	(0.000, 0.137)	(0.065, 1.195)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.693)		
Body mass index (kg/m2): <25			
N	1074	512	3319
Number of HIV-1 diagnoses in study	0	7	
Person-years of follow-up	959.51	445.95	
HIV-1 incidence per 100 person-years	0.000	1.570	0.132
95% CI	(0.000, 0.384)	(0.631, 3.234)	(0.031, 0.569)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	11.851	
95% CI	(0.000, 2.778)	(2.309, 60.816)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.248)		
Body mass index (kg/m2): ≥25			
N	1060	556	3429
Number of HIV-1 diagnoses in study	0	9	
Person-years of follow-up	979.84	503.43	
HIV-1 incidence per 100 person-years	0.000	1.788	0.339
95% CI	(0.000, 0.376)	(0.817, 3.394)	(0.136, 0.844)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	5.274	
95% CI	(0.000, 0.716)	(1.718, 16.194)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.203)		

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Highest level of education: < some secondary school education			
N	250	108	1133
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	236.83	105.00	
HIV-1 incidence per 100 person-years	0.000	1.905	3.520
95% CI	(0.000, 1.558)	(0.231, 6.880)	(1.960, 6.322)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.541	
95% CI	(0.000, 0.251)	(0.120, 2.436)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.539)		
Highest level of education: some secondary school education or higher			
N	1882	959	6263
Number of HIV-1 diagnoses in study	0	14	
Person-years of follow-up	1700.96	842.88	
HIV-1 incidence per 100 person-years	0.000	1.661	1.262
95% CI	(0.000, 0.217)	(0.908, 2.787)	(0.866, 1.841)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	1.316	
95% CI	(0.000, 0.093)	(0.690, 2.509)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.118)		
Modified VOICE Risk Score: <5			
N	186	75	672
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	167.18	64.77	
HIV-1 incidence per 100 person-years	0.000	0.000	1.688
95% CI	(0.000, 2.207)	(0.000, 5.695)	(0.666, 4.275)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.000	
95% CI	(0.000, 0.856)	(0.000, 2.210)	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		
Modified VOICE Risk Score: ≥5			
N	1884	960	6540
Number of HIV-1 diagnoses in study	0	15	
Person-years of follow-up	1712.55	853.69	
HIV-1 incidence per 100 person-years	0.000	1.757	1.550
95% CI	(0.000, 0.215)	(0.983, 2.898)	(1.074, 2.237)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	1.134	
95% CI	(0.000, 0.075)	(0.607, 2.118)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.110)		

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Taken drugs before or during sex in past 12 weeks prior to baseline: yes			
N	87	44	239
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	79.25	37.86	
HIV-1 incidence per 100 person-years	0.000	5.283	0.990
95% CI	(0.000, 4.655)	(0.640, 19.083)	(0.137, 7.135)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	5.334	
95% CI	(0.000, 8.645)	(0.478, 59.530)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.659)		
Taken drugs before or during sex in past 12 weeks prior to baseline: no			
N	2031	1018	6362
Number of HIV-1 diagnoses in study	0	14	
Person-years of follow-up	1845.49	904.99	
HIV-1 incidence per 100 person-years	0.000	1.547	0.211
95% CI	(0.000, 0.200)	(0.846, 2.596)	(0.091, 0.490)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	7.333	
95% CI	(0.000, 0.592)	(2.720, 19.768)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.117)		
Sex worker: yes			
N	159	91	602
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	157.67	81.78	
HIV-1 incidence per 100 person-years	0.000	2.446	NA
95% CI	(0.000, 2.340)	(0.296, 8.835)	
Rate ratio (randomized study drug groups over bHIV incidence)	NA	NA	
95% CI	NA	NA	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.801)		
Sex worker: no			
N	326	155	1093
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	293.96	136.32	
HIV-1 incidence per 100 person-years	0.000	1.467	0.427
95% CI	(0.000, 1.255)	(0.178, 5.300)	(0.103, 1.766)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	3.438	
95% CI	(0.000, 2.648)	(0.473, 25.007)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.610)		

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Used a needle to inject drugs in past 12 weeks: yes			
N	11	6	29
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	10.83	5.66	
HIV-1 incidence per 100 person-years	0.000	0.000	NA
95% CI	(0.000, 34.059)	(0.000, 65.153)	
Rate ratio (randomized study drug groups over bHIV incidence)	NA	NA	
95% CI	NA	NA	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		
Used a needle to inject drugs in past 12 weeks: no			
N	2106	1058	6573
Number of HIV-1 diagnoses in study	0	16	
Person-years of follow-up	1912.68	938.95	
HIV-1 incidence per 100 person-years	0.000	1.704	0.240
95% CI	(0.000, 0.193)	(0.974, 2.767)	(0.110, 0.522)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	7.112	
95% CI	(0.000, 0.489)	(2.833, 17.851)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.101)		
Six or more drinks on one occasion: yes			
N	1375	708	4230
Number of HIV-1 diagnoses in study	0	9	
Person-years of follow-up	1269.05	633.41	
HIV-1 incidence per 100 person-years	0.000	1.421	0.272
95% CI	(0.000, 0.291)	(0.650, 2.697)	(0.109, 0.683)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	5.216	
95% CI	(0.000, 0.690)	(1.690, 16.099)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.197)		
Six or more drinks on one occasion: never			
N	708	336	2241
Number of HIV-1 diagnoses in study	0	7	
Person-years of follow-up	625.20	293.32	
HIV-1 incidence per 100 person-years	0.000	2.386	0.190
95% CI	(0.000, 0.590)	(0.959, 4.917)	(0.045, 0.801)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	12.547	
95% CI	(0.000, 2.874)	(2.490, 63.238)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.251)		

Incidence Parameter	SC LEN (N=2134)	F/TDF (N=1068)	bHIV Incidence (N=8094)
Alcohol before or during sex in past 12 weeks: yes			
N	810	430	2536
Number of HIV-1 diagnoses in study	0	9	
Person-years of follow-up	759.31	388.82	
HIV-1 incidence per 100 person-years	0.000	2.315	0.357
95% CI	(0.000, 0.486)	(1.058, 4.394)	(0.130, 0.980)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	6.477	
95% CI	(0.000, 0.922)	(1.946, 21.552)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.202)		
Alcohol before or during sex in past 12 weeks: no			
N	1301	624	4024
Number of HIV-1 diagnoses in study	0	7	
Person-years of follow-up	1157.79	545.31	
HIV-1 incidence per 100 person-years	0.000	1.284	0.166
95% CI	(0.000, 0.319)	(0.516, 2.645)	(0.050, 0.546)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	7.755	
95% CI	(0.000, 1.475)	(1.902, 31.618)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.252)		

Source: Table 20 of the CSR.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990).
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals for rate ratios versus bHIV incidence are based on a Wald test (Gao et al. 2021) or a likelihood ratio test if there were 0 infections (Shao and Gao 2024) .
Confidence intervals for rate ratios versus F/TDF are from a Poisson model or an exact conditional Poisson model if there were 0 infections.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1 or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; CSR, clinical study report; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; NA, not available; SC, subcutaneous; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

16.2. Additional Subgroup Analyses for Primary and Key Secondary Efficacy Endpoint, PURPOSE 2

This section supplements the analyses and interpretation presented in Section 6.2.2.4.4. Of note, the sample sizes for many subgroups were small, which limits the ability to detect trends with certainty. Numerous subgroup analyses were conducted without any adjustment for the multiple analyses, which could result in spurious findings due to chance.

Analyses were conducted to assess the treatment effect for subgroups defined by various demographic factors and clinical characteristics at baseline. Two participants in the LEN group had incident HIV-1 infection. The treatment effect was generally consistent across analyzed subgroups.

Table 84. HIV-1 Incidence by Subgroup in the LEN vs. F/TDF Groups and the bHIV Incidence, Full Analysis Set and All Screened Set, PURPOSE 2

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Age (years): 16 to ≤25			
N	750	343	1564
Number of HIV-1 diagnoses in study	2	6	
Person-years of follow-up	606.07	274.77	
HIV-1 incidence per 100 person-years	0.330	2.184	3.011
95% CI	(0.040, 1.192)	(0.801, 4.753)	(1.804, 5.026)
Rate ratio (randomized study drug groups over bHIV incidence)	0.110	0.725	
95% CI	(0.025, 0.480)	(0.280, 1.875)	
Rate ratio (SC LEN over F/TDF)	0.151		
95% CI	(0.031, 0.749)		
Age (years): >25 to <35			
N	912	423	1852
Number of HIV-1 diagnoses in study	0	1	
Person-years of follow-up	821.46	380.47	
HIV-1 incidence per 100 person-years	0.000	0.263	2.680
95% CI	(0.000, 0.449)	(0.007, 1.464)	(1.607, 4.470)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.098	
95% CI	(0.000, 0.093)	(0.013, 0.743)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 8.800)		
Age (years): ≥35			
N	517	320	1218
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	510.54	311.30	
HIV-1 incidence per 100 person-years	0.000	0.642	1.105
95% CI	(0.000, 0.723)	(0.078, 2.321)	(0.411, 2.972)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.582	
95% CI	(0.000, 0.454)	(0.106, 3.193)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 2.117)		
Race: Black			
N	816	425	1991
Number of HIV-1 diagnoses in study	2	6	
Person-years of follow-up	802.10	405.46	
HIV-1 incidence per 100 person-years	0.249	1.480	3.254
95% CI	(0.030, 0.901)	(0.543, 3.221)	(2.004, 5.285)
Rate ratio (randomized study drug groups over bHIV incidence)	0.077	0.455	
95% CI	(0.018, 0.333)	(0.178, 1.159)	
Rate ratio (SC LEN over F/TDF)	0.169		
95% CI	(0.034, 0.835)		

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Race: Non-Black			
N	1355	659	2630
Number of HIV-1 diagnoses in study	0	3	
Person-years of follow-up	1129.30	558.61	
HIV-1 incidence per 100 person-years	0.000	0.537	1.784
95% CI	(0.000, 0.327)	(0.111, 1.569)	(1.066, 2.986)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.301	
95% CI	(0.000, 0.102)	(0.087, 1.044)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.848)		
Gender identity: CGM			
N	1693	844	3585
Number of HIV-1 diagnoses in study	1	6	
Person-years of follow-up	1469.60	734.18	
HIV-1 incidence per 100 person-years	0.068	0.817	2.310
95% CI	(0.002, 0.379)	(0.300, 1.779)	(1.535, 3.478)
Rate ratio (randomized study drug groups over bHIV incidence)	0.029	0.354	
95% CI	(0.004, 0.218)	(0.144, 0.869)	
Rate ratio (SC LEN over F/TDF)	0.083		
95% CI	(0.010, 0.692)		
Gender identity: TGW			
N	315	161	731
Number of HIV-1 diagnoses in study	1	1	
Person-years of follow-up	293.67	150.03	
HIV-1 incidence per 100 person-years	0.341	0.667	2.747
95% CI	(0.009, 1.897)	(0.017, 3.714)	(1.240, 6.085)
Rate ratio (randomized study drug groups over bHIV incidence)	0.124	0.243	
95% CI	(0.015, 1.028)	(0.029, 2.011)	
Rate ratio (SC LEN over F/TDF)	0.511		
95% CI	(0.032, 8.168)		
Gender identity: TGM			
N	29	14	53
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	27.84	14.30	
HIV-1 incidence per 100 person-years	0.000	0.000	NA
95% CI	(0.000, 13.252)	(0.000, 25.802)	
Rate ratio (randomized study drug groups over bHIV incidence)	NA	NA	
95% CI	NA	NA	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Gender identity: GNB			
N	136	63	252
Number of HIV-1 diagnoses in study	0	2[a]	
Person-years of follow-up	139.19	64.21	
HIV-1 incidence per 100 person-years	0.000	3.115	2.864
95% CI	(0.000, 2.650)	(0.377, 11.251)	(0.838, 9.783)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	1.088	
95% CI	(0.000, 0.734)	(0.171, 6.931)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.602)		
Ethnicity: Hispanic			
N	1376	673	2822
Number of HIV-1 diagnoses in study	0	3	
Person-years of follow-up	1184.24	583.35	
HIV-1 incidence per 100 person-years	0.000	0.514	1.908
95% CI	(0.000, 0.311)	(0.106, 1.503)	(1.106, 3.290)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.270	
95% CI	(0.000, 0.092)	(0.077, 0.946)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 0.845)		
Ethnicity: Non-Hispanic			
N	802	413	1811
Number of HIV-1 diagnoses in study	2	6	
Person-years of follow-up	752.83	383.20	
HIV-1 incidence per 100 person-years	0.266	1.566	3.184
95% CI	(0.032, 0.960)	(0.575, 3.408)	(1.971, 5.143)
Rate ratio (randomized study drug groups over bHIV incidence)	0.083	0.492	
95% CI	(0.019, 0.362)	(0.193, 1.250)	
Rate ratio (SC LEN over F/TDF)	0.170		
95% CI	(0.034, 0.841)		
Country: South Africa			
N	244	112	685
Number of HIV-1 diagnoses in study	2	5	
Person-years of follow-up	235.55	107.77	
HIV-1 incidence per 100 person-years	0.849	4.640	5.371
95% CI	(0.103, 3.067)	(1.506, 10.827)	(2.676, 10.779)
Rate ratio (randomized study drug groups over bHIV incidence)	0.158	0.864	
95% CI	(0.034, 0.746)	(0.282, 2.647)	
Rate ratio (SC LEN over F/TDF)	0.183		
95% CI	(0.036, 0.943)		

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Country: Mexico			
N	8	4	25
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	4.04	2.00	
HIV-1 incidence per 100 person-years	0.000	0.000	NA
95% CI	(0.000, 91.285)	(0.000, 184.318)	
Rate ratio (randomized study drug groups over bHIV incidence)	NA	NA	
95% CI	NA	NA	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		
Country: United States			
N	440	234	927
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	505.98	274.67	
HIV-1 incidence per 100 person-years	0.000	0.728	1.394
95% CI	(0.000, 0.729)	(0.088, 2.630)	(0.533, 3.643)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.522	
95% CI	(0.000, 0.345)	(0.097, 2.821)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.885)		
Country: Peru			
N	309	138	594
Number of HIV-1 diagnoses in study	0	1	
Person-years of follow-up	179.45	81.04	
HIV-1 incidence per 100 person-years	0.000	1.234	2.653
95% CI	(0.000, 2.056)	(0.031, 6.875)	(1.074, 6.554)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.465	
95% CI	(0.000, 0.498)	(0.054, 4.028)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 8.581)		
Country: Thailand			
N	250	139	486
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	158.89	89.29	
HIV-1 incidence per 100 person-years	0.000	0.000	2.349
95% CI	(0.000, 2.322)	(0.000, 4.131)	(0.950, 5.808)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.000	
95% CI	(0.000, 0.635)	(0.000, 1.130)	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Country: Argentina			
N	161	64	284
Number of HIV-1 diagnoses in study	0	0	
Person-years of follow-up	119.09	46.22	
HIV-1 incidence per 100 person-years	0.000	0.000	2.810
95% CI	(0.000, 3.098)	(0.000, 7.981)	(0.853, 9.261)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.000	
95% CI	(0.000, 0.831)	(0.000, 2.141)	
Rate ratio (SC LEN over F/TDF)	NA		
95% CI	NA		
Country: Brazil			
N	767	395	1633
Number of HIV-1 diagnoses in study	0	1	
Person-years of follow-up	735.06	365.55	
HIV-1 incidence per 100 person-years	0.000	0.274	1.861
95% CI	(0.000, 0.502)	(0.007, 1.524)	(0.919, 3.769)
Rate ratio (randomized study drug groups over bHIV incidence)	0.000	0.147	
95% CI	(0.000, 0.160)	(0.018, 1.180)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 9.449)		
Highest level of education: <Some college or university degree			
N	1074	510	2257
Number of HIV-1 diagnoses in study	2	7	
Person-years of follow-up	931.75	448.05	
HIV-1 Incidence per 100 person-years	0.215	1.562	1.810
95% CI	(0.026, 0.775)	(0.628, 3.219)	(1.003, 3.269)
Rate ratio (randomized group over bHIV)	0.119	0.863	
95% CI	(0.026, 0.535)	(0.335, 2.226)	
Rate ratio (SC LEN over F/TDF)	0.137		
95% CI	(0.029, 0.661)		

Incidence Parameter	SC LEN (N=2179)	F/TDF (N=1086)	bHIV Incidence (N=4634)
Highest level of education: Some college or university degree			
N	1104	574	2168
Number of HIV-1 diagnoses in study	0	2	
Person-years of follow-up	1006.24	517.30	
HIV-1 incidence per 100 person-years	0.000	0.387	1.927
95% CI	(0.000, 0.367)	(0.047, 1.397)	(1.134, 3.273)
Rate ratio (randomized group over bHIV)	0.000	0.201	
95% CI	(0.000, 0.106)	(0.046, 0.885)	
Rate ratio (SC LEN over F/TDF)	0.000		
95% CI	(0.000, 1.785)		

Source: Table 14 of the CSR.
[a] Both participants were assigned male at birth.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990) .
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals for rate ratios versus bHIV incidence used the delta method (Gao et al. 2021) or a likelihood-based method if there were 0 infections (Shao and Gao 2024).
Confidence intervals for rate ratios versus F/TDF are from a Poisson model or an exact conditional Poisson model if there were 0 infections.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1 or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CGM, cisgender men; CI, confidence interval; CSR, clinical study report; GNB, gender nonbinary people; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; NA, not available; SC, subcutaneous; TGM, transgender men; TGW, transgender women; F/TDF, emtricitabine/tenofovir disoproxil fumarate.

16.3. Sensitivity Analysis of the Primary and Key Secondary Endpoints

SAHPRA inspected site 24838 (same site with site ID 11413 for PURPOSE 1) for PURPOSE 2 and identified the following issues:

- Inadequate care of participants (delay/lack of STI treatment for two participants)
- Lack of investigational product (IP) management

SAHPRA recommended excluding data of the identified site from the efficacy analyses. We conducted sensitivity analyses by excluding site 11413 from PURPOSE 1 and site 24838 from PURPOSE 2. The results are shown below in Table 85, Table 86, Table 87, and Table 88 from these sensitivity analyses we have the following conclusions:

- For PURPOSE 1, removing data from site 11413 does not change the conclusion. The p-values of the comparisons between LEN group to either bHIV incidence or F/TDF was still <0.0001, which is still less than the pre-specified alpha level of the IA (0.0026).
- For PURPOSE 2, after removing data from site 24838, the p-values of the comparisons between LEN group to bHIV incidence was still <0.0001. However, when we compared the rate ratio of LEN group to the F/TDF group, the p-value is increased to 0.00435 which was larger than the pre-specified alpha level of the IA (0.0026).

We evaluated the potential impact of the IP events at Site 24838 provided by the Applicant (the inadequate care of participants would not be expected to impact the efficacy results). Based on

the facts that the primary endpoint was an objective measure (a virologic test that was confirmed at the central laboratory) and that the identified IP issues did not occur in participants who developed incident HIV-1 infections, we think it is unlikely that these events would have appreciably impacted the efficacy data. Consequently, we will still consider the original overall analyses as the primary efficacy analysis to support the approval.

Table 85. Statistical Comparisons of the HIV-1 Incidence in the LEN Group vs. the bHIV Incidence, Full Analysis Set and All Screened Set Removing Site 11413, PURPOSE 1

HIV Incidence	SC LEN (N=1983)	bHIV Incidence (N=7605)
Number of diagnoses of HIV-1		
In study	0	—
On randomized study drug	0	—
On open-label oral PrEP	0	—
Off study drug PrEP	0	—
HIV-1 incidence in study		
Person-years of follow-up	1777.67	—
HIV-1 incidence per 100 person-years	0.000	2.502
95% CI	(0.000, 0.208)	(1.880, 3.330)
Rate ratio (SC LEN over bHIV incidence)	0.000	—
95% CI	(0.000, 0.044)	—
One-sided *P* value for rate ratio ≥1 (H_{01})	<0.0001	—
One-sided *P* value for rate ratio ≥0.8 (H_{02})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990).
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals/*P* values for rate ratios versus bHIV incidence are based on a Wald test (Gao et al. 2021) or a likelihood ratio test if there were 0 infections (Shao and Gao 2024).
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

Table 86. Statistical Comparisons of the HIV-1 Incidences in the LEN vs. F/TDF Groups, Full Analysis Set Removing Site 11413, PURPOSE 1

Incidence Parameter	SC LEN (N=1983)	F/TDF (N=1009)
Number of diagnoses of HIV-1		
In study	0	14
On randomized study drug	0	12
On open-label oral PrEP	0	0
Off study drug PrEP	0	2

Incidence Parameter	SC LEN (N=1983)	F/TDF (N=1009)
HIV-1 incidence in study		
Person-years of follow-up	1777.67	886.54
HIV-1 incidence per 100 person-years	0.000	1.579
95% CI	(0.000, 0.208)	(0.863, 2.650)
Rate difference (SC LEN minus F/TDF)	−1.579	—
95% CI	(−2.650, −0.834)	—
One-sided *P* value for rate difference ≥0.8/100 PY (H_{05})	<0.0001	—
Rate ratio (SC LEN over F/TDF)	0.000	—
95% CI	(0.000, 0.119)	—
One-sided *P* value for rate ratio ≥1 (H_{06})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CIs for HIV-1 incidence in the randomized study drug groups are based on a method appropriate for single Poisson rates (Ulm 1990).
Exact CIs/*P* values for rate differences versus F/TDF are based on a hybrid approach (Li et al. 2011).
Confidence intervals/*P* values for rate ratio versus F/TDF are from a Poisson model or an exact conditional Poisson model if there were 0 infections.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1 or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person-years; SC, subcutaneous.

Table 87. Statistical Comparisons of the HIV-1 Incidence in the LEN Group vs. the bHIV Incidence, Full Analysis Set and All Screened Set Removing Site 24838, PURPOSE 2

Incidence Parameter	SC LEN (N=2138)	bHIV Incidence (N=4509)
Number of diagnoses of HIV-1		
In study	2	—
On randomized study drug	2	—
On open-label oral PrEP	0	—
Off study drug PrEP	0	—
HIV-1 incidence in study		
Person-years of follow-up	1893.17	—
HIV-1 incidence per 100 person-years	0.111	2.165
95% CI	(0.013, 0.382)	(1.474, 3.182)
Rate ratio (SC LEN over bHIV incidence)	0.049	—
95% CI	(0.012, 0.206)	—
One-sided *P* value for rate ratio ≥1 (H_{01})	<0.0001	—
One-sided *P* value for rate ratio ≥0.8 (H_{02})	<0.0001	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CI for HIV-1 incidence in the randomized study drug group is based on a method appropriate for single Poisson rates (Ulm 1990).
Confidence intervals for bHIV incidence are based on (Gao et al. 2021).
Confidence intervals/*P* values for rate ratios versus bHIV incidence used the delta method (Gao et al. 2021).
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: bHIV, background HIV-1; CI, confidence interval; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

Table 88. Statistical Comparisons of the HIV-1 Incidences in the LEN vs. F/TDF Groups, Full Analysis Set Removing Site 24838, PURPOSE 2

Incidence Parameter	SC LEN (N=2138)	F/TDF (N=1073)
Number of diagnoses of HIV-1		
In study	2	8
On randomized study drug	2	5
On open-label oral PrEP	0	0
Off study drug PrEP	0	3

Incidence Parameter	SC LEN (N=2138)	F/TDF (N=1073)
HIV-1 incidence in study		
Person-years of follow-up	1893.17	951.54
HIV-1 incidence per 100 person-years	0.111	0.841
95% CI	(0.013, 0.382)	(0.363, 1.657)
Rate difference (SC LEN minus F/TDF)	−0.735	—
95% CI	(−1.556, −0.183)	—
One-sided *P* value for rate difference ≥0.8/100 PY (H_{03})	<0.0001	—
Rate ratio (SC LEN over F/TDF)	0.126	—
95% CI	(0.013, 0.630)	—
One-sided *P* value for rate ratio ≥1 (H_{04})	0.00435	—

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
Exact CI for HIV-1 incidence in the randomized study drug group is based on a method appropriate for single Poisson rates (Ulm 1990).
Exact CI/*P* value for rate difference versus F/TDF are based on a hybrid approach (Li et al. 2011). Confidence interval/*P* value for rate ratio versus F/TDF are from a Poisson model.
Person-year is the sum of all participants' total number of years (1 year =365.25 days) of follow-up in the study between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date (either rapid, central, or other local laboratory tests, including follow-up visits) for participants without HIV-1.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person-years; SC, subcutaneous.

16.4. Incidence Rate Estimation Using the Screening Phase Data

To assess the robustness of the bHIV estimates, we could calculate bHIV estimates using several different approaches. Based on the result from ECHO Trial Consortium, the overall HIV incidence was estimated to be 3.81 per 100 person years (95% CI: 3.45–4.21).

For both PURPOSE trials, some HIV-1 infections occurred between the screening visit and the randomization visit. We utilized the data collected during this short period of time to estimate the incidence rates.

For PURPOSE 1, there were 8 infections and the total PY of follow-up was 288.8. The estimated incidence rate was 2.771 per 100 PY with 95% CI of (1.196, 5.459).

For PURPOSE 2, there were 9 infections and the total person year of follow-up was 199.42. The estimated incidence rate was 4.513 per 100 PY with 95% CI of (1.732, 7.905).

Please note that this estimate could be biased because only participants who were diagnosed with HIV-1 (with diagnosis dates available) and participants who were randomized (with randomization date available) were included. The duration was calculated as date of randomization (or date of diagnosis of HIV-1 infection for those who were infected) – date of screening +1. Therefore, only participants who were in the randomization population or had a recorded HIV-1 infection occurred before the randomization were included the analysis. Therefore, the analysis population is only a subset of the screening population, and the estimated incidence rate may not reflect the true rate.

Table 89. HIV-1 Incidence Rates Estimated Between Screening and Randomization, PURPOSE 1 and PURPOSE 2

Study	Number of Participants Evaluated	Number of Diagnoses of HIV-1	Person-Years of Follow-Up	HIV-1 Incidence Per 100 Person-Years	95% CI
PURPOSE 1	5370	8[a]	288.756	2.771	(1.196, 5.459)
PURPOSE 2	3294	9[b]	199.420	4.513	(1.732, 7.905)

Source: Reviewer's analysis using adsl.xpt and adtte.xpt.
[a] This includes 7 participants who were diagnosed on Day 1 of the RBP Phase and 1 participant who did not enter the RBP Phase of the study.
[b] This includes 6 participants who were diagnosed on Day 1 of the RBP Phase and 3 participants who either did not enter the RBP Phase of the study or did not receive treatment.

This approach alleviated some of the concerns with respect to differences in risk factors between populations in the incidence Phase and randomization Phase mentioned in the efficacy review issue section. However, the follow-up time is short and the number of infections is too small to provide a robust estimate. In addition, there are missing follow-up data for some participants as mentioned above. Thus, currently, we do not have a good method to robustly estimate the bHIV incidence rate.

16.5. Patient-Reported Outcomes

PURPOSE 1 and PURPOSE 2 included exploratory objectives that evaluated the acceptability of LEN injections every 6 months for HIV-1 PrEP in participants at risk of HIV-1. Participant assessments of PrEP impacts and NPRS, administration preference, and administration and dosing (pertaining to injection acceptability) were collected using questionnaires. The Applicant did not seek labeling based on any of the collected patient experience data. Therefore, these data were not reviewed in detail but are briefly summarized here.

PURPOSE 1

- Median self-reported injection pain (NPRS) scores were similar between participants who received LEN or placebo injections. There were no changes from Day 1 injections in median NPRS scores at Week 26 or at Week 52 for all study drug groups.
- At baseline, most participants (67%) preferred an injection. There were no noticeable changes from baseline in preference for pills or injection at Week 26 or Week 52.
- At baseline, most participants in each study drug group felt they would be more protected by an injection (approximately 60%) than a daily pill (approximately 26%) and there were no notable changes from baseline at Week 26 or Week 52.
- At baseline, most participants reported that they would be able to take their PrEP medication without missing a dose by injection every 6 months (approximately 60%) versus a daily pill (approximately 26%) and there were no noticeable changes from baseline at Week 26 or Week 52.

PURPOSE 2

- Median self-reported injection pain (NPRS) scores were similar between participants who received LEN or placebo injection. There were no changes from Day 1 injections in median NPRS scores at Week 26 or at Week 52.

- At baseline, most participants (78%) preferred an injection and there was no noticeable difference between the study drug groups. There were no notable changes from baseline at Week 26 or Week 52.
- At baseline, most participants in each study drug group felt they would be more protected by an injection (approximately 66%) than a daily pill (approximately 12%) and there were no notable changes from baseline at Week 26 or Week 52.
- At baseline, the majority reported that they would be able to take their PrEP medication without missing a dose by injection every 6 months (approximately 76%) versus a daily pill (approximately 10%) and there were no notable changes from baseline at Week 26 or Week 52.

17. Clinical Safety

This section contains supplemental safety analyses not included in Section 7.6 and additional analyses supporting the safety conclusions included in Sections 8.3 and 8.4.

17.1. PURPOSE 1

17.1.1. Serious Adverse Events, PURPOSE 1

Section 7.6.1.3 presents an assessment of SAEs and drug-related SAEs. Below is a complete tabulation of SAEs regardless of causality for PURPOSE 1.

Table 90. Participants with Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Any SAE	59 (2.8)	85 (4.0)	35 (3.3)	-1.2 (-2.3, -0.1) *	-0.5 (-1.9, 0.7)	0.7 (-0.7, 2.0)
Blood and lymphatic system disorders (SOC)	2 (0.1)	1 (0.0)	0	0.0 (-0.2, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Hypochromic anaemia	2 (0.1)	0	0	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Anaemia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Cardiac disorders (SOC)	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Ischaemic cardiomyopathy	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Nonreassuring foetal heart rate pattern	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Eye disorders (SOC)	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Cataract	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Gastrointestinal disorders (SOC)	0	2 (0.1)	3 (0.3)	-0.1 (-0.3, 0.1)	-0.3 (-0.8, -0.1) *	-0.2 (-0.7, 0.1)
Haematemesis	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Peptic ulcer	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Abdominal pain lower	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Gastritis	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Hepatobiliary disorders (SOC)	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Cholelithiasis	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Infections and infestations (SOC)	12 (0.6)	16 (0.7)	3 (0.3)	-0.2 (-0.7, 0.3)	0.3 (-0.3, 0.7)	0.5 (-0.1, 1.0)
Malaria	3 (0.1)	5 (0.2)	0	-0.1 (-0.4, 0.2)	0.1 (-0.2, 0.4)	0.2 (-0.1, 0.5)
Brain empyema	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Gastroenteritis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Helicobacter infection	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Pyelonephritis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Pyelonephritis acute	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Sinusitis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Subcutaneous abscess	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Tonsillitis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Urinary tract infection	1 (0.0)	3 (0.1)	0	-0.1 (-0.4, 0.1)	0.0 (-0.3, 0.3)	0.1 (-0.2, 0.4)
Injection site abscess	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Lower respiratory tract infection	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Pelvic inflammatory disease	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Peritonitis	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Pneumonia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Postoperative wound infection	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Sepsis	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Appendicitis	1 (0.0)	1 (0.0)	1 (0.1)	-0.0 (-0.2, 0.2)	-0.0 (-0.5, 0.2)	-0.0 (-0.5, 0.2)
Hepatitis A	0	1 (0.0)	1 (0.1)	-0.0 (-0.3, 0.1)	-0.1 (-0.5, 0.1)	-0.0 (-0.5, 0.2)
Salpingitis	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Injury, poisoning and procedural complications (SOC)	9 (0.4)	13 (0.6)	5 (0.5)	-0.2 (-0.7, 0.3)	-0.0 (-0.7, 0.4)	0.1 (-0.5, 0.7)
Overdose	3 (0.1)	1 (0.0)	0	0.1 (-0.1, 0.4)	0.1 (-0.2, 0.4)	0.0 (-0.3, 0.3)
Ankle fracture	2 (0.1)	0	0	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Foot fracture	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Limb injury	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Road traffic accident	1 (0.0)	2 (0.1)	0	-0.0 (-0.3, 0.2)	0.0 (-0.3, 0.3)	0.1 (-0.3, 0.3)
Thermal burn	1 (0.0)	1 (0.0)	0	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Eye injury	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Gun shot wound	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Pelvic fracture	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Radius fracture	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Rib fracture	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Stab wound	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Tendon injury	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Tibia fracture	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Toxicity to various agents	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Anaemia postoperative	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Animal bite	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Humerus fracture	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Lower limb fracture	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Investigations (SOC)	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Blood pressure increased	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Ovarian cancer	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Nervous system disorders (SOC)	4 (0.2)	3 (0.1)	1 (0.1)	0.0 (-0.2, 0.4)	0.1 (-0.3, 0.4)	0.0 (-0.4, 0.3)
Syncope	2 (0.1)	1 (0.0)	0	0.0 (-0.2, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Monoparesis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Seizure	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Headache	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Neuromyelitis optica spectrum disorder	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Pregnancy, puerperium and perinatal conditions (SOC)	30 (1.4)	37 (1.7)	17 (1.6)	-0.3 (-1.1, 0.4)	-0.2 (-1.2, 0.7)	0.1 (-0.9, 1.0)
Foetal death	3 (0.1)	0	0	0.1 (-0.0, 0.4)	0.1 (-0.2, 0.4)	0.0 (-0.4, 0.2)
Abortion missed	2 (0.1)	2 (0.1)	0	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.3)	0.1 (-0.3, 0.3)
Abortion spontaneous complete	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Abortion spontaneous incomplete	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Hyperemesis gravidarum	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Polyhydramnios	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Retained products of conception	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Ruptured ectopic pregnancy	1 (0.0)	2 (0.1)	0	-0.0 (-0.3, 0.2)	0.0 (-0.3, 0.3)	0.1 (-0.3, 0.3)
Abortion threatened	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Anembryonic gestation	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Ectopic pregnancy	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Haemorrhage in pregnancy	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Pre-eclampsia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Prolonged labour	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Cephalo-pelvic disproportion	2 (0.1)	1 (0.0)	1 (0.1)	0.0 (-0.2, 0.3)	-0.0 (-0.4, 0.3)	-0.0 (-0.5, 0.2)
Gestational hypertension	2 (0.1)	1 (0.0)	1 (0.1)	0.0 (-0.2, 0.3)	-0.0 (-0.4, 0.3)	-0.0 (-0.5, 0.2)
Foetal distress syndrome	1 (0.0)	0	1 (0.1)	0.0 (-0.1, 0.3)	-0.0 (-0.5, 0.2)	-0.1 (-0.5, 0.1)
Abortion incomplete	0	1 (0.0)	1 (0.1)	-0.0 (-0.3, 0.1)	-0.1 (-0.5, 0.1)	-0.0 (-0.5, 0.2)
Abortion of ectopic pregnancy	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Stillbirth	0	1 (0.0)	1 (0.1)	-0.0 (-0.3, 0.1)	-0.1 (-0.5, 0.1)	-0.0 (-0.5, 0.2)
Abortion spontaneous	15 (0.7)	28 (1.3)	9 (0.8)	-0.6 (-1.3, -0.0) *	-0.1 (-0.9, 0.5)	0.5 (-0.4, 1.2)
Obstructed labour	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Product issues (SOC)	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Device dislocation	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Psychiatric disorders (SOC)	6 (0.3)	8 (0.4)	0	-0.1 (-0.5, 0.3)	0.3 (-0.1, 0.6)	0.4 (0.0, 0.7) *
Intentional self-injury	2 (0.1)	4 (0.2)	0	-0.1 (-0.4, 0.2)	0.1 (-0.3, 0.3)	0.2 (-0.2, 0.5)
Suicide attempt	2 (0.1)	3 (0.1)	0	-0.0 (-0.3, 0.2)	0.1 (-0.3, 0.3)	0.1 (-0.2, 0.4)
Depression	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Psychotic disorder	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Suicidal ideation	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Renal and urinary disorders (SOC)	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Proteinuria	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Reproductive system and breast disorders (SOC)	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Abnormal uterine bleeding	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Threatened uterine rupture	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)	0	2 (0.1)	4 (0.4)	-0.1 (-0.3, 0.1)	-0.4 (-1.0, -0.1) *	-0.3 (-0.9, 0.0)
Asphyxia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Asthma	0	1 (0.0)	4 (0.4)	-0.0 (-0.3, 0.1)	-0.4 (-1.0, -0.1) *	-0.3 (-0.9, -0.0) *
Social circumstances (SOC)	1 (0.0)	2 (0.1)	1 (0.1)	-0.0 (-0.3, 0.2)	-0.0 (-0.5, 0.2)	0.0 (-0.4, 0.3)
Victim of homicide	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Victim of sexual abuse	1 (0.0)	0	1 (0.1)	0.0 (-0.1, 0.3)	-0.0 (-0.5, 0.2)	-0.1 (-0.5, 0.1)
Vascular disorders (SOC)	0	3 (0.1)	0	-0.1 (-0.4, 0.0)	0.0 (-0.4, 0.2)	0.1 (-0.2, 0.4)
Haemorrhage	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Hypertension	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Superficial vein thrombosis	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HL=injection site reactions) began on or after first SC LEN or placebo injection date.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; incl, including; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class.

17.1.2. Adverse Events Leading to Treatment Discontinuation, PURPOSE 1

Section 7.6.1.4 provides an assessment of adverse events leading to treatment discontinuation in PURPOSE 1. Details on LEN participants who experienced AEs leading to discontinuation of creatinine renal clearance decreased and hepatic enzyme increased (each occurring in one participant) are described further below.

Participant (b) (6) experienced Grade 2 Creatinine Renal Clearance Decreased on Study Day 110. The participant's creatinine clearance decreased from 76.2 mL/min on Study Day 1 to 54.6 mL/min on Study Day 110 and is reported as unresolved. The investigators did not assess the AE as related to study drug though did not provide a specific alternative explanation for the deceased creatinine. However, per the narrative, concomitant medications which are found to be temporally related to the time of the event (Study Day 110) include chlorphenamine and hydrocortisone for a dermatologic allergic reaction. The participants creatinine increased from 0.78 mg/dL to 1.02 mg/dL and then returned to 0.83 mg/dL. The clinical review team concludes that it is reasonable for the change in creatinine to not be related to LEN due to the transient nature of the AE and improvement seen in the creatinine measurement despite continued LEN exposure.

Participant (b) (6) experienced Grade 4 Hepatic Enzyme Increased on Study Day 58 reported as resolved on Study Day 122. LEN was withdrawn on Study Day 165. Table 91 below displays the hepatic-related laboratory assessment for the participant. The participant was concomitantly receiving ethinyl estradiol and levonorgestrel from Study Day −20 to Study Day 88. The investigators assessed the hepatic elevations were likely due to the oral contraception medications and not to LEN. The clinical review team agrees with the investigator assessment that this AE leading to discontinuation is not likely related to the use of LEN as resolution was temporally associated with discontinuation of the oral contraceptives and during a period of continued LEN exposure.

Table 91. Hepatic-Related Laboratory Assessments, Participant (b) (6), PURPOSE 1

Day	ALT/AST (U/L)	Bili (mg/dL)	Alk Phos (U/L)	GGT (U/L)
1	28/20	0.4	98	**69**[a]
32	**449/89**	0.6	135	**133**
38	81/17	0.4	**136**	**94**
58	**1004/356**	0.8	106	**142**
65	**1093/344**	0.7	**123**	**142**
80	**1385/651**	1.1	**147**	**146**
87	**1571/614**	**1.9**	**157**	**152**
108	38/18	0.5	**150**	**50**
122	10/16	0.5	115	24

Source: Clinical Reviewer's Analysis, Applicant supplied data, participant narrative.
[a] Numbers in bold indicate abnormal values.
Abbreviations: ALT, alanine aminotransferase; ALK phos, alkaline phosphatase; AST, aspartate aminotransferase; bili, bilirubin; GGT, gamma-glutamyl transferase.

An analysis by OND custom medical query (narrow) of AEs leading to treatment discontinuation did not reveal any additional safety concerns.

17.1.3. Treatment-Emergent Adverse Events, PURPOSE 1

Section 7.6.1.5 presents drug-related TEAEs. Below is a tabulation of TEAEs occurring in at least 0.5% of the participants regardless of causality in any group. Similar to the drug-related TEAEs, ISRs were reported more frequently in LEN recipients, but other TEAEs were either balanced between groups or favored LEN.

Table 92. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.5% of Participants in Any Arm, Safety Population, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Any AE	1893 (88.5)	1779 (83.3)	881 (82.3)	5.1 (3.1, 7.2) *	6.1 (3.5, 8.8) *	1.0 (-1.7, 3.8)
Blood and lymphatic system disorders (SOC)	68 (3.2)	54 (2.5)	43 (4.0)	0.6 (-0.4, 1.7)	-0.8 (-2.3, 0.5)	-1.5 (-3.0, -0.2) *
Anaemia	48 (2.2)	44 (2.1)	36 (3.4)	0.2 (-0.7, 1.1)	-1.1 (-2.5, 0.0)	-1.3 (-2.7, -0.2) *
Eye disorders (SOC)	26 (1.2)	28 (1.3)	16 (1.5)	-0.1 (-0.8, 0.6)	-0.3 (-1.3, 0.5)	-0.2 (-1.2, 0.6)
Conjunctivitis allergic	12 (0.6)	9 (0.4)	6 (0.6)	0.1 (-0.3, 0.6)	-0.0 (-0.7, 0.5)	-0.1 (-0.8, 0.3)
Vision blurred	0	4 (0.2)	3 (0.3)	-0.2 (-0.5, -0.0) *	-0.3 (-0.8, -0.1) *	-0.1 (-0.6, 0.3)
Gastrointestinal disorders (SOC)	492 (23.0)	651 (30.5)	336 (31.4)	-7.5 (-10.1, -4.9) *	-8.4 (-11.7, -5.1) *	-0.9 (-4.3, 2.5)
Peptic ulcer	16 (0.7)	12 (0.6)	5 (0.5)	0.2 (-0.3, 0.7)	0.3 (-0.4, 0.8)	0.1 (-0.6, 0.6)
Diarrhoea	133 (6.2)	161 (7.5)	67 (6.3)	-1.3 (-2.9, 0.2)	-0.0 (-1.9, 1.7)	1.3 (-0.6, 3.1)
Dyspepsia	11 (0.5)	10 (0.5)	6 (0.6)	0.0 (-0.4, 0.5)	-0.0 (-0.7, 0.5)	-0.1 (-0.8, 0.4)
Gastritis	51 (2.4)	60 (2.8)	27 (2.5)	-0.4 (-1.4, 0.5)	-0.1 (-1.4, 0.9)	0.3 (-1.0, 1.4)
Abdominal distension	1 (0.0)	10 (0.5)	3 (0.3)	-0.4 (-0.8, -0.1) *	-0.2 (-0.8, 0.0)	0.2 (-0.4, 0.6)
Abdominal pain	45 (2.1)	61 (2.9)	25 (2.3)	-0.8 (-1.7, 0.2)	-0.2 (-1.4, 0.8)	0.5 (-0.7, 1.6)
Abdominal pain lower	25 (1.2)	30 (1.4)	15 (1.4)	-0.2 (-0.9, 0.5)	-0.2 (-1.2, 0.5)	0.0 (-1.0, 0.8)
Abdominal pain upper	17 (0.8)	22 (1.0)	11 (1.0)	-0.2 (-0.8, 0.3)	-0.2 (-1.1, 0.4)	0.0 (-0.9, 0.7)
Abdominal wall pain	0	1 (0.0)	3 (0.3)	-0.0 (-0.3, 0.1)	-0.3 (-0.8, -0.1) *	-0.2 (-0.8, 0.0)
Gingival pain	1 (0.0)	8 (0.4)	4 (0.4)	-0.3 (-0.7, -0.1) *	-0.3 (-0.9, -0.0) *	0.0 (-0.6, 0.4)
Constipation	12 (0.6)	24 (1.1)	11 (1.0)	-0.6 (-1.2, -0.0) *	-0.5 (-1.3, 0.1)	0.1 (-0.8, 0.8)
Toothache	23 (1.1)	27 (1.3)	18 (1.7)	-0.2 (-0.9, 0.5)	-0.6 (-1.6, 0.2)	-0.4 (-1.5, 0.4)
Vomiting	125 (5.8)	235 (11.0)	107 (10.0)	-5.2 (-6.8, -3.5) *	-4.2 (-6.3, -2.2) *	1.0 (-1.3, 3.2)
Nausea	144 (6.7)	234 (11.0)	142 (13.3)	-4.2 (-5.9, -2.5) *	-6.5 (-8.9, -4.3) *	-2.3 (-4.8, 0.1)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)	1503 (70.2)	835 (39.1)	410 (38.3)	31.1 (28.3, 33.9) *	31.9 (28.4, 35.4) *	0.8 (-2.8, 4.3)
Injection site nodule	1365 (63.8)	347 (16.3)	183 (17.1)	47.5 (44.9, 50.1) *	46.7 (43.6, 49.6) *	-0.8 (-3.7, 1.8)
Injection site pain	669 (31.3)	521 (24.4)	237 (22.1)	6.9 (4.2, 9.5) *	9.1 (5.9, 12.2) *	2.3 (-0.9, 5.3)
Injection site induration	91 (4.3)	22 (1.0)	10 (0.9)	3.2 (2.3, 4.2) *	3.3 (2.3, 4.4) *	0.1 (-0.8, 0.8)
Injection site pruritus	50 (2.3)	25 (1.2)	13 (1.2)	1.2 (0.4, 2.0) *	1.1 (0.1, 2.0) *	-0.0 (-1.0, 0.7)
Injection site discolouration	22 (1.0)	8 (0.4)	1 (0.1)	0.7 (0.2, 1.2) *	0.9 (0.4, 1.5) *	0.3 (-0.2, 0.7)
Injection site erythema	24 (1.1)	29 (1.4)	11 (1.0)	-0.2 (-0.9, 0.4)	0.1 (-0.8, 0.8)	0.3 (-0.6, 1.1)
Pyrexia	24 (1.1)	22 (1.0)	13 (1.2)	0.1 (-0.5, 0.7)	-0.1 (-1.0, 0.7)	-0.2 (-1.1, 0.5)
Influenza like illness	74 (3.5)	68 (3.2)	39 (3.6)	0.3 (-0.8, 1.4)	-0.2 (-1.7, 1.1)	-0.5 (-1.9, 0.8)
Injection site swelling	96 (4.5)	121 (5.7)	50 (4.7)	-1.2 (-2.5, 0.1)	-0.2 (-1.8, 1.3)	1.0 (-0.7, 2.5)
Fatigue	31 (1.4)	33 (1.5)	19 (1.8)	-0.1 (-0.8, 0.6)	-0.3 (-1.4, 0.5)	-0.2 (-1.3, 0.7)
Malaise	7 (0.3)	5 (0.2)	7 (0.7)	0.1 (-0.3, 0.5)	-0.3 (-1.0, 0.1)	-0.4 (-1.1, 0.0)
Asthenia	4 (0.2)	8 (0.4)	7 (0.7)	-0.2 (-0.6, 0.2)	-0.5 (-1.2, -0.0) *	-0.3 (-1.0, 0.2)
Infections and infestations (SOC)	1191 (55.7)	1171 (54.8)	578 (54.0)	0.8 (-2.2, 3.8)	1.6 (-2.0, 5.3)	0.8 (-2.8, 4.5)
Genitourinary chlamydia infection	300 (14.0)	317 (14.8)	129 (12.1)	-0.8 (-2.9, 1.3)	2.0 (-0.6, 4.3)	2.8 (0.3, 5.2) *
Upper respiratory tract infection	271 (12.7)	274 (12.8)	121 (11.3)	-0.2 (-2.2, 1.8)	1.4 (-1.1, 3.7)	1.5 (-0.9, 3.8)
Malaria	61 (2.9)	71 (3.3)	21 (2.0)	-0.5 (-1.5, 0.6)	0.9 (-0.3, 1.9)	1.4 (0.2, 2.5) *
Syphilis	45 (2.1)	48 (2.2)	15 (1.4)	-0.1 (-1.0, 0.7)	0.7 (-0.3, 1.6)	0.8 (-0.2, 1.8)
Lower respiratory tract infection	30 (1.4)	16 (0.7)	9 (0.8)	0.7 (0.0, 1.3) *	0.6 (-0.3, 1.3)	-0.1 (-0.9, 0.5)
Vulvovaginal candidiasis	146 (6.8)	172 (8.1)	67 (6.3)	-1.2 (-2.8, 0.3)	0.6 (-1.3, 2.3)	1.8 (-0.1, 3.6)
Nasopharyngitis	43 (2.0)	55 (2.6)	16 (1.5)	-0.6 (-1.5, 0.3)	0.5 (-0.5, 1.4)	1.1 (0.0, 2.0) *
Gynaecological chlamydia infection	26 (1.2)	19 (0.9)	8 (0.7)	0.3 (-0.3, 1.0)	0.5 (-0.3, 1.1)	0.1 (-0.6, 0.8)
Genitourinary tract gonococcal infection	141 (6.6)	157 (7.4)	66 (6.2)	-0.8 (-2.3, 0.8)	0.4 (-1.5, 2.1)	1.2 (-0.7, 2.9)
Influenza	65 (3.0)	55 (2.6)	28 (2.6)	0.5 (-0.5, 1.5)	0.4 (-0.9, 1.6)	-0.0 (-1.3, 1.1)
Body tinea	18 (0.8)	22 (1.0)	5 (0.5)	-0.2 (-0.8, 0.4)	0.4 (-0.3, 0.9)	0.6 (-0.1, 1.2)
Urogenital trichomoniasis	38 (1.8)	45 (2.1)	15 (1.4)	-0.3 (-1.2, 0.5)	0.4 (-0.6, 1.2)	0.7 (-0.3, 1.6)
Viral upper respiratory tract infection	14 (0.7)	7 (0.3)	3 (0.3)	0.3 (-0.1, 0.8)	0.4 (-0.2, 0.9)	0.0 (-0.5, 0.4)
Bacterial vaginosis	14 (0.7)	11 (0.5)	4 (0.4)	0.1 (-0.3, 0.6)	0.3 (-0.3, 0.8)	0.1 (-0.5, 0.6)
Pharyngitis	12 (0.6)	10 (0.5)	4 (0.4)	0.1 (-0.4, 0.6)	0.2 (-0.4, 0.7)	0.1 (-0.5, 0.6)
Cystitis	11 (0.5)	7 (0.3)	4 (0.4)	0.2 (-0.2, 0.6)	0.1 (-0.5, 0.6)	-0.0 (-0.7, 0.4)
Bacteraemia	2 (0.1)	9 (0.4)	0	-0.3 (-0.7, -0.0) *	0.1 (-0.3, 0.3)	0.4 (0.1, 0.8) *
Respiratory tract infection	10 (0.5)	14 (0.7)	4 (0.4)	-0.2 (-0.7, 0.3)	0.1 (-0.5, 0.6)	0.3 (-0.3, 0.8)
Tinea versicolour	20 (0.9)	14 (0.7)	9 (0.8)	0.3 (-0.3, 0.9)	0.1 (-0.7, 0.7)	-0.2 (-1.0, 0.4)
Typhoid fever	12 (0.6)	18 (0.8)	5 (0.5)	-0.3 (-0.8, 0.2)	0.1 (-0.6, 0.6)	0.4 (-0.3, 0.9)
Helicobacter infection	19 (0.9)	28 (1.3)	9 (0.8)	-0.4 (-1.1, 0.2)	0.0 (-0.8, 0.7)	0.5 (-0.4, 1.2)
Tonsillitis	35 (1.6)	29 (1.4)	17 (1.6)	0.3 (-0.5, 1.0)	0.0 (-1.0, 0.9)	-0.2 (-1.3, 0.6)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Latent syphilis	18 (0.8)	9 (0.4)	9 (0.8)	0.4 (-0.1, 0.9)	-0.0 (-0.8, 0.6)	-0.4 (-1.2, 0.1)
Gonococcal infection	2 (0.1)	0	2 (0.2)	0.1 (-0.1, 0.3)	-0.1 (-0.6, 0.2)	-0.2 (-0.7, -0.0) *
Subcutaneous abscess	12 (0.6)	15 (0.7)	7 (0.7)	-0.1 (-0.7, 0.4)	-0.1 (-0.8, 0.4)	0.0 (-0.7, 0.6)
Mastitis	1 (0.0)	0	2 (0.2)	0.0 (-0.1, 0.3)	-0.1 (-0.6, 0.1)	-0.2 (-0.7, -0.0) *
Rhinitis	9 (0.4)	10 (0.5)	6 (0.6)	-0.0 (-0.5, 0.4)	-0.1 (-0.8, 0.3)	-0.1 (-0.8, 0.4)
Abdominal wall abscess	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Vulvovaginal mycotic infection	0	2 (0.1)	2 (0.2)	-0.1 (-0.3, 0.1)	-0.2 (-0.7, -0.0) *	-0.1 (-0.6, 0.2)
Conjunctivitis	15 (0.7)	14 (0.7)	10 (0.9)	0.0 (-0.5, 0.6)	-0.2 (-1.1, 0.4)	-0.3 (-1.1, 0.3)
Trichomoniasis	52 (2.4)	73 (3.4)	29 (2.7)	-1.0 (-2.0, 0.0)	-0.3 (-1.6, 0.8)	0.7 (-0.6, 1.9)
Viral infection	2 (0.1)	1 (0.0)	4 (0.4)	0.0 (-0.2, 0.3)	-0.3 (-0.9, 0.0)	-0.3 (-0.9, -0.0) *
Vulvovaginitis gonococcal	18 (0.8)	20 (0.9)	12 (1.1)	-0.1 (-0.7, 0.5)	-0.3 (-1.2, 0.4)	-0.2 (-1.1, 0.5)
Vulvovaginitis chlamydial	40 (1.9)	39 (1.8)	24 (2.2)	0.0 (-0.8, 0.9)	-0.4 (-1.6, 0.6)	-0.4 (-1.6, 0.6)
Pelvic inflammatory disease	35 (1.6)	39 (1.8)	22 (2.1)	-0.2 (-1.0, 0.6)	-0.4 (-1.6, 0.5)	-0.2 (-1.4, 0.7)
Vulvovaginitis	9 (0.4)	21 (1.0)	9 (0.8)	-0.6 (-1.1, -0.1) *	-0.4 (-1.2, 0.1)	0.1 (-0.7, 0.8)
Vaginitis chlamydial	23 (1.1)	23 (1.1)	17 (1.6)	-0.0 (-0.6, 0.6)	-0.5 (-1.5, 0.3)	-0.5 (-1.5, 0.3)
Gastroenteritis	50 (2.3)	70 (3.3)	31 (2.9)	-0.9 (-2.0, 0.0)	-0.6 (-1.9, 0.6)	0.4 (-1.0, 1.6)
Urinary tract infection	307 (14.3)	305 (14.3)	163 (15.2)	0.1 (-2.0, 2.2)	-0.9 (-3.6, 1.7)	-0.9 (-3.6, 1.6)
Vulvovaginitis trichomonal	34 (1.6)	26 (1.2)	27 (2.5)	0.4 (-0.3, 1.1)	-0.9 (-2.1, 0.1)	-1.3 (-2.5, -0.3) *
Injury, poisoning and procedural complications (SOC)	84 (3.9)	91 (4.3)	38 (3.6)	-0.3 (-1.5, 0.9)	0.4 (-1.1, 1.7)	0.7 (-0.8, 2.1)
Human bite	2 (0.1)	0	3 (0.3)	0.1 (-0.1, 0.3)	-0.2 (-0.7, 0.1)	-0.3 (-0.8, -0.1) *
Humerus fracture	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Lower limb fracture	0	0	3 (0.3)	0.0 (-0.2, 0.2)	-0.3 (-0.8, -0.1) *	-0.3 (-0.8, -0.1) *
Skin abrasion	0	6 (0.3)	3 (0.3)	-0.3 (-0.6, -0.1) *	-0.3 (-0.8, -0.1) *	0.0 (-0.6, 0.4)
Soft tissue injury	12 (0.6)	12 (0.6)	9 (0.8)	-0.0 (-0.5, 0.5)	-0.3 (-1.1, 0.3)	-0.3 (-1.1, 0.3)
Investigations (SOC)	88 (4.1)	83 (3.9)	37 (3.5)	0.2 (-1.0, 1.4)	0.7 (-0.8, 2.0)	0.4 (-1.0, 1.7)
Creatinine renal clearance decreased	17 (0.8)	15 (0.7)	4 (0.4)	0.1 (-0.4, 0.6)	0.4 (-0.2, 1.0)	0.3 (-0.3, 0.8)
Blood creatine phosphokinase increased	6 (0.3)	9 (0.4)	0	-0.1 (-0.6, 0.2)	0.3 (-0.1, 0.6)	0.4 (0.1, 0.8) *
Weight increased	17 (0.8)	16 (0.7)	6 (0.6)	0.0 (-0.5, 0.6)	0.2 (-0.5, 0.8)	0.2 (-0.5, 0.8)
Blood pressure increased	9 (0.4)	14 (0.7)	3 (0.3)	-0.2 (-0.7, 0.2)	0.1 (-0.4, 0.6)	0.4 (-0.2, 0.9)
Alanine aminotransferase increased	5 (0.2)	0	2 (0.2)	0.2 (0.1, 0.5) *	0.0 (-0.5, 0.4)	-0.2 (-0.7, -0.0) *
Weight decreased	10 (0.5)	6 (0.3)	7 (0.7)	0.2 (-0.2, 0.6)	-0.2 (-0.9, 0.3)	-0.4 (-1.1, 0.1)
Metabolism and nutrition disorders (SOC)	78 (3.6)	92 (4.3)	47 (4.4)	-0.7 (-1.9, 0.5)	-0.7 (-2.3, 0.6)	-0.1 (-1.7, 1.4)
Abnormal loss of weight	18 (0.8)	7 (0.3)	8 (0.7)	0.5 (0.1, 1.0) *	0.1 (-0.7, 0.7)	-0.4 (-1.2, 0.1)
Increased appetite	14 (0.7)	24 (1.1)	7 (0.7)	-0.5 (-1.1, 0.1)	-0.0 (-0.7, 0.6)	0.5 (-0.3, 1.1)
Decreased appetite	27 (1.3)	48 (2.2)	28 (2.6)	-1.0 (-1.8, -0.2) *	-1.4 (-2.6, -0.4) *	-0.4 (-1.6, 0.7)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	87 (4.1)	71 (3.3)	41 (3.8)	0.7 (-0.4, 1.9)	0.2 (-1.3, 1.6)	-0.5 (-2.0, 0.8)
Back pain	44 (2.1)	25 (1.2)	16 (1.5)	0.9 (0.1, 1.7) *	0.6 (-0.5, 1.5)	-0.3 (-1.3, 0.5)
Myalgia	11 (0.5)	3 (0.1)	1 (0.1)	0.4 (0.0, 0.8) *	0.4 (-0.0, 0.8)	0.0 (-0.4, 0.3)
Arthralgia	12 (0.6)	13 (0.6)	6 (0.6)	-0.0 (-0.5, 0.4)	-0.0 (-0.7, 0.5)	0.0 (-0.7, 0.6)
Flank pain	3 (0.1)	0	2 (0.2)	0.1 (-0.0, 0.4)	-0.0 (-0.5, 0.3)	-0.2 (-0.7, -0.0) *
Costochondritis	2 (0.1)	0	3 (0.3)	0.1 (-0.1, 0.3)	-0.2 (-0.7, 0.1)	-0.3 (-0.8, -0.1) *
Muscle spasms	3 (0.1)	5 (0.2)	6 (0.6)	-0.1 (-0.4, 0.2)	-0.4 (-1.1, -0.0) *	-0.3 (-1.0, 0.1)
Nervous system disorders (SOC)	378 (17.7)	450 (21.1)	220 (20.6)	-3.4 (-5.8, -1.0) *	-2.9 (-5.9, -0.0) *	0.5 (-2.5, 3.4)
Headache	285 (13.3)	352 (16.5)	155 (14.5)	-3.2 (-5.3, -1.0) *	-1.2 (-3.8, 1.3)	2.0 (-0.7, 4.6)
Dizziness	120 (5.6)	141 (6.6)	79 (7.4)	-1.0 (-2.4, 0.4)	-1.8 (-3.7, -0.0) *	-0.8 (-2.8, 1.0)
Pregnancy, puerperium and perinatal conditions (SOC)	40 (1.9)	50 (2.3)	22 (2.1)	-0.5 (-1.4, 0.4)	-0.2 (-1.3, 0.8)	0.3 (-0.9, 1.3)
Abortion spontaneous	15 (0.7)	28 (1.3)	9 (0.8)	-0.6 (-1.3, -0.0) *	-0.1 (-0.9, 0.5)	0.5 (-0.4, 1.2)
Obstructed labour	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Morning sickness	2 (0.1)	4 (0.2)	6 (0.6)	-0.1 (-0.4, 0.2)	-0.5 (-1.1, -0.1) *	-0.4 (-1.0, 0.0)
Psychiatric disorders (SOC)	31 (1.4)	35 (1.6)	15 (1.4)	-0.2 (-1.0, 0.6)	0.0 (-0.9, 0.9)	0.2 (-0.8, 1.1)
Nightmare	5 (0.2)	2 (0.1)	5 (0.5)	0.1 (-0.1, 0.5)	-0.2 (-0.9, 0.2)	-0.4 (-1.0, -0.0) *
Insomnia	3 (0.1)	13 (0.6)	6 (0.6)	-0.5 (-0.9, -0.1) *	-0.4 (-1.1, -0.0) *	0.0 (-0.7, 0.6)
Renal and urinary disorders (SOC)	36 (1.7)	31 (1.5)	21 (2.0)	0.2 (-0.5, 1.0)	-0.3 (-1.4, 0.7)	-0.5 (-1.6, 0.4)
Dysuria	22 (1.0)	20 (0.9)	14 (1.3)	0.1 (-0.5, 0.7)	-0.3 (-1.2, 0.5)	-0.4 (-1.3, 0.4)
Reproductive system and breast disorders (SOC)	391 (18.3)	401 (18.8)	210 (19.6)	-0.5 (-2.8, 1.8)	-1.4 (-4.3, 1.5)	-0.8 (-3.8, 2.0)
Vaginal haemorrhage	17 (0.8)	17 (0.8)	3 (0.3)	-0.0 (-0.6, 0.6)	0.5 (-0.1, 1.0)	0.5 (-0.1, 1.0)
Vulvovaginal pruritus	23 (1.1)	25 (1.2)	7 (0.7)	-0.1 (-0.8, 0.6)	0.4 (-0.3, 1.1)	0.5 (-0.3, 1.2)
Menometrorrhagia	17 (0.8)	9 (0.4)	6 (0.6)	0.4 (-0.1, 0.9)	0.2 (-0.5, 0.8)	-0.1 (-0.8, 0.3)
Intermenstrual bleeding	26 (1.2)	27 (1.3)	14 (1.3)	-0.0 (-0.7, 0.6)	-0.1 (-1.0, 0.7)	-0.0 (-1.0, 0.7)
Adnexa uteri cyst	0	0	2 (0.2)	0.0 (-0.2, 0.2)	-0.2 (-0.7, -0.0) *	-0.2 (-0.7, -0.0) *
Vaginal discharge	166 (7.8)	191 (8.9)	87 (8.1)	-1.2 (-2.9, 0.5)	-0.4 (-2.5, 1.6)	0.8 (-1.3, 2.8)
Dysmenorrhoea	24 (1.1)	28 (1.3)	17 (1.6)	-0.2 (-0.9, 0.5)	-0.5 (-1.5, 0.3)	-0.3 (-1.3, 0.6)
Heavy menstrual bleeding	65 (3.0)	78 (3.7)	38 (3.6)	-0.6 (-1.7, 0.5)	-0.5 (-2.0, 0.7)	0.1 (-1.4, 1.4)
Abnormal uterine bleeding	70 (3.3)	60 (2.8)	45 (4.2)	0.5 (-0.6, 1.5)	-0.9 (-2.5, 0.4)	-1.4 (-2.9, -0.1) *

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)	76 (3.6)	79 (3.7)	41 (3.8)	-0.1 (-1.3, 1.0)	-0.3 (-1.8, 1.0)	-0.1 (-1.6, 1.2)
Oropharyngeal pain	13 (0.6)	18 (0.8)	5 (0.5)	-0.2 (-0.8, 0.3)	0.1 (-0.5, 0.7)	0.4 (-0.3, 0.9)
Cough	31 (1.4)	27 (1.3)	17 (1.6)	0.2 (-0.5, 0.9)	-0.1 (-1.2, 0.7)	-0.3 (-1.3, 0.5)
Nasal congestion	9 (0.4)	9 (0.4)	6 (0.6)	-0.0 (-0.4, 0.4)	-0.1 (-0.8, 0.3)	-0.1 (-0.8, 0.3)
Rhinitis allergic	8 (0.4)	9 (0.4)	7 (0.7)	-0.0 (-0.5, 0.4)	-0.3 (-1.0, 0.2)	-0.2 (-1.0, 0.3)
Skin and subcutaneous tissue disorders (SOC)	130 (6.1)	119 (5.6)	56 (5.2)	0.5 (-0.9, 1.9)	0.8 (-0.9, 2.5)	0.3 (-1.4, 1.9)
Rash pruritic	14 (0.7)	4 (0.2)	3 (0.3)	0.5 (0.1, 0.9) *	0.4 (-0.2, 0.9)	-0.1 (-0.6, 0.3)
Dermatitis	11 (0.5)	10 (0.5)	4 (0.4)	0.0 (-0.4, 0.5)	0.1 (-0.5, 0.6)	0.1 (-0.5, 0.6)
Pruritus	13 (0.6)	20 (0.9)	6 (0.6)	-0.3 (-0.9, 0.2)	0.0 (-0.7, 0.6)	0.4 (-0.3, 1.0)
Rash	34 (1.6)	33 (1.5)	21 (2.0)	0.0 (-0.7, 0.8)	-0.4 (-1.5, 0.5)	-0.4 (-1.5, 0.5)
Urticaria	6 (0.3)	2 (0.1)	8 (0.7)	0.2 (-0.1, 0.5)	-0.5 (-1.2, 0.0)	-0.7 (-1.4, -0.2) *

Source: [Data Scientist] adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class

With the OND custom medical query where like terms were combined, no additional safety signals were identified for LEN which are not already captured in labeling. Please see Table 93 below.

Table 93. Participants With Adverse Events by System Organ Class and OND Custom Medical Query (Narrow), Safety Population, PURPOSE 1

System Organ Class OCMQ (Narrow)	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)						
Anemia	66 (3.1)	61 (2.9)	45 (4.2)	0.2 (-0.8, 1.3)	-1.1 (-2.6, 0.2)	-1.3 (-2.9, -0.0) *
Cardiac disorders (SOC)						
Systemic hypertension	19 (0.9)	23 (1.1)	7 (0.7)	-0.2 (-0.8, 0.4)	0.2 (-0.5, 0.8)	0.4 (-0.3, 1.1)
Arrhythmia	4 (0.2)	2 (0.1)	0	0.1 (-0.2, 0.4)	0.2 (-0.2, 0.5)	0.1 (-0.3, 0.3)
Palpitations	3 (0.1)	5 (0.2)	1 (0.1)	-0.1 (-0.4, 0.2)	0.0 (-0.4, 0.3)	0.1 (-0.3, 0.5)
Myocardial ischemia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Tachycardia	2 (0.1)	3 (0.1)	1 (0.1)	-0.0 (-0.3, 0.2)	-0.0 (-0.4, 0.3)	0.0 (-0.4, 0.3)

System Organ Class OCMQ (Narrow)	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Ear and labyrinth disorders (SOC)						
Vertigo	1 (0.0)	1 (0.0)	1 (0.1)	-0.0 (-0.2, 0.2)	-0.0 (-0.5, 0.2)	-0.0 (-0.5, 0.2)
Endocrine disorders (SOC)						
Hypoglycemia	4 (0.2)	1 (0.0)	0	0.1 (-0.1, 0.4)	0.2 (-0.2, 0.5)	0.0 (-0.3, 0.3)
Hyperglycemia	6 (0.3)	7 (0.3)	5 (0.5)	-0.0 (-0.4, 0.3)	-0.2 (-0.8, 0.2)	-0.1 (-0.8, 0.3)
Gastrointestinal disorders (SOC)						
Dry mouth	0	2 (0.1)	0	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Diarrhea	135 (6.3)	164 (7.7)	68 (6.4)	-1.4 (-2.9, 0.2)	-0.0 (-1.9, 1.7)	1.3 (-0.6, 3.1)
Dyspepsia	28 (1.3)	32 (1.5)	15 (1.4)	-0.2 (-0.9, 0.5)	-0.1 (-1.1, 0.7)	0.1 (-0.9, 0.9)
Constipation	12 (0.6)	24 (1.1)	11 (1.0)	-0.6 (-1.2, -0.0) *	-0.5 (-1.3, 0.1)	0.1 (-0.8, 0.8)
Abdominal pain	89 (4.2)	114 (5.3)	52 (4.9)	-1.2 (-2.5, 0.1)	-0.7 (-2.3, 0.8)	0.5 (-1.2, 2.0)
Vomiting	127 (5.9)	236 (11.1)	107 (10.0)	-5.1 (-6.8, -3.5) *	-4.1 (-6.2, -2.1) *	1.1 (-1.3, 3.2)
Nausea	144 (6.7)	234 (11.0)	142 (13.3)	-4.2 (-5.9, -2.5) *	-6.5 (-8.9, -4.3) *	-2.3 (-4.8, 0.1)
General disorders and administration site conditions (SOC)						
Local administration reaction	1473 (68.8)	754 (35.3)	365 (34.1)	33.5 (30.7, 36.3) *	34.7 (31.2, 38.1) *	1.2 (-2.3, 4.7)
Volume depletion	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Fall	0	0	1 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Peripheral edema	4 (0.2)	3 (0.1)	3 (0.3)	0.0 (-0.2, 0.4)	-0.1 (-0.6, 0.3)	-0.1 (-0.7, 0.2)
Pyrexia	24 (1.1)	22 (1.0)	13 (1.2)	0.1 (-0.5, 0.7)	-0.1 (-1.0, 0.7)	-0.2 (-1.1, 0.5)
Fatigue	42 (2.0)	45 (2.1)	33 (3.1)	-0.1 (-1.0, 0.7)	-1.1 (-2.4, -0.0) *	-1.0 (-2.3, 0.1)
Decreased appetite	27 (1.3)	48 (2.2)	28 (2.6)	-1.0 (-1.8, -0.2) *	-1.4 (-2.6, -0.4) *	-0.4 (-1.6, 0.7)
Dizziness	123 (5.7)	143 (6.7)	80 (7.5)	-1.0 (-2.4, 0.5)	-1.7 (-3.7, 0.1)	-0.8 (-2.8, 1.1)
Hepatobiliary disorders (SOC)						
Hepatic injury	5 (0.2)	2 (0.1)	6 (0.6)	0.1 (-0.1, 0.5)	-0.3 (-1.0, 0.1)	-0.5 (-1.1, -0.1) *
Immune system disorders (SOC)						
Hypersensitivity	6 (0.3)	6 (0.3)	0	-0.0 (-0.4, 0.4)	0.3 (-0.1, 0.6)	0.3 (-0.1, 0.6)
Angioedema	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Infections and infestations (SOC)						
Bacterial infection	837 (39.1)	837 (39.2)	392 (36.6)	-0.1 (-3.0, 2.8)	2.5 (-1.1, 6.0)	2.6 (-1.0, 6.1)
Nasopharyngitis	328 (15.3)	329 (15.4)	148 (13.8)	-0.1 (-2.2, 2.1)	1.5 (-1.1, 4.0)	1.6 (-1.1, 4.1)
Viral infection	100 (4.7)	85 (4.0)	40 (3.7)	0.7 (-0.5, 1.9)	0.9 (-0.6, 2.3)	0.2 (-1.3, 1.6)
Purulent material	44 (2.1)	36 (1.7)	15 (1.4)	0.4 (-0.5, 1.2)	0.7 (-0.4, 1.6)	0.3 (-0.7, 1.1)
Fungal infection	191 (8.9)	220 (10.3)	90 (8.4)	-1.4 (-3.2, 0.4)	0.5 (-1.6, 2.5)	1.9 (-0.3, 3.9)
Pneumonia	3 (0.1)	4 (0.2)	0	-0.0 (-0.4, 0.2)	0.1 (-0.2, 0.4)	0.2 (-0.2, 0.5)

System Organ Class OCMQ (Narrow)	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Metabolism and nutrition disorders (SOC)						
Lipid disorder	10 (0.5)	7 (0.3)	2 (0.2)	0.1 (-0.3, 0.6)	0.3 (-0.2, 0.7)	0.1 (-0.4, 0.5)
Cachexia	18 (0.8)	7 (0.3)	8 (0.7)	0.5 (0.1, 1.0) *	0.1 (-0.7, 0.7)	-0.4 (-1.2, 0.1)
Musculoskeletal and connective tissue disorders (SOC)						
Back pain	47 (2.2)	25 (1.2)	18 (1.7)	1.0 (0.3, 1.8) *	0.5 (-0.6, 1.5)	-0.5 (-1.5, 0.3)
Myalgia	11 (0.5)	3 (0.1)	1 (0.1)	0.4 (0.0, 0.8) *	0.4 (-0.0, 0.8)	0.0 (-0.4, 0.3)
Rhabdomyolysis	2 (0.1)	0	0	0.1 (-0.1, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Arthritis	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Tendinopathy	0	3 (0.1)	0	-0.1 (-0.4, 0.0)	0.0 (-0.4, 0.2)	0.1 (-0.2, 0.4)
Arthralgia	12 (0.6)	13 (0.6)	6 (0.6)	-0.0 (-0.5, 0.4)	-0.0 (-0.7, 0.5)	0.0 (-0.7, 0.6)
Fracture	5 (0.2)	5 (0.2)	5 (0.5)	-0.0 (-0.3, 0.3)	-0.2 (-0.9, 0.2)	-0.2 (-0.9, 0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)						
Malignancy	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Nervous system disorders (SOC)						
Syncope	5 (0.2)	4 (0.2)	1 (0.1)	0.0 (-0.3, 0.4)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.4)
Seizure	2 (0.1)	2 (0.1)	0	-0.0 (-0.3, 0.3)	0.1 (-0.3, 0.3)	0.1 (-0.3, 0.3)
Somnolence	7 (0.3)	10 (0.5)	3 (0.3)	-0.1 (-0.6, 0.3)	0.0 (-0.5, 0.4)	0.2 (-0.4, 0.6)
Tremor	1 (0.0)	1 (0.0)	0	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Dysgeusia	0	1 (0.0)	1 (0.1)	-0.0 (-0.3, 0.1)	-0.1 (-0.5, 0.1)	-0.0 (-0.5, 0.2)
Paresthesia	8 (0.4)	11 (0.5)	5 (0.5)	-0.1 (-0.6, 0.3)	-0.1 (-0.7, 0.4)	0.0 (-0.6, 0.5)
Headache	288 (13.5)	357 (16.7)	158 (14.8)	-3.3 (-5.4, -1.1) *	-1.3 (-3.9, 1.2)	2.0 (-0.8, 4.6)
Psychiatric disorders (SOC)						
Self-harm	6 (0.3)	8 (0.4)	0	-0.1 (-0.5, 0.3)	0.3 (-0.1, 0.6)	0.4 (0.0, 0.7) *
Depression	6 (0.3)	8 (0.4)	1 (0.1)	-0.1 (-0.5, 0.3)	0.2 (-0.3, 0.5)	0.3 (-0.2, 0.7)
Study agent abuse potential	7 (0.3)	7 (0.3)	2 (0.2)	-0.0 (-0.4, 0.4)	0.1 (-0.4, 0.5)	0.1 (-0.4, 0.5)
Anxiety	4 (0.2)	2 (0.1)	1 (0.1)	0.1 (-0.2, 0.4)	0.1 (-0.3, 0.4)	0.0 (-0.4, 0.3)
Psychosis	2 (0.1)	1 (0.0)	0	0.0 (-0.2, 0.3)	0.1 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Irritability	1 (0.0)	0	0	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Parasomnia	7 (0.3)	4 (0.2)	6 (0.6)	0.1 (-0.2, 0.5)	-0.2 (-0.9, 0.2)	-0.4 (-1.0, 0.0)
Insomnia	3 (0.1)	13 (0.6)	6 (0.6)	-0.5 (-0.9, -0.1) *	-0.4 (-1.1, -0.0) *	0.0 (-0.7, 0.6)
Renal and urinary disorders (SOC)						
Renal & urinary tract infection	465 (21.7)	470 (22.0)	232 (21.7)	-0.3 (-2.8, 2.2)	0.0 (-3.0, 3.0)	0.3 (-2.8, 3.3)
Urinary retention	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Acute kidney injury	1 (0.0)	0	1 (0.1)	0.0 (-0.1, 0.3)	-0.0 (-0.5, 0.2)	-0.1 (-0.5, 0.1)

System Organ Class OCMQ (Narrow)	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Reproductive system and breast disorders (SOC)						
Decreased menstrual bleeding	11 (0.5)	13 (0.6)	4 (0.4)	-0.1 (-0.6, 0.4)	0.1 (-0.5, 0.6)	0.2 (-0.4, 0.7)
Sexual dysfunction	6 (0.3)	5 (0.2)	2 (0.2)	0.0 (-0.3, 0.4)	0.1 (-0.4, 0.5)	0.0 (-0.5, 0.4)
Amenorrhea	9 (0.4)	7 (0.3)	4 (0.4)	0.1 (-0.3, 0.5)	0.0 (-0.6, 0.5)	-0.0 (-0.7, 0.4)
Bacterial vaginosis	86 (4.0)	85 (4.0)	50 (4.7)	0.0 (-1.1, 1.2)	-0.7 (-2.3, 0.8)	-0.7 (-2.3, 0.8)
Abnormal uterine bleeding	191 (8.9)	192 (9.0)	106 (9.9)	-0.1 (-1.8, 1.6)	-1.0 (-3.2, 1.1)	-0.9 (-3.2, 1.2)
Excessive menstrual bleeding	150 (7.0)	143 (6.7)	89 (8.3)	0.3 (-1.2, 1.8)	-1.3 (-3.4, 0.6)	-1.6 (-3.7, 0.3)
Respiratory, thoracic and mediastinal disorders (SOC)						
Dyspnea	3 (0.1)	1 (0.0)	0	0.1 (-0.1, 0.4)	0.1 (-0.2, 0.4)	0.0 (-0.3, 0.3)
Respiratory failure	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Cough	32 (1.5)	28 (1.3)	18 (1.7)	0.2 (-0.5, 0.9)	-0.2 (-1.2, 0.7)	-0.4 (-1.4, 0.5)
Bronchospasm	2 (0.1)	3 (0.1)	4 (0.4)	-0.0 (-0.3, 0.2)	-0.3 (-0.9, 0.0)	-0.2 (-0.8, 0.1)
Skin and subcutaneous tissue disorders (SOC)						
Pruritus	100 (4.7)	74 (3.5)	30 (2.8)	1.2 (0.0, 2.4) *	1.9 (0.5, 3.2) *	0.7 (-0.7, 1.9)
Rash	103 (4.8)	88 (4.1)	48 (4.5)	0.7 (-0.6, 1.9)	0.3 (-1.3, 1.8)	-0.4 (-2.0, 1.1)
Erythema	25 (1.2)	31 (1.5)	12 (1.1)	-0.3 (-1.0, 0.4)	0.0 (-0.9, 0.8)	0.3 (-0.6, 1.1)
Alopecia	0	1 (0.0)	0	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Urticaria	7 (0.3)	2 (0.1)	8 (0.7)	0.2 (-0.1, 0.6)	-0.4 (-1.2, 0.1)	-0.7 (-1.4, -0.2) *
Vascular disorders (SOC)						
Hemorrhage	86 (4.0)	78 (3.7)	37 (3.5)	0.4 (-0.8, 1.5)	0.6 (-0.9, 1.9)	0.2 (-1.3, 1.5)
Hypotension	3 (0.1)	1 (0.0)	1 (0.1)	0.1 (-0.1, 0.4)	0.0 (-0.4, 0.3)	-0.0 (-0.5, 0.2)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific preferred terms under each OCMQ, see the table “Adverse Events by System Organ Class, OND custom medical query (narrow) and Preferred Term…”
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table. See the table “Patients With Adverse Events by Preferred Term Not Captured in OND custom medical query (Narrow)…”
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; incl, including; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND custom medical query; PT, preferred term; SC, subcutaneous; SOC, system organ class.

17.1.4. Laboratory Findings, PURPOSE 1

Section 7.6.1.6 provides an assessment of laboratory findings in PURPOSE 1. The proportion of participants in each group with laboratory abnormalities in chemistry, hematology, and kidney function as outliers are shown in Table 94, Table 95, and Table 96 below. The only imbalance among the multiple comparisons that did not favor LEN over F/TDF was ALT elevations. A total of 39/2140 (1.8%) LEN recipients versus 9/1070 (0.9%) F/TDF recipients had incident ALT >3× upper limit of normal (ULN). However, as discussed further in Section 7.6.1.7, these elevations were transient, improved while on LEN, and often had plausible alternative etiologies. Furthermore, ALT and AST measurements did not increase over time in the LEN group overall (see Figure 51 and Figure 52 below).

Table 94. Participants With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, PURPOSE 1

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Sodium, low (mEq/L)						
Level 1 (<132)	3/2127 (0.1)	4/2118 (0.2)	2/1058 (0.2)	-0.0 (-0.4, 0.2)	-0.0 (-0.6, 0.3)	-0.0 (-0.5, 0.3)
Level 2 (<130)	1/2127 (0.0)	1/2118 (0.0)	1/1058 (0.1)	-0.0 (-0.2, 0.2)	-0.0 (-0.5, 0.2)	-0.0 (-0.5, 0.2)
Level 3 (<125)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Sodium, high (mEq/L)						
Level 1 (>150)	0/2127 (0)	1/2118 (0.0)	0/1058 (0)	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Level 2 (>155)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (>160)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Potassium, low (mEq/L)						
Level 1 (<3.6)	147/2127 (6.9)	155/2118 (7.3)	84/1058 (7.9)	-0.4 (-2.0, 1.1)	-1.0 (-3.1, 0.9)	-0.6 (-2.7, 1.3)
Level 2 (<3.4)	37/2127 (1.7)	30/2118 (1.4)	12/1058 (1.1)	0.3 (-0.4, 1.1)	0.6 (-0.3, 1.4)	0.3 (-0.6, 1.1)
Level 3 (<3)	1/2127 (0.0)	1/2118 (0.0)	0/1058 (0)	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.3)	0.0 (-0.3, 0.3)
Potassium, high (mEq/L)						
Level 1 (>5.5)	19/2127 (0.9)	19/2118 (0.9)	11/1058 (1.0)	-0.0 (-0.6, 0.6)	-0.1 (-1.0, 0.5)	-0.1 (-1.0, 0.5)
Level 2 (>6)	3/2127 (0.1)	6/2118 (0.3)	4/1058 (0.4)	-0.1 (-0.5, 0.2)	-0.2 (-0.8, 0.1)	-0.1 (-0.7, 0.3)
Level 3 (>6.5)	0/2127 (0)	3/2118 (0.1)	1/1058 (0.1)	-0.1 (-0.4, 0.0)	-0.1 (-0.5, 0.1)	0.0 (-0.4, 0.3)
Chloride, low (mEq/L)						
Level 1 (<95)	1/2127 (0.0)	3/2118 (0.1)	1/1058 (0.1)	-0.1 (-0.4, 0.1)	-0.0 (-0.5, 0.2)	0.0 (-0.4, 0.3)
Level 2 (<88)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (<80)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Chloride, high (mEq/L)						
Level 1 (>108)	294/2127 (13.8)	271/2118 (12.8)	156/1058 (14.7)	1.0 (-1.0, 3.1)	-0.9 (-3.6, 1.6)	-1.9 (-4.6, 0.6)
Level 2 (>112)	4/2127 (0.2)	5/2118 (0.2)	1/1058 (0.1)	-0.0 (-0.4, 0.3)	0.1 (-0.4, 0.4)	0.1 (-0.3, 0.5)
Level 3 (>115)	0/2127 (0)	1/2118 (0.0)	0/1058 (0)	-0.0 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.0 (-0.3, 0.3)
Bicarbonate, low (mEq/L)						
Level 1 (<20)	1518/2127 (71.4)	1528/2118 (72.1)	749/1058 (70.8)	-0.8 (-3.5, 1.9)	0.6 (-2.7, 4.0)	1.3 (-2.0, 4.7)
Level 2 (<18)	624/2127 (29.3)	597/2118 (28.2)	292/1058 (27.6)	1.2 (-1.6, 3.9)	1.7 (-1.6, 5.0)	0.6 (-2.8, 3.9)
Level 3 (<15)	38/2127 (1.8)	25/2118 (1.2)	10/1058 (0.9)	0.6 (-0.1, 1.4)	0.8 (-0.1, 1.6)	0.2 (-0.6, 0.9)
Bicarbonate, high (mEq/L)						
Level 3 (>30)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Glucose, low (mg/dL)						
Level 1 (<70)	613/2127 (28.8)	591/2118 (27.9)	312/1058 (29.5)	0.9 (-1.8, 3.6)	-0.7 (-4.1, 2.6)	-1.6 (-5.0, 1.7)
Level 2 (<54)	58/2127 (2.7)	72/2118 (3.4)	38/1058 (3.6)	-0.7 (-1.7, 0.4)	-0.9 (-2.3, 0.4)	-0.2 (-1.7, 1.1)
Level 3 (<40)	1/2127 (0.0)	1/2118 (0.0)	1/1058 (0.1)	-0.0 (-0.2, 0.2)	-0.0 (-0.5, 0.2)	-0.0 (-0.5, 0.2)
Glucose, fasting, high (mg/dL)						
Level 1 (≥100 to 125)	205/2025 (10.1)	192/2018 (9.5)	97/1011 (9.6)	0.6 (-1.2, 2.5)	0.5 (-1.8, 2.7)	-0.1 (-2.4, 2.1)
Level 2 (≥126)	29/2025 (1.4)	35/2018 (1.7)	15/1011 (1.5)	-0.3 (-1.1, 0.5)	-0.1 (-1.1, 0.8)	0.3 (-0.8, 1.1)
Glucose, random, high (mg/dL)						
Level 2 (≥200)	1/1886 (0.1)	1/1863 (0.1)	2/911 (0.2)	-0.0 (-0.3, 0.3)	-0.2 (-0.7, 0.1)	-0.2 (-0.7, 0.1)
Level 3 (>250)	0/1886 (0)	1/1863 (0.1)	0/911 (0)	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.4, 0.3)
Calcium, low (mg/dL)						
Level 1 (<8.4)	25/2127 (1.2)	31/2118 (1.5)	19/1058 (1.8)	-0.3 (-1.0, 0.4)	-0.6 (-1.7, 0.2)	-0.3 (-1.4, 0.6)
Level 2 (<8)	9/2127 (0.4)	14/2118 (0.7)	11/1058 (1.0)	-0.2 (-0.7, 0.2)	-0.6 (-1.5, -0.0) *	-0.4 (-1.2, 0.3)
Level 3 (<7.5)	6/2127 (0.3)	8/2118 (0.4)	4/1058 (0.4)	-0.1 (-0.5, 0.3)	-0.1 (-0.7, 0.3)	-0.0 (-0.6, 0.4)
Calcium, high (mg/dL)						
Level 1 (>10.5)	63/2127 (3.0)	46/2118 (2.2)	33/1058 (3.1)	0.8 (-0.2, 1.8)	-0.2 (-1.5, 1.1)	-0.9 (-2.3, 0.2)
Level 2 (>11)	2/2127 (0.1)	4/2118 (0.2)	2/1058 (0.2)	-0.1 (-0.4, 0.2)	-0.1 (-0.6, 0.2)	-0.0 (-0.5, 0.3)
Level 3 (>12)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Magnesium, low (mg/dL)						
Level 1 (<1.5)	22/2127 (1.0)	26/2118 (1.2)	14/1058 (1.3)	-0.2 (-0.9, 0.5)	-0.3 (-1.2, 0.5)	-0.1 (-1.1, 0.7)
Level 2 (<1.2)	7/2127 (0.3)	8/2118 (0.4)	5/1058 (0.5)	-0.0 (-0.5, 0.3)	-0.1 (-0.8, 0.3)	-0.1 (-0.8, 0.4)
Level 3 (<0.9)	4/2127 (0.2)	4/2118 (0.2)	1/1058 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.4, 0.4)	0.1 (-0.4, 0.4)
Magnesium, high (mg/dL)						
Level 1 (>2.3)	436/2127 (20.5)	382/2118 (18.0)	229/1058 (21.6)	2.5 (0.1, 4.8) *	-1.1 (-4.2, 1.8)	-3.6 (-6.6, -0.7) *
Level 2 (>4)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (>7)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Phosphate, low (mg/dL)						
Level 1 (<2.5)	267/2127 (12.6)	310/2118 (14.6)	114/1058 (10.8)	-2.1 (-4.2, -0.0) *	1.8 (-0.6, 4.1)	3.9 (1.4, 6.2) *
Level 2 (<2)	29/2127 (1.4)	33/2118 (1.6)	11/1058 (1.0)	-0.2 (-0.9, 0.5)	0.3 (-0.6, 1.1)	0.5 (-0.4, 1.3)
Level 3 (<1.4)	1/2127 (0.0)	1/2118 (0.0)	1/1058 (0.1)	-0.0 (-0.2, 0.2)	-0.0 (-0.5, 0.2)	-0.0 (-0.5, 0.2)
Protein, total, low (g/dL)						
Level 1 (<6)	9/2127 (0.4)	10/2118 (0.5)	2/1058 (0.2)	-0.0 (-0.5, 0.4)	0.2 (-0.3, 0.6)	0.3 (-0.2, 0.7)
Level 2 (<5.4)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (<5)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Albumin, low (g/dL)						
Level 1 (<3.1)	4/2127 (0.2)	1/2118 (0.0)	1/1058 (0.1)	0.1 (-0.1, 0.4)	0.1 (-0.4, 0.4)	-0.0 (-0.5, 0.2)
Level 2 (<2.5)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (<2)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
CPK, high (U/L)						
Level 1 (>3× ULN)	120/2127 (5.6)	130/2118 (6.1)	70/1058 (6.6)	-0.5 (-1.9, 0.9)	-1.0 (-2.9, 0.7)	-0.5 (-2.4, 1.3)
Level 2 (>5× ULN)	62/2127 (2.9)	53/2118 (2.5)	28/1058 (2.6)	0.4 (-0.6, 1.4)	0.3 (-1.0, 1.4)	-0.1 (-1.4, 1.0)
Level 3 (>10× ULN)	29/2127 (1.4)	25/2118 (1.2)	12/1058 (1.1)	0.2 (-0.5, 0.9)	0.2 (-0.7, 1.0)	0.0 (-0.9, 0.8)
Lipase, high (U/L)						
Level 1 (>1.1× ULN)	13/2127 (0.6)	12/2118 (0.6)	4/1058 (0.4)	0.0 (-0.4, 0.5)	0.2 (-0.4, 0.7)	0.2 (-0.4, 0.7)
Level 2 (>1.5× ULN)	5/2127 (0.2)	7/2118 (0.3)	1/1058 (0.1)	-0.1 (-0.5, 0.3)	0.1 (-0.3, 0.5)	0.2 (-0.2, 0.6)
Level 3 (>3× ULN)	2/2127 (0.1)	0/2118 (0)	1/1058 (0.1)	0.1 (-0.1, 0.3)	-0.0 (-0.4, 0.3)	-0.1 (-0.5, 0.1)

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	3/2127 (0.1)	1/2118 (0.0)	1/1058 (0.1)	0.1 (-0.1, 0.4)	0.0 (-0.4, 0.3)	-0.0 (-0.5, 0.2)
Level 2 (>27)	1/2127 (0.0)	0/2118 (0)	0/1058 (0)	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)
Level 3 (>31)	1/2127 (0.0)	0/2118 (0)	0/1058 (0)	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)

Source: [Data Scientist] adlb.xpt; Software: R.
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; N_w, number of participants with data; ULN, upper limit of normal.

Table 95. Participants With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 1

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Complete blood count						
WBC, low (10^3 cells/µL)						
Level 1 (<3.5)	366/2128 (17.2)	443/2118 (20.9)	221/1058 (20.9)	-3.7 (-6.1, -1.4) *	-3.7 (-6.7, -0.8) *	0.0 (-3.0, 3.0)
Level 2 (<3)	134/2128 (6.3)	162/2118 (7.6)	79/1058 (7.5)	-1.4 (-2.9, 0.2)	-1.2 (-3.2, 0.6)	0.2 (-1.9, 2.1)
Level 3 (<1)	0/2128 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
WBC, high (10^3 cells/µL)						
Level 1 (>10.8)	100/2128 (4.7)	98/2118 (4.6)	37/1058 (3.5)	0.1 (-1.2, 1.4)	1.2 (-0.3, 2.6)	1.1 (-0.4, 2.5)
Level 2 (>13)	24/2128 (1.1)	17/2118 (0.8)	6/1058 (0.6)	0.3 (-0.3, 1.0)	0.6 (-0.2, 1.2)	0.2 (-0.5, 0.8)
Level 3 (>15)	4/2128 (0.2)	5/2118 (0.2)	3/1058 (0.3)	-0.0 (-0.4, 0.3)	-0.1 (-0.7, 0.3)	-0.0 (-0.6, 0.3)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 g/dL dec. from baseline)	292/2128 (13.7)	278/2118 (13.1)	149/1058 (14.1)	0.6 (-1.5, 2.7)	-0.4 (-3.0, 2.1)	-1.0 (-3.6, 1.5)
Level 3 (>2 g/dL dec. from baseline)	145/2128 (6.8)	120/2118 (5.7)	70/1058 (6.6)	1.1 (-0.3, 2.6)	0.2 (-1.7, 2.0)	-1.0 (-2.8, 0.8)

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Hemoglobin, high (g/dL)						
Level 2 (>2 g/dL inc. from baseline)	137/2128 (6.4)	137/2118 (6.5)	52/1058 (4.9)	-0.0 (-1.5, 1.5)	1.5 (-0.2, 3.1)	1.6 (-0.2, 3.2)
Level 3 (>3 g/dL inc. from baseline)	46/2128 (2.2)	28/2118 (1.3)	13/1058 (1.2)	0.8 (0.1, 1.7) *	0.9 (-0.1, 1.8)	0.1 (-0.9, 0.9)
Platelets, low (10^3 cells/μL)						
Level 1 (<140)	23/2128 (1.1)	33/2118 (1.6)	18/1057 (1.7)	-0.5 (-1.2, 0.2)	-0.6 (-1.7, 0.2)	-0.1 (-1.2, 0.7)
Level 2 (<125)	12/2128 (0.6)	17/2118 (0.8)	8/1057 (0.8)	-0.2 (-0.8, 0.3)	-0.2 (-1.0, 0.4)	0.0 (-0.7, 0.7)
Level 3 (<100)	5/2128 (0.2)	4/2118 (0.2)	3/1057 (0.3)	0.0 (-0.3, 0.4)	-0.0 (-0.6, 0.3)	-0.1 (-0.7, 0.3)
WBC differential						
Lymphocytes, low (10^3 cells/μL)						
Level 1 (<1)	132/2128 (6.2)	192/2118 (9.1)	83/1058 (7.8)	-2.9 (-4.5, -1.3) *	-1.6 (-3.7, 0.2)	1.2 (-0.9, 3.2)
Level 2 (<0.75)	25/2128 (1.2)	48/2118 (2.3)	21/1058 (2.0)	-1.1 (-1.9, -0.3) *	-0.8 (-1.9, 0.1)	0.3 (-0.9, 1.3)
Level 3 (<0.5)	3/2128 (0.1)	4/2118 (0.2)	2/1058 (0.2)	-0.0 (-0.4, 0.2)	-0.0 (-0.6, 0.3)	-0.0 (-0.5, 0.3)
Lymphocytes, high (10^3 cells/μL)						
Level 1 (>4)	22/2128 (1.0)	19/2118 (0.9)	6/1058 (0.6)	0.1 (-0.5, 0.8)	0.5 (-0.3, 1.1)	0.3 (-0.4, 0.9)
Level 2 (>10)	0/2128 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Level 3 (>20)	0/2128 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
Neutrophils, low (10^3 cells/μL)						
Level 1 (<2)	833/2128 (39.1)	873/2118 (41.2)	417/1058 (39.4)	-2.1 (-5.0, 0.9)	-0.3 (-3.9, 3.3)	1.8 (-1.8, 5.4)
Level 2 (<1)	59/2128 (2.8)	61/2118 (2.9)	26/1058 (2.5)	-0.1 (-1.1, 0.9)	0.3 (-1.0, 1.4)	0.4 (-0.9, 1.5)
Level 3 (<0.5)	0/2128 (0)	0/2118 (0)	1/1058 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.5, 0.1)	-0.1 (-0.5, 0.1)
Eosinophils, high (10^3 cells/μL)						
Level 1 (>0.65)	74/2128 (3.5)	58/2118 (2.7)	29/1058 (2.7)	0.7 (-0.3, 1.8)	0.7 (-0.6, 1.9)	-0.0 (-1.3, 1.1)
Level 2 (>1.5)	7/2128 (0.3)	3/2118 (0.1)	3/1058 (0.3)	0.2 (-0.1, 0.6)	0.0 (-0.5, 0.4)	-0.1 (-0.7, 0.2)
Level 3 (>5)	1/2128 (0.0)	0/2118 (0)	0/1058 (0)	0.0 (-0.1, 0.3)	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.2)

Source: [Data Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; dec., decrease; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; inc., increase; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; N_w, number of participants with data; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells.

Table 96. Participants With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 1

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Creatinine, high (mg/dL)						
Level 1 (≥1.5X baseline)	18/2127 (0.8)	14/2118 (0.7)	10/1058 (0.9)	0.2 (-0.4, 0.7)	-0.1 (-0.9, 0.6)	-0.3 (-1.1, 0.3)
Level 2 (≥2X baseline)	2/2127 (0.1)	0/2118 (0)	1/1058 (0.1)	0.1 (-0.1, 0.3)	-0.0 (-0.4, 0.3)	-0.1 (-0.5, 0.1)
Level 3 (≥3X baseline)	0/2127 (0)	0/2118 (0)	0/1058 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)
eGFR, low (mL/min/1.73 m^2)						
Level 1 (≥25% decrease)	68/2124 (3.2)	71/2117 (3.4)	42/1056 (4.0)	-0.2 (-1.2, 0.9)	-0.8 (-2.3, 0.5)	-0.6 (-2.1, 0.7)
Level 2 (≥50% decrease)	1/2124 (0.0)	0/2117 (0)	2/1056 (0.2)	0.0 (-0.1, 0.3)	-0.1 (-0.6, 0.1)	-0.2 (-0.7, -0.0) *
Level 3 (≥75% decrease)	0/2124 (0)	0/2117 (0)	0/1056 (0)	0.0 (-0.2, 0.2)	0.0 (-0.4, 0.2)	0.0 (-0.4, 0.2)

Source: [Data Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data.

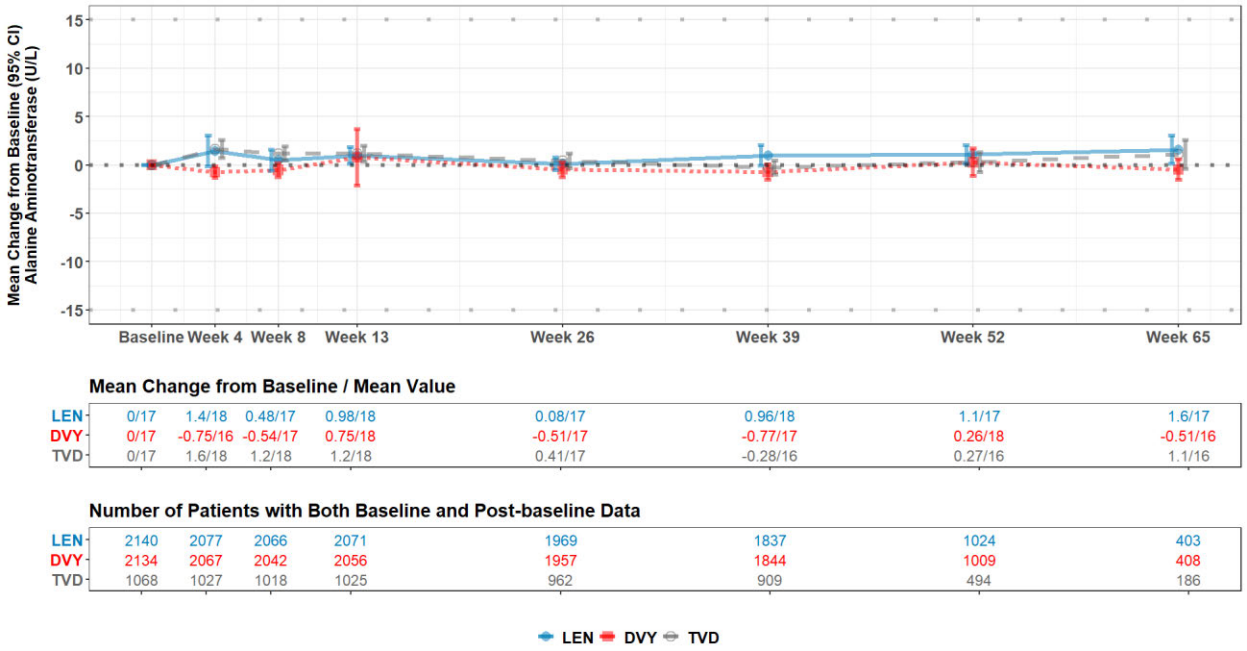
Table 97. Participants With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 1

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5× ULN)	83/2127 (3.9)	80/2118 (3.8)	39/1058 (3.7)	0.1 (-1.0, 1.3)	0.2 (-1.3, 1.6)	0.1 (-1.4, 1.4)
Level 2 (>2× ULN)	12/2127 (0.6)	10/2118 (0.5)	5/1058 (0.5)	0.1 (-0.4, 0.6)	0.1 (-0.6, 0.6)	-0.0 (-0.7, 0.5)
Level 3 (>3× ULN)	0/2127 (0)	2/2118 (0.1)	0/1058 (0)	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)
Alanine aminotransferase, high (U/L)						
Level 1 (>3× ULN)	39/2127 (1.8)	20/2118 (0.9)	9/1058 (0.9)	0.9 (0.2, 1.6) *	1.0 (0.1, 1.8) *	0.1 (-0.7, 0.7)
Level 2 (>5× ULN)	12/2127 (0.6)	6/2118 (0.3)	2/1058 (0.2)	0.3 (-0.1, 0.7)	0.4 (-0.2, 0.8)	0.1 (-0.4, 0.5)
Level 3 (>10× ULN)	6/2127 (0.3)	4/2118 (0.2)	1/1058 (0.1)	0.1 (-0.2, 0.4)	0.2 (-0.3, 0.5)	0.1 (-0.4, 0.4)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3× ULN)	18/2127 (0.8)	14/2118 (0.7)	6/1058 (0.6)	0.2 (-0.4, 0.7)	0.3 (-0.4, 0.9)	0.1 (-0.6, 0.6)
Level 2 (>5× ULN)	9/2127 (0.4)	7/2118 (0.3)	2/1058 (0.2)	0.1 (-0.3, 0.5)	0.2 (-0.3, 0.6)	0.1 (-0.4, 0.5)
Level 3 (>10× ULN)	4/2127 (0.2)	4/2118 (0.2)	1/1058 (0.1)	-0.0 (-0.3, 0.3)	0.1 (-0.4, 0.4)	0.1 (-0.4, 0.4)

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5× ULN)	35/2127 (1.6)	23/2118 (1.1)	11/1058 (1.0)	0.6 (-0.1, 1.3)	0.6 (-0.3, 1.4)	0.0 (-0.8, 0.8)
Level 2 (>2× ULN)	9/2127 (0.4)	6/2118 (0.3)	4/1058 (0.4)	0.1 (-0.2, 0.6)	0.0 (-0.6, 0.5)	-0.1 (-0.7, 0.3)
Level 3 (>3× ULN)	0/2127 (0)	2/2118 (0.1)	0/1058 (0)	-0.1 (-0.3, 0.1)	0.0 (-0.4, 0.2)	0.1 (-0.3, 0.3)

Source: [Data Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot." and "Cholestatic Drug-Induced Liver Injury Screening Plot." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot…"
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

Figure 51. Mean Change From Baseline, ALT, Safety Population, PURPOSE 1



Mean Change from Baseline / Mean Value

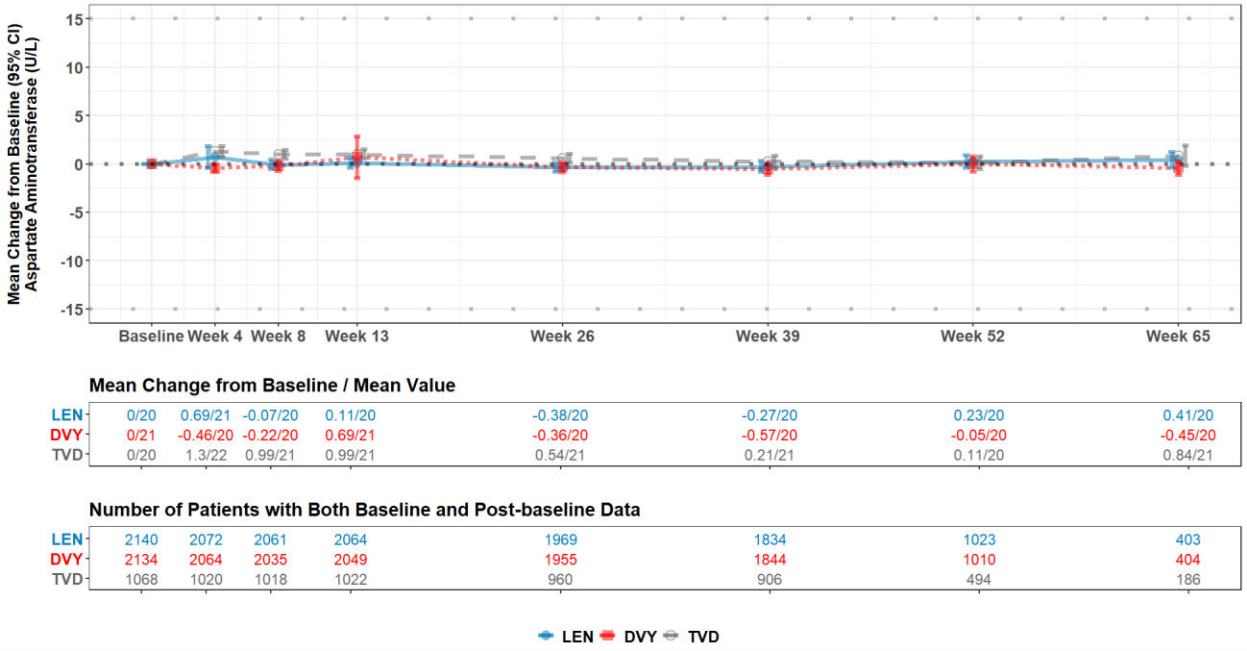
	Baseline	Week 4	Week 8	Week 13	Week 26	Week 39	Week 52	Week 65
LEN	0/17	1.4/18	0.48/17	0.98/18	0.08/17	0.96/18	1.1/17	1.6/17
DVY	0/17	-0.75/16	-0.54/17	0.75/18	-0.51/17	-0.77/17	0.26/18	-0.51/16
TVD	0/17	1.6/18	1.2/18	1.2/18	0.41/17	-0.28/16	0.27/16	1.1/16

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 13	Week 26	Week 39	Week 52	Week 65
LEN	2140	2077	2066	2071	1969	1837	1024	403
DVY	2134	2067	2042	2056	1957	1844	1009	408
TVD	1068	1027	1018	1025	962	909	494	186

Source: [Data Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; DVY, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

Figure 52. Mean Change From Baseline, AST, Safety Population, PURPOSE 1



Mean Change from Baseline / Mean Value

	Baseline	Week 4	Week 8	Week 13	Week 26	Week 39	Week 52	Week 65
LEN	0/20	0.69/21	-0.07/20	0.11/20	-0.38/20	-0.27/20	0.23/20	0.41/20
DVY	0/21	-0.46/20	-0.22/20	0.69/21	-0.36/20	-0.57/20	-0.05/20	-0.45/20
TVD	0/20	1.3/22	0.99/21	0.99/21	0.54/21	0.21/21	0.11/20	0.84/21

Number of Patients with Both Baseline and Post-baseline Data

	Baseline	Week 4	Week 8	Week 13	Week 26	Week 39	Week 52	Week 65
LEN	2140	2072	2061	2064	1969	1834	1023	403
DVY	2134	2064	2035	2049	1955	1844	1010	404
TVD	1068	1020	1018	1022	960	906	494	186

Source: [Data Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; DVY, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

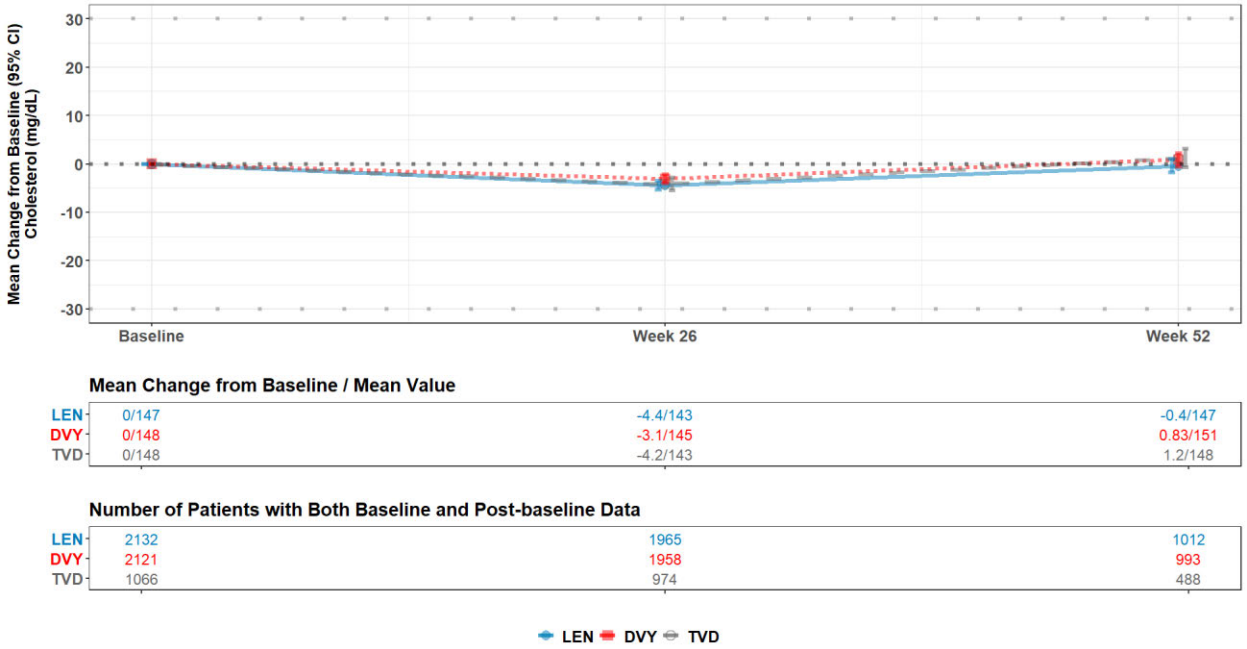
Table 98 displays proportion of participants with lipid-related laboratory outliers and Figure 53, Figure 54, and Figure 55 display the mean change from baseline for lipid data over time in PURPOSE 1. No clinically relevant differences were seen between groups.

Table 98. Participants With One or More Lipid Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 1

Laboratory Parameter	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)	LEN vs. F/TAF Risk Difference % (95% CI)	LEN vs. F/TDF Risk Difference % (95% CI)	F/TAF vs. F/TDF Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)						
Level 1 (>200)	118/1992 (5.9)	134/1988 (6.7)	58/986 (5.9)	-0.8 (-2.3, 0.7)	0.0 (-1.9, 1.8)	0.9 (-1.1, 2.6)
Level 2 (>210)	72/1992 (3.6)	84/1988 (4.2)	35/986 (3.5)	-0.6 (-1.8, 0.6)	0.1 (-1.5, 1.4)	0.7 (-0.9, 2.1)
Level 3 (>225)	34/1992 (1.7)	43/1988 (2.2)	17/986 (1.7)	-0.5 (-1.3, 0.4)	-0.0 (-1.1, 0.9)	0.4 (-0.7, 1.4)
HDL, males, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
HDL, females, low (mg/dL)						
Level 1 (<50)	1461/1992 (73.3)	1460/1988 (73.4)	720/986 (73.0)	-0.1 (-2.8, 2.6)	0.3 (-3.0, 3.7)	0.4 (-2.9, 3.8)
Level 2 (<40)	707/1992 (35.5)	711/1988 (35.8)	359/986 (36.4)	-0.3 (-3.2, 2.7)	-0.9 (-4.6, 2.7)	-0.6 (-4.3, 3.0)
Level 3 (<20)	9/1992 (0.5)	10/1988 (0.5)	4/986 (0.4)	-0.1 (-0.5, 0.4)	0.0 (-0.6, 0.5)	0.1 (-0.6, 0.6)
LDL, high (mg/dL)						
Level 1 (>130)	116/1992 (5.8)	143/1988 (7.2)	58/986 (5.9)	-1.4 (-2.9, 0.2)	-0.1 (-2.0, 1.7)	1.3 (-0.6, 3.1)
Level 2 (>160)	19/1992 (1.0)	19/1988 (1.0)	11/986 (1.1)	-0.0 (-0.6, 0.6)	-0.2 (-1.1, 0.6)	-0.2 (-1.1, 0.6)
Level 3 (>190)	3/1992 (0.2)	6/1988 (0.3)	1/986 (0.1)	-0.2 (-0.5, 0.2)	0.0 (-0.4, 0.4)	0.2 (-0.3, 0.6)
Triglycerides, high (mg/dL)						
Level 1 (>150)	111/1992 (5.6)	104/1988 (5.2)	43/986 (4.4)	0.3 (-1.1, 1.8)	1.2 (-0.5, 2.8)	0.9 (-0.8, 2.4)
Level 2 (>300)	4/1992 (0.2)	3/1988 (0.2)	3/986 (0.3)	0.0 (-0.3, 0.4)	-0.1 (-0.7, 0.3)	-0.2 (-0.7, 0.2)
Level 3 (>500)	0/1992 (0)	0/1988 (0)	1/986 (0.1)	0.0 (-0.2, 0.2)	-0.1 (-0.6, 0.1)	-0.1 (-0.6, 0.1)

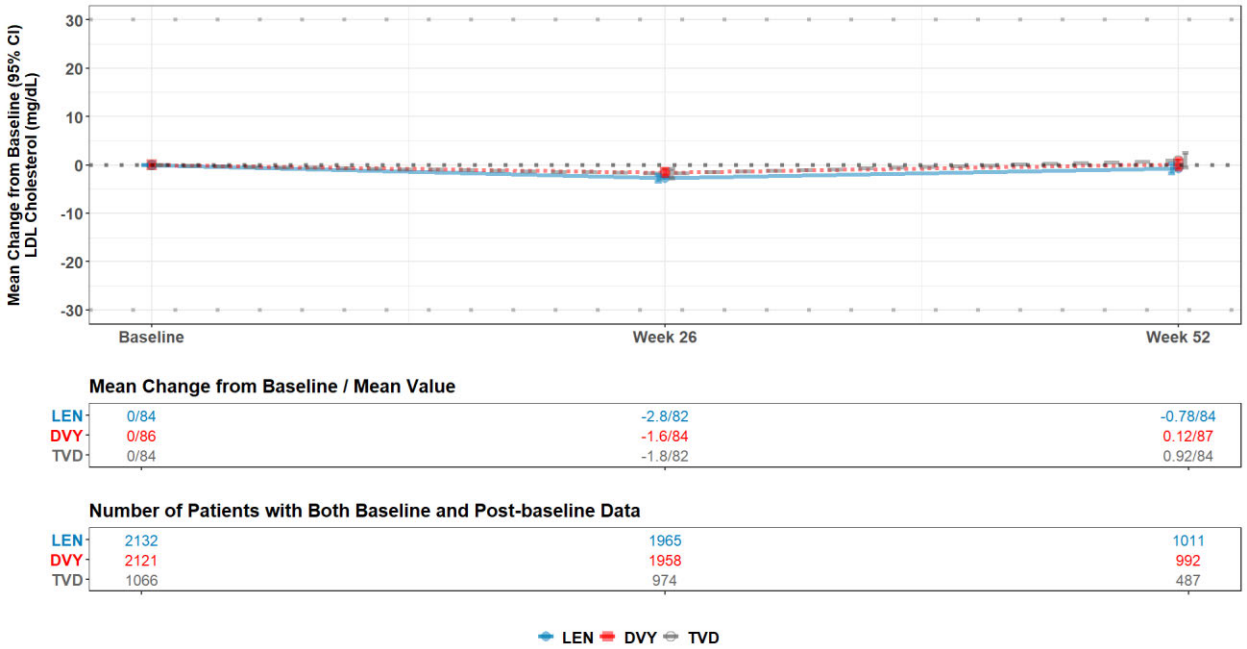
Source: [Data Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; N_w, number of participants with data.

Figure 53. Mean Change From Baseline, Cholesterol, Safety Population, PURPOSE 1



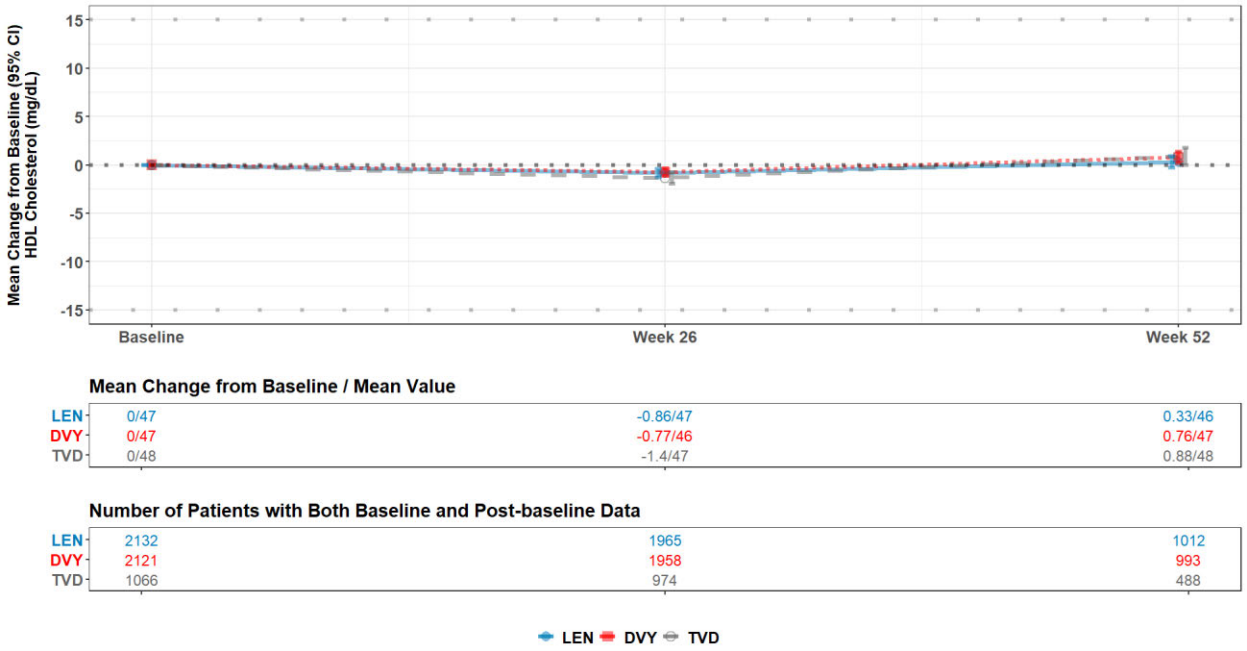
Source: [Data Scientist] adlb.xpt; Software: R.
The timeframe (e.g., by day, week, month) that corresponds best with the pre-specified visit # is used as the study visit (± protocol-defined # days).
Difference is shown between total treatment and comparator.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; DVY, emtricitabine/tenofovir alafenamide; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

Figure 54. Mean Change From Baseline, LDL Cholesterol, Safety Population, PURPOSE 1



Source: [Data Scientist] adlb.xpt; Software: R.
The timeframe (e.g., by day, week, month) that corresponds best with the pre-specified visit # is used as the study visit (± protocol-defined # days).
Difference is shown between total treatment and comparator.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; DVY, emtricitabine/tenofovir alafenamide; LDL, low-density lipoprotein; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; TVD, emtricitabine/tenofovir disoproxil fumarate.

Figure 55. Mean Change From Baseline, HDL Cholesterol, Safety Population, PURPOSE 1



Source: [Data Scientist] adlb.xpt; Software: R.
The timeframe (e.g., by day, week, month) that corresponds best with the pre-specified visit # is used as the study visit (± protocol-defined # days).
Difference is shown between total treatment and comparator.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; DVY, emtricitabine/tenofovir alafenamide; HDL, high-density lipoprotein; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

17.1.5. Assessment of Drug-Induced Liver Injury, PURPOSE 1

Details of the assessment of drug-induced liver injury can be found in Section 7.6.1.7. In addition to the referenced findings, the incidence of cholestatic DILI screening labs was also similar between study groups as seen in Table 99 below.

Table 99. Participants in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, PURPOSE 1

Quadrant	LEN N=2140 n/N_w (%)	F/TAF N=2135 n/N_w (%)	F/TDF N=1070 n/N_w (%)
Bilirubin ≥2× ULN and ALP ≥2× ULN (right upper)	0/2127 (0)	2/2118 (0.1)	1/1058 (0.1)
Bilirubin ≥2× ULN and ALP <2× ULN (left upper)	9/2127 (0.4)	5/2118 (0.2)	3/1058 (0.3)
Bilirubin <2× ULN and ALP ≥2× ULN (right lower)	12/2127 (0.6)	8/2118 (0.4)	5/1058 (0.5)
Total	21/2127 (1)	15/2118 (0.7)	9/1058 (0.9)

Source: [Data Scientist] adlb.xpt; Software: R.
A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN. The within 30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

17.2. PURPOSE 2

17.2.1. Serious Adverse Events, PURPOSE 2

SAEs in PURPOSE 2 are discussed in Section 7.6.2.3. Below is a complete tabulation of SAEs regardless of causality. None of the SAEs reported are considered by investigators to be related to study drug in either group. Of note, none of the SAE PTs of "Abscess Limb" are associated with the injection sites.

Table 100. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, PURPOSE 2

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Any SAE	71 (3.3)	43 (4.0)	-0.7 (-2.2, 0.6)
Blood and lymphatic system disorders (SOC)	1 (0.0)	0	0.0 (-0.3, 0.3)
Sickle cell anaemia with crisis	1 (0.0)	0	0.0 (-0.3, 0.3)
Cardiac disorders (SOC)	3 (0.1)	0	0.1 (-0.2, 0.4)
Atrial fibrillation	2 (0.1)	0	0.1 (-0.3, 0.3)
Acute myocardial infarction	1 (0.0)	0	0.0 (-0.3, 0.3)
Ear and labyrinth disorders (SOC)	0	1 (0.1)	-0.1 (-0.5, 0.1)
Vertigo	0	1 (0.1)	-0.1 (-0.5, 0.1)
Endocrine disorders (SOC)	1 (0.0)	0	0.0 (-0.3, 0.3)
Thyrotoxic periodic paralysis	1 (0.0)	0	0.0 (-0.3, 0.3)
Gastrointestinal disorders (SOC)	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Colitis	1 (0.0)	0	0.0 (-0.3, 0.3)
Colitis ulcerative	1 (0.0)	0	0.0 (-0.3, 0.3)
Strangulated umbilical hernia	1 (0.0)	0	0.0 (-0.3, 0.3)
Haemorrhoids	0	1 (0.1)	-0.1 (-0.5, 0.1)
General disorders and administration site conditions (SOC)	1 (0.0)	3 (0.3)	-0.2 (-0.8, 0.0)
Death	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Ill-defined disorder	0	1 (0.1)	-0.1 (-0.5, 0.1)
Lithiasis	0	1 (0.1)	-0.1 (-0.5, 0.1)
Hepatobiliary disorders (SOC)	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Hepatitis acute	1 (0.0)	0	0.0 (-0.3, 0.3)
Cholecystitis acute	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Infections and infestations (SOC)	31 (1.4)	15 (1.4)	0.0 (-0.9, 0.8)
Abscess limb	3 (0.1)	0	0.1 (-0.2, 0.4)
Cellulitis	2 (0.1)	0	0.1 (-0.3, 0.3)
Dengue haemorrhagic fever	2 (0.1)	0	0.1 (-0.3, 0.3)
Bacterial infection	1 (0.0)	0	0.0 (-0.3, 0.3)
Complicated appendicitis	1 (0.0)	0	0.0 (-0.3, 0.3)
Dengue fever	1 (0.0)	0	0.0 (-0.3, 0.3)
Encephalitis viral	1 (0.0)	0	0.0 (-0.3, 0.3)
Enteritis infectious	1 (0.0)	0	0.0 (-0.3, 0.3)
Meningoencephalitis viral	1 (0.0)	0	0.0 (-0.3, 0.3)
Peritonsillar abscess	1 (0.0)	0	0.0 (-0.3, 0.3)
Pneumonia bacterial	1 (0.0)	0	0.0 (-0.3, 0.3)
Sepsis	1 (0.0)	0	0.0 (-0.3, 0.3)
Tonsillitis bacterial	1 (0.0)	0	0.0 (-0.3, 0.3)
Hepatitis A	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Pneumonia	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Gastroenteritis	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Osteomyelitis	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Abdominal infection	0	1 (0.1)	-0.1 (-0.5, 0.1)
Anal abscess	0	1 (0.1)	-0.1 (-0.5, 0.1)
Erysipelas	0	1 (0.1)	-0.1 (-0.5, 0.1)
Large intestine infection	0	1 (0.1)	-0.1 (-0.5, 0.1)
Pyelonephritis	0	1 (0.1)	-0.1 (-0.5, 0.1)
Pyelonephritis acute	0	1 (0.1)	-0.1 (-0.5, 0.1)
Appendicitis	7 (0.3)	6 (0.6)	-0.2 (-0.9, 0.2)
Injury, poisoning and procedural complications (SOC)	9 (0.4)	7 (0.6)	-0.2 (-0.9, 0.3)
Ankle fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Craniofacial fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Femur fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Patella fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Skin abrasion	1 (0.0)	0	0.0 (-0.3, 0.3)
Subdural haemorrhage	1 (0.0)	0	0.0 (-0.3, 0.3)
Tibia fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Traumatic fracture	1 (0.0)	0	0.0 (-0.3, 0.3)
Road traffic accident	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Abdominal injury	0	1 (0.1)	-0.1 (-0.5, 0.1)
Alcohol poisoning	0	1 (0.1)	-0.1 (-0.5, 0.1)
Chest injury	0	1 (0.1)	-0.1 (-0.5, 0.1)
Foreign body aspiration	0	1 (0.1)	-0.1 (-0.5, 0.1)
Joint injury	0	1 (0.1)	-0.1 (-0.5, 0.1)
Skin laceration	0	1 (0.1)	-0.1 (-0.5, 0.1)
Upper limb fracture	0	1 (0.1)	-0.1 (-0.5, 0.1)
Wound necrosis	0	1 (0.1)	-0.1 (-0.5, 0.1)
Investigations (SOC)	1 (0.0)	0	0.0 (-0.3, 0.3)
Transaminases abnormal	1 (0.0)	0	0.0 (-0.3, 0.3)
Metabolism and nutrition disorders (SOC)	1 (0.0)	0	0.0 (-0.3, 0.3)
Dehydration	1 (0.0)	0	0.0 (-0.3, 0.3)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Fibromyalgia	1 (0.0)	0	0.0 (-0.3, 0.3)
Bone lesion	0	1 (0.1)	-0.1 (-0.5, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Adenocarcinoma of colon	1 (0.0)	0	0.0 (-0.3, 0.3)
Brain neoplasm	1 (0.0)	0	0.0 (-0.3, 0.3)
Acute myeloid leukaemia	0	1 (0.1)	-0.1 (-0.5, 0.1)
Nervous system disorders (SOC)	3 (0.1)	2 (0.2)	-0.0 (-0.5, 0.3)
Cerebrovascular accident	2 (0.1)	0	0.1 (-0.3, 0.3)
Subarachnoid haemorrhage	1 (0.0)	0	0.0 (-0.3, 0.3)
Seizure	0	1 (0.1)	-0.1 (-0.5, 0.1)
Syncope	0	1 (0.1)	-0.1 (-0.5, 0.1)

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Psychiatric disorders (SOC)	14 (0.6)	8 (0.7)	-0.1 (-0.8, 0.5)
Completed suicide	1 (0.0)	0	0.0 (-0.3, 0.3)
Depression suicidal	1 (0.0)	0	0.0 (-0.3, 0.3)
Psychotic disorder	1 (0.0)	0	0.0 (-0.3, 0.3)
Substance use disorder	1 (0.0)	0	0.0 (-0.3, 0.3)
Depression	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Suicide attempt	7 (0.3)	3 (0.3)	0.0 (-0.5, 0.4)
Mental disorder	0	1 (0.1)	-0.1 (-0.5, 0.1)
Schizophrenia	0	1 (0.1)	-0.1 (-0.5, 0.1)
Substance-induced psychotic disorder	0	1 (0.1)	-0.1 (-0.5, 0.1)
Substance dependence	0	1 (0.1)	-0.1 (-0.5, 0.1)
Major depression	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Anxiety	0	2 (0.2)	-0.2 (-0.7, -0.0) *
Suicidal ideation	3 (0.1)	4 (0.4)	-0.2 (-0.8, 0.1)
Renal and urinary disorders (SOC)	3 (0.1)	1 (0.1)	0.0 (-0.4, 0.3)
Ureteric stenosis	1 (0.0)	0	0.0 (-0.3, 0.3)
Ureterolithiasis	1 (0.0)	0	0.0 (-0.3, 0.3)
Nephrolithiasis	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Reproductive system and breast disorders (SOC)	0	1 (0.1)	-0.1 (-0.5, 0.1)
Testicular mass	0	1 (0.1)	-0.1 (-0.5, 0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	0	2 (0.2)	-0.2 (-0.7, -0.0) *
Pleural effusion	0	1 (0.1)	-0.1 (-0.5, 0.1)
Pneumothorax	0	1 (0.1)	-0.1 (-0.5, 0.1)
Skin and subcutaneous tissue disorders (SOC)	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Cellulite	1 (0.0)	0	0.0 (-0.3, 0.3)
Urticaria	1 (0.0)	0	0.0 (-0.3, 0.3)
Diabetic foot	0	1 (0.1)	-0.1 (-0.5, 0.1)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; incl, including; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class.

An analysis by OND custom medical query (narrow) of SAEs leading to treatment discontinuation did not reveal any additional safety concerns.

17.2.2. Treatment-Emergent Adverse Events, PURPOSE 2

TEAEs occurring in PURPOSE 2 and ADRs are discussed in Section 7.6.2.5. Below is a tabulation of TEAEs occurring in at least 0.6% of the participants regardless of causality in any group and the participants with AEs by SOC and OND custom medical query (narrow). No clinically meaningful safety signals were identified that are not already included in labeling. The only imbalances of TEAEs favoring F/TDF not included in labeling were acne (1% LEN versus

0.1% F/TDF recipients) and dermatitis (0.6% LEN versus 0.1% F/TDF recipients). However, these were rare overall, did not result in discontinuation of study drug, were mild to moderate, and were felt to be more likely the result of multiple comparisons rather than a true signal.

An analysis by OND custom medical query (narrow) of AEs leading to treatment discontinuation did not reveal any additional safety concerns.

Table 101. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.6% of Participants in Any Group, Safety Population, PURPOSE 2

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Any AE	2029 (92.9)	976 (89.7)	3.2 (1.2, 5.4) *
Blood and lymphatic system disorders (SOC)	17 (0.8)	19 (1.7)	-1.0 (-2.0, -0.2) *
Ear and labyrinth disorders (SOC)	9 (0.4)	12 (1.1)	-0.7 (-1.5, -0.1) *
Eye disorders (SOC)	20 (0.9)	5 (0.5)	0.5 (-0.2, 1.0)
Gastrointestinal disorders (SOC)	443 (20.3)	254 (23.3)	-3.1 (-6.1, -0.1) *
Proctalgia	14 (0.6)	2 (0.2)	0.5 (-0.1, 0.9)
Dyspepsia	25 (1.1)	9 (0.8)	0.3 (-0.5, 1.0)
Vomiting	36 (1.6)	18 (1.7)	-0.0 (-1.1, 0.9)
Gastrooesophageal reflux disease	13 (0.6)	8 (0.7)	-0.1 (-0.9, 0.4)
Odynophagia	17 (0.8)	10 (0.9)	-0.1 (-1.0, 0.5)
Diarrhoea	146 (6.7)	75 (6.9)	-0.2 (-2.1, 1.6)
Anal fissure	19 (0.9)	12 (1.1)	-0.2 (-1.1, 0.4)
Abdominal pain upper	29 (1.3)	17 (1.6)	-0.2 (-1.2, 0.6)
Constipation	13 (0.6)	10 (0.9)	-0.3 (-1.1, 0.3)
Abdominal discomfort	6 (0.3)	7 (0.6)	-0.4 (-1.1, 0.1)
Flatulence	6 (0.3)	7 (0.6)	-0.4 (-1.1, 0.1)
Proctitis	11 (0.5)	11 (1.0)	-0.5 (-1.3, 0.1)
Haemorrhoids	20 (0.9)	17 (1.6)	-0.6 (-1.6, 0.1)
Toothache	24 (1.1)	19 (1.7)	-0.6 (-1.7, 0.2)
Abdominal pain	26 (1.2)	23 (2.1)	-0.9 (-2.0, -0.0) *
Nausea	89 (4.1)	67 (6.2)	-2.1 (-3.8, -0.5) *
General disorders and administration site conditions (SOC)	1827 (83.7)	769 (70.7)	13.0 (9.9, 16.2) *
Injection site nodule	1383 (63.4)	427 (39.2)	24.1 (20.5, 27.6) *
Injection site induration	342 (15.7)	110 (10.1)	5.6 (3.1, 7.9) *
Injection site pain	1231 (56.4)	581 (53.4)	3.0 (-0.6, 6.6)
Injection site pruritus	74 (3.4)	30 (2.8)	0.6 (-0.7, 1.8)
Injection site discolouration	15 (0.7)	4 (0.4)	0.3 (-0.3, 0.8)
Influenza like illness	15 (0.7)	6 (0.6)	0.1 (-0.6, 0.7)
Injection site warmth	51 (2.3)	24 (2.2)	0.1 (-1.1, 1.2)
Injection site oedema	17 (0.8)	10 (0.9)	-0.1 (-1.0, 0.5)
Pyrexia	53 (2.4)	28 (2.6)	-0.1 (-1.4, 0.9)
Malaise	11 (0.5)	9 (0.8)	-0.3 (-1.1, 0.2)
Fatigue	21 (1.0)	16 (1.5)	-0.5 (-1.5, 0.2)
Injection site haematoma	9 (0.4)	12 (1.1)	-0.7 (-1.5, -0.1) *
Injection site bruising	67 (3.1)	42 (3.9)	-0.8 (-2.3, 0.5)
Injection site erythema	377 (17.3)	211 (19.4)	-2.1 (-5.0, 0.7)
Injection site swelling	149 (6.8)	104 (9.6)	-2.7 (-4.9, -0.8) *
Hepatobiliary disorders (SOC)	20 (0.9)	15 (1.4)	-0.5 (-1.4, 0.3)
Hepatic steatosis	4 (0.2)	8 (0.7)	-0.6 (-1.3, -0.1) *
Immune system disorders (SOC)	15 (0.7)	10 (0.9)	-0.2 (-1.0, 0.4)

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Infections and infestations (SOC)	1269 (58.1)	630 (57.9)	0.2 (-3.3, 3.8)
Oropharyngeal gonococcal infection	283 (13.0)	119 (10.9)	2.0 (-0.4, 4.3)
Anal gonococcal infection	233 (10.7)	99 (9.1)	1.6 (-0.6, 3.7)
Anal chlamydia infection	289 (13.2)	128 (11.8)	1.5 (-1.0, 3.8)
Latent syphilis	114 (5.2)	44 (4.0)	1.2 (-0.4, 2.6)
Urethritis gonococcal	29 (1.3)	7 (0.6)	0.7 (-0.1, 1.4)
Dengue fever	56 (2.6)	21 (1.9)	0.6 (-0.5, 1.6)
Urethritis chlamydial	37 (1.7)	13 (1.2)	0.5 (-0.4, 1.3)
Sinusitis	38 (1.7)	14 (1.3)	0.5 (-0.5, 1.3)
Genitourinary chlamydia infection	54 (2.5)	22 (2.0)	0.5 (-0.7, 1.5)
Acarodermatitis	15 (0.7)	3 (0.3)	0.4 (-0.2, 0.9)
Proctitis chlamydial	50 (2.3)	21 (1.9)	0.4 (-0.8, 1.3)
Tonsillitis	47 (2.2)	20 (1.8)	0.3 (-0.8, 1.3)
Primary syphilis	20 (0.9)	7 (0.6)	0.3 (-0.5, 0.9)
Gastroenteritis	66 (3.0)	31 (2.8)	0.2 (-1.2, 1.3)
Syphilis	71 (3.3)	34 (3.1)	0.1 (-1.3, 1.3)
Urinary tract infection	33 (1.5)	16 (1.5)	0.0 (-1.0, 0.9)
Folliculitis	12 (0.5)	7 (0.6)	-0.1 (-0.8, 0.4)
Furuncle	12 (0.5)	7 (0.6)	-0.1 (-0.8, 0.4)
Pharyngitis	34 (1.6)	18 (1.7)	-0.1 (-1.1, 0.8)
Genital herpes	10 (0.5)	7 (0.6)	-0.2 (-0.9, 0.3)
Proctitis gonococcal	30 (1.4)	17 (1.6)	-0.2 (-1.2, 0.6)
Secondary syphilis	19 (0.9)	12 (1.1)	-0.2 (-1.1, 0.4)
Upper respiratory tract infection	148 (6.8)	77 (7.1)	-0.3 (-2.2, 1.5)
Conjunctivitis	7 (0.3)	7 (0.6)	-0.3 (-1.0, 0.1)
Genitourinary tract gonococcal infection	26 (1.2)	17 (1.6)	-0.4 (-1.4, 0.4)
Nasopharyngitis	69 (3.2)	39 (3.6)	-0.4 (-1.9, 0.8)
Urethritis	38 (1.7)	24 (2.2)	-0.5 (-1.6, 0.5)
Influenza	120 (5.5)	66 (6.1)	-0.6 (-2.4, 1.1)
COVID-19	69 (3.2)	44 (4.0)	-0.9 (-2.4, 0.4)
Pharyngeal chlamydia infection	55 (2.5)	40 (3.7)	-1.2 (-2.6, 0.1)
Injury, poisoning and procedural complications (SOC)	144 (6.6)	63 (5.8)	0.8 (-1.0, 2.5)
Investigations (SOC)	90 (4.1)	59 (5.4)	-1.3 (-3.0, 0.2)
Blood pressure increased	24 (1.1)	10 (0.9)	0.2 (-0.7, 0.9)
Creatinine renal clearance decreased	26 (1.2)	25 (2.3)	-1.1 (-2.2, -0.2) *
Metabolism and nutrition disorders (SOC)	66 (3.0)	43 (4.0)	-0.9 (-2.4, 0.4)
Decreased appetite	6 (0.3)	12 (1.1)	-0.8 (-1.7, -0.3) *
Musculoskeletal and connective tissue disorders (SOC)	151 (6.9)	67 (6.2)	0.8 (-1.1, 2.5)
Myalgia	32 (1.5)	13 (1.2)	0.3 (-0.7, 1.1)
Back pain	46 (2.1)	20 (1.8)	0.3 (-0.8, 1.2)
Arthralgia	24 (1.1)	12 (1.1)	-0.0 (-0.9, 0.7)
Pain in extremity	7 (0.3)	8 (0.7)	-0.4 (-1.1, 0.1)
Neck pain	4 (0.2)	8 (0.7)	-0.6 (-1.3, -0.1) *
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	26 (1.2)	11 (1.0)	0.2 (-0.7, 0.9)
Anogenital warts	17 (0.8)	9 (0.8)	-0.0 (-0.8, 0.6)
Nervous system disorders (SOC)	213 (9.8)	128 (11.8)	-2.0 (-4.4, 0.2)
Dizziness	35 (1.6)	19 (1.7)	-0.1 (-1.2, 0.7)
Syncope	17 (0.8)	14 (1.3)	-0.5 (-1.4, 0.2)
Headache	119 (5.5)	76 (7.0)	-1.5 (-3.4, 0.2)

System Organ Class Preferred Term	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Psychiatric disorders (SOC)	141 (6.5)	77 (7.1)	-0.6 (-2.5, 1.2)
Depression	31 (1.4)	9 (0.8)	0.6 (-0.2, 1.3)
Insomnia	29 (1.3)	16 (1.5)	-0.1 (-1.1, 0.7)
Anxiety	38 (1.7)	21 (1.9)	-0.2 (-1.3, 0.7)
Renal and urinary disorders (SOC)	66 (3.0)	37 (3.4)	-0.4 (-1.8, 0.9)
Dysuria	25 (1.1)	16 (1.5)	-0.3 (-1.3, 0.5)
Reproductive system and breast disorders (SOC)	54 (2.5)	30 (2.8)	-0.3 (-1.6, 0.8)
Respiratory, thoracic and mediastinal disorders (SOC)	130 (6.0)	68 (6.2)	-0.3 (-2.1, 1.4)
Rhinorrhoea	14 (0.6)	2 (0.2)	0.5 (-0.1, 0.9)
Oropharyngeal pain	42 (1.9)	20 (1.8)	0.1 (-1.0, 1.0)
Rhinitis allergic	18 (0.8)	9 (0.8)	-0.0 (-0.8, 0.6)
Cough	26 (1.2)	13 (1.2)	-0.0 (-0.9, 0.7)
Nasal congestion	9 (0.4)	7 (0.6)	-0.2 (-0.9, 0.3)
Skin and subcutaneous tissue disorders (SOC)	171 (7.8)	66 (6.1)	1.8 (-0.1, 3.5)
Acne	21 (1.0)	1 (0.1)	0.9 (0.4, 1.4) *
Dermatitis	14 (0.6)	1 (0.1)	0.5 (0.1, 1.0) *
Skin lesion	14 (0.6)	4 (0.4)	0.3 (-0.3, 0.8)
Pruritus	17 (0.8)	6 (0.6)	0.2 (-0.5, 0.8)
Rash	16 (0.7)	10 (0.9)	-0.2 (-1.0, 0.4)
Vascular disorders (SOC)	40 (1.8)	17 (1.6)	0.3 (-0.8, 1.2)
Hypertension	30 (1.4)	9 (0.8)	0.5 (-0.3, 1.3)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; incl, including; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

Table 102. Participants With Adverse Events by System Organ Class and OND Custom Medical Query (Narrow), Safety Population, PURPOSE 2

System Organ Class OCMQ (Narrow)	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)			
Thrombosis	2 (0.1)	0	0.1 (-0.3, 0.3)
Leukopenia	1 (0.0)	0	0.0 (-0.3, 0.3)
Thrombosis arterial	1 (0.0)	0	0.0 (-0.3, 0.3)
Thrombosis venous	1 (0.0)	0	0.0 (-0.3, 0.3)
Thrombocytopenia	2 (0.1)	2 (0.2)	-0.1 (-0.6, 0.2)
Anemia	5 (0.2)	5 (0.5)	-0.2 (-0.9, 0.2)
Cardiac disorders (SOC)			
Systemic hypertension	57 (2.6)	22 (2.0)	0.6 (-0.6, 1.6)
Arrhythmia	8 (0.4)	2 (0.2)	0.2 (-0.3, 0.6)
Acute coronary syndrome	1 (0.0)	0	0.0 (-0.3, 0.3)
Cardiac conduction disturbance	1 (0.0)	0	0.0 (-0.3, 0.3)
Myocardial infarction	1 (0.0)	0	0.0 (-0.3, 0.3)
Myocardial ischemia	1 (0.0)	0	0.0 (-0.3, 0.3)
Tachycardia	4 (0.2)	3 (0.3)	-0.1 (-0.6, 0.2)
Palpitations	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)

System Organ Class OCMQ (Narrow)	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Ear and labyrinth disorders (SOC)			
Vertigo	4 (0.2)	4 (0.4)	-0.2 (-0.8, 0.2)
Endocrine disorders (SOC)			
Hypoglycemia	6 (0.3)	2 (0.2)	0.1 (-0.4, 0.4)
Hyperglycemia	13 (0.6)	9 (0.8)	-0.2 (-1.0, 0.3)
Gastrointestinal disorders (SOC)			
Dry mouth	3 (0.1)	0	0.1 (-0.2, 0.4)
Vomiting	36 (1.6)	18 (1.7)	-0.0 (-1.1, 0.9)
Dyspepsia	51 (2.3)	26 (2.4)	-0.1 (-1.3, 1.0)
Diarrhea	151 (6.9)	78 (7.2)	-0.3 (-2.2, 1.5)
Constipation	13 (0.6)	10 (0.9)	-0.3 (-1.1, 0.3)
Abdominal pain	64 (2.9)	48 (4.4)	-1.5 (-3.0, -0.2) *
Nausea	90 (4.1)	67 (6.2)	-2.0 (-3.8, -0.5) *
General disorders and administration site conditions (SOC)			
Local administration reaction	1817 (83.2)	754 (69.3)	13.9 (10.8, 17.1) *
Fall	6 (0.3)	0	0.3 (-0.1, 0.6)
Peripheral edema	6 (0.3)	1 (0.1)	0.2 (-0.3, 0.5)
Dizziness	50 (2.3)	26 (2.4)	-0.1 (-1.3, 0.9)
Pyrexia	54 (2.5)	28 (2.6)	-0.1 (-1.4, 1.0)
Volume depletion	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Fatigue	41 (1.9)	25 (2.3)	-0.4 (-1.6, 0.6)
Decreased appetite	6 (0.3)	12 (1.1)	-0.8 (-1.7, -0.3) *
Hepatobiliary disorders (SOC)			
Cholecystitis	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Hepatic injury	14 (0.6)	9 (0.8)	-0.2 (-1.0, 0.4)
Immune system disorders (SOC)			
Angioedema	1 (0.0)	0	0.0 (-0.3, 0.3)
Hypersensitivity	12 (0.5)	9 (0.8)	-0.3 (-1.1, 0.3)
Infections and infestations (SOC)			
Bacterial infection	896 (41.0)	407 (37.4)	3.6 (0.1, 7.1) *
Pneumonia	14 (0.6)	4 (0.4)	0.3 (-0.3, 0.8)
Purulent material	34 (1.6)	14 (1.3)	0.3 (-0.7, 1.1)
Fungal infection	54 (2.5)	28 (2.6)	-0.1 (-1.4, 1.0)
Nasopharyngitis	140 (6.4)	71 (6.5)	-0.1 (-2.0, 1.6)
Viral infection	320 (14.7)	170 (15.6)	-1.0 (-3.7, 1.6)
Metabolism and nutrition disorders (SOC)			
Lipid disorder	26 (1.2)	8 (0.7)	0.5 (-0.3, 1.1)
Cachexia	6 (0.3)	6 (0.6)	-0.3 (-0.9, 0.2)
Musculoskeletal and connective tissue disorders (SOC)			
Fracture	21 (1.0)	7 (0.6)	0.3 (-0.4, 0.9)
Myalgia	33 (1.5)	13 (1.2)	0.3 (-0.6, 1.1)
Back pain	52 (2.4)	23 (2.1)	0.3 (-0.9, 1.3)
Rhabdomyolysis	4 (0.2)	1 (0.1)	0.1 (-0.3, 0.4)
Tendinopathy	4 (0.2)	1 (0.1)	0.1 (-0.3, 0.4)
Gout	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Arthralgia	24 (1.1)	12 (1.1)	-0.0 (-0.9, 0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)

System Organ Class OCMQ (Narrow)	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Nervous system disorders (SOC)			
Stroke TIA	4 (0.2)	0	0.2 (-0.2, 0.5)
Dysgeusia	3 (0.1)	0	0.1 (-0.2, 0.4)
Tremor	2 (0.1)	0	0.1 (-0.3, 0.3)
Somnolence	10 (0.5)	5 (0.5)	-0.0 (-0.6, 0.5)
Seizure	0	2 (0.2)	-0.2 (-0.7, -0.0) *
Paresthesia	15 (0.7)	10 (0.9)	-0.2 (-1.0, 0.4)
Syncope	17 (0.8)	14 (1.3)	-0.5 (-1.4, 0.2)
Headache	134 (6.1)	82 (7.5)	-1.4 (-3.4, 0.4)
Psychiatric disorders (SOC)			
Depression	34 (1.6)	16 (1.5)	0.1 (-0.9, 0.9)
Arthritis	5 (0.2)	2 (0.2)	0.0 (-0.5, 0.4)
Anxiety	53 (2.4)	26 (2.4)	0.0 (-1.2, 1.1)
Self-harm	14 (0.6)	7 (0.6)	-0.0 (-0.7, 0.5)
Irritability	0	1 (0.1)	-0.1 (-0.5, 0.1)
Psychosis	4 (0.2)	3 (0.3)	-0.1 (-0.6, 0.2)
Study agent abuse potential	8 (0.4)	5 (0.5)	-0.1 (-0.7, 0.3)
Insomnia	30 (1.4)	16 (1.5)	-0.1 (-1.1, 0.7)
Mania	1 (0.0)	2 (0.2)	-0.1 (-0.6, 0.1)
Parasomnia	2 (0.1)	4 (0.4)	-0.3 (-0.9, 0.0)
Renal and urinary disorders (SOC)			
Renal and urinary tract infection	152 (7.0)	75 (6.9)	0.1 (-1.9, 1.9)
Acute kidney injury	1 (0.0)	1 (0.1)	-0.0 (-0.5, 0.2)
Reproductive system and breast disorders (SOC)			
Bacterial vaginosis	1 (0.0)	0	0.0 (-0.3, 0.3)
Excessive menstrual bleeding	1 (0.0)	0	0.0 (-0.3, 0.3)
Erectile dysfunction	7 (0.3)	3 (0.3)	0.0 (-0.5, 0.4)
Abnormal uterine bleeding	2 (0.1)	2 (0.2)	-0.1 (-0.6, 0.2)
Sexual dysfunction	11 (0.5)	7 (0.6)	-0.1 (-0.9, 0.4)
Respiratory, thoracic and mediastinal disorders (SOC)			
Cough	30 (1.4)	14 (1.3)	0.1 (-0.9, 0.9)
Respiratory failure	2 (0.1)	1 (0.1)	-0.0 (-0.4, 0.3)
Bronchospasm	4 (0.2)	4 (0.4)	-0.2 (-0.8, 0.2)
Dyspnea	1 (0.0)	3 (0.3)	-0.2 (-0.8, 0.0)
Skin and subcutaneous tissue disorders (SOC)			
Rash	81 (3.7)	30 (2.8)	1.0 (-0.4, 2.2)
Alopecia	14 (0.6)	3 (0.3)	0.4 (-0.2, 0.8)
Urticaria	13 (0.6)	3 (0.3)	0.3 (-0.3, 0.8)
Pruritus	97 (4.4)	45 (4.1)	0.3 (-1.3, 1.7)
Erythema	377 (17.3)	214 (19.7)	-2.4 (-5.3, 0.4)

System Organ Class OCMQ (Narrow)	LEN N=2183 n (%)	F/TDF N=1088 n (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Vascular disorders (SOC)			
Hypotension	3 (0.1)	5 (0.5)	-0.3 (-0.9, 0.0)
Hemorrhage	134 (6.1)	74 (6.8)	-0.7 (-2.6, 1.1)

Source:[Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific preferred terms under each OCMQ, see the table "Adverse Events by System Organ Class, OND custom medical query (narrow) and Preferred Term…"
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in OND custom medical query (Narrow)…"
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; incl, including; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; OCMQ, OND custom medical query; PT, preferred term; SC, subcutaneous; SOC, system organ class; TIA, transient ischemic attack.

17.2.3. Laboratory Findings, PURPOSE 2

Key laboratory parameters are presented and discussed in Sections 7.6.2.6 and 7.6.2.7. The proportion of participants with chemistry, hematology, kidney function, and liver biochemistry analyte laboratory abnormalities as outliers are shown in Table 103, Table 104, and Table 105.

While there are more participants in the LEN group with Potassium levels <3.6, the mean change from baseline does not vary significantly, and is similar to F/TDF. This is displayed in Figure 56 below. There was a mild imbalance favoring LEN in participants with elevated Chloride and elevated Magnesium that were also not considered clinically relevant.

Additionally, there are more participants in the LEN group with elevated leukocytes, however, the mean change from baseline is not clinically relevant. In addition, changes over time for leukocytes were similar in the LEN versus F/TDF groups as seen in Figure 57. There was a mild imbalance favoring LEN in participants with decreased Lymphocytes and decreased Neutrophils.

As shown in Table 105, the proportions of participants with Creatinine and eGFR outliers show a mild imbalance favoring LEN. 2 participants (0.2%) in the F/TDF group experienced ≥50% decrease in eGFR and a ≥2x baseline increase in creatinine compared to no participants in the LEN group. Additionally, 63 (6.3%) of participants in the F/TDF group experienced a ≥25% decrease in eGFR compared to 66 (3.3%) of recipients in the LEN group. This is a known safety issue with F/TDF.

Table 106 shows the proportion of participants with outliers in >1.5× ULN bilirubin elevation is higher in the LEN group (3%, versus 1.7% in the F/TDF group). However, the imbalance is not seen in participants with >2× ULN and >3× ULN elevations of bilirubin. Furthermore, the mean change from baseline of bilirubin over time is not clinically meaningful and did not show a trend of increasing over time in either treatment group (see Figure 58).

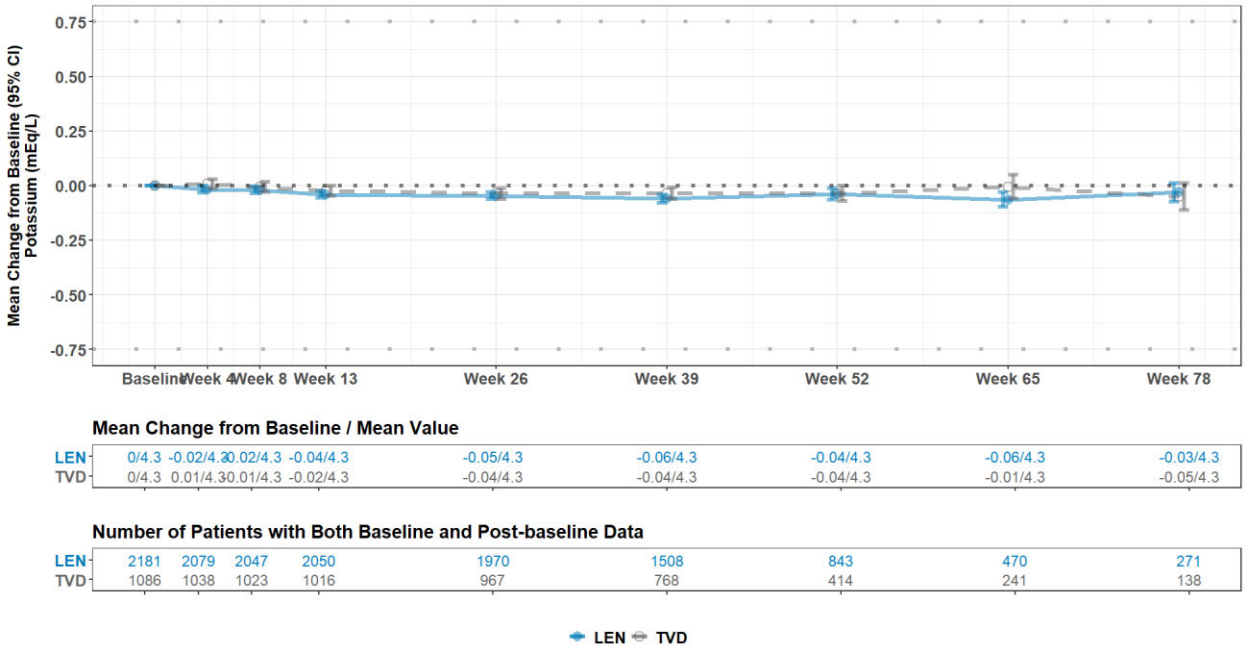
Table 103. Participants With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, PURPOSE 2

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	7/2153 (0.3)	8/1073 (0.7)	-0.4 (-1.2, 0.1)
Level 2 (<130)	1/2153 (0.0)	1/1073 (0.1)	-0.0 (-0.5, 0.2)
Level 3 (<125)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Sodium, high (mEq/L)			
Level 1 (>150)	4/2153 (0.2)	3/1073 (0.3)	-0.1 (-0.6, 0.2)
Level 2 (>155)	1/2153 (0.0)	1/1073 (0.1)	-0.0 (-0.5, 0.2)
Level 3 (>160)	1/2153 (0.0)	0/1073 (0)	0.0 (-0.3, 0.3)
Potassium, low (mEq/L)			
Level 1 (<3.6)	90/2153 (4.2)	29/1073 (2.7)	1.5 (0.1, 2.7) *
Level 2 (<3.4)	18/2153 (0.8)	8/1073 (0.7)	0.1 (-0.7, 0.7)
Level 3 (<3)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Potassium, high (mEq/L)			
Level 1 (>5.5)	44/2153 (2.0)	18/1073 (1.7)	0.4 (-0.7, 1.3)
Level 2 (>6)	13/2153 (0.6)	6/1073 (0.6)	0.0 (-0.7, 0.6)
Level 3 (>6.5)	2/2153 (0.1)	2/1073 (0.2)	-0.1 (-0.6, 0.2)
Chloride, low (mEq/L)			
Level 1 (<95)	17/2153 (0.8)	9/1073 (0.8)	-0.0 (-0.9, 0.6)
Level 2 (<88)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Level 3 (<80)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Chloride, high (mEq/L)			
Level 1 (>108)	80/2153 (3.7)	35/1073 (3.3)	0.5 (-1.0, 1.7)
Level 2 (>112)	3/2153 (0.1)	4/1073 (0.4)	-0.2 (-0.8, 0.1)
Level 3 (>115)	0/2153 (0)	2/1073 (0.2)	-0.2 (-0.7, -0.0) *
Bicarbonate, low (mEq/L)			
Level 1 (<20)	622/2151 (28.9)	322/1073 (30.0)	-1.1 (-4.5, 2.2)
Level 2 (<18)	139/2151 (6.5)	68/1073 (6.3)	0.1 (-1.8, 1.9)
Level 3 (<15)	8/2151 (0.4)	2/1073 (0.2)	0.2 (-0.3, 0.6)
Bicarbonate, high (mEq/L)			
Level 3 (>30)	3/2151 (0.1)	1/1073 (0.1)	0.0 (-0.4, 0.3)
Glucose, low (mg/dL)			
Level 1 (<70)	321/2153 (14.9)	156/1073 (14.5)	0.4 (-2.3, 2.9)
Level 2 (<54)	42/2153 (2.0)	20/1073 (1.9)	0.1 (-1.0, 1.0)
Level 3 (<40)	2/2153 (0.1)	4/1073 (0.4)	-0.3 (-0.9, 0.0)
Glucose, fasting, high (mg/dL)			
Level 1 (≥100 to 125)	508/1979 (25.7)	267/995 (26.8)	-1.2 (-4.6, 2.2)
Level 2 (≥126)	100/1979 (5.1)	46/995 (4.6)	0.4 (-1.3, 2.0)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	14/1209 (1.2)	6/607 (1.0)	0.2 (-1.1, 1.1)
Level 3 (>250)	5/1209 (0.4)	4/607 (0.7)	-0.2 (-1.3, 0.4)
Calcium, low (mg/dL)			
Level 1 (<8.4)	72/2153 (3.3)	25/1073 (2.3)	1.0 (-0.3, 2.2)
Level 2 (<8)	36/2153 (1.7)	14/1073 (1.3)	0.4 (-0.6, 1.2)
Level 3 (<7.5)	17/2153 (0.8)	5/1073 (0.5)	0.3 (-0.4, 0.9)
Calcium, high (mg/dL)			
Level 1 (>10.5)	47/2153 (2.2)	19/1073 (1.8)	0.4 (-0.7, 1.4)
Level 2 (>11)	4/2153 (0.2)	4/1073 (0.4)	-0.2 (-0.8, 0.2)
Level 3 (>12)	1/2153 (0.0)	1/1073 (0.1)	-0.0 (-0.5, 0.2)

Magnesium, low (mg/dL)			
Level 1 (<1.5)	39/2153 (1.8)	10/1073 (0.9)	0.9 (-0.0, 1.7)
Level 2 (<1.2)	14/2153 (0.7)	3/1073 (0.3)	0.4 (-0.2, 0.9)
Level 3 (<0.9)	4/2153 (0.2)	0/1073 (0)	0.2 (-0.2, 0.5)
Magnesium, high (mg/dL)			
Level 1 (>2.3)	1038/2153 (48.2)	579/1073 (54.0)	-5.7 (-9.4, -2.1) *
Level 2 (>4)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Level 3 (>7)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	276/2153 (12.8)	120/1073 (11.2)	1.6 (-0.8, 3.9)
Level 2 (<2)	50/2153 (2.3)	14/1073 (1.3)	1.0 (-0.0, 1.9)
Level 3 (<1.4)	2/2153 (0.1)	1/1073 (0.1)	-0.0 (-0.4, 0.3)
Protein, total, low (g/dL)			
Level 1 (<6)	19/2153 (0.9)	13/1073 (1.2)	-0.3 (-1.2, 0.4)
Level 2 (<5.4)	1/2153 (0.0)	2/1073 (0.2)	-0.1 (-0.6, 0.1)
Level 3 (<5)	0/2153 (0)	1/1073 (0.1)	-0.1 (-0.5, 0.1)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/2153 (0)	1/1073 (0.1)	-0.1 (-0.5, 0.1)
Level 2 (<2.5)	0/2153 (0)	1/1073 (0.1)	-0.1 (-0.5, 0.1)
Level 3 (<2)	0/2153 (0)	0/1073 (0)	0.0 (-0.4, 0.2)
CPK, high (U/L)			
Level 1 (>3× ULN)	266/2153 (12.4)	144/1073 (13.4)	-1.1 (-3.6, 1.3)
Level 2 (>5× ULN)	166/2153 (7.7)	90/1073 (8.4)	-0.7 (-2.8, 1.3)
Level 3 (>10× ULN)	87/2153 (4.0)	51/1073 (4.8)	-0.7 (-2.3, 0.7)
Lipase, high (U/L)			
Level 1 (>1.1× ULN)	82/2152 (3.8)	45/1073 (4.2)	-0.4 (-1.9, 1.0)
Level 2 (>1.5× ULN)	48/2152 (2.2)	28/1073 (2.6)	-0.4 (-1.6, 0.7)
Level 3 (>3× ULN)	16/2152 (0.7)	7/1073 (0.7)	0.1 (-0.6, 0.7)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	83/2153 (3.9)	42/1073 (3.9)	-0.1 (-1.6, 1.3)
Level 2 (>27)	15/2153 (0.7)	12/1073 (1.1)	-0.4 (-1.3, 0.2)
Level 3 (>31)	5/2153 (0.2)	7/1073 (0.7)	-0.4 (-1.1, 0.0)

Source: [Data Scientist] adlb.xpt; Software: R.
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; N_w, number of participants with data; ULN, upper limit of normal.

Figure 56. Mean Change From Baseline, Potassium, Safety Population, PURPOSE 2



Source:[Clinical Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; LEN, lenacapavir; TVD, emtricitabine/tenofovir disoproxil fumarate.

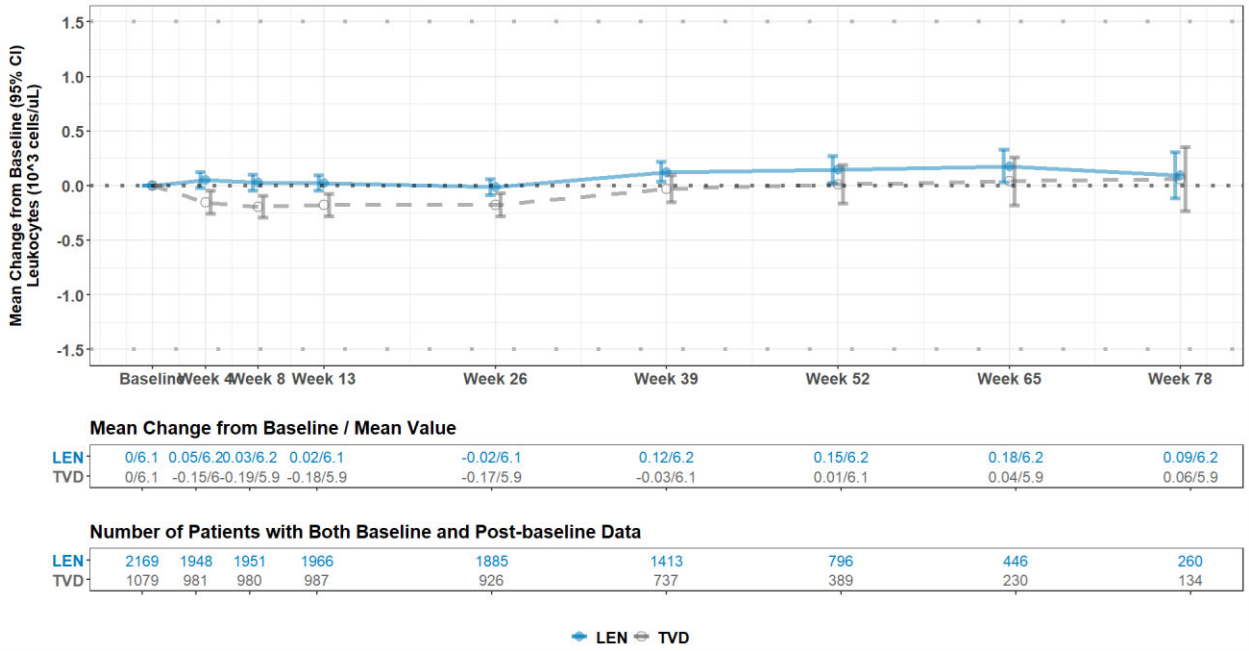
Table 104. Participants With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 2

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Complete blood count			
WBC, low (10^3 cells/μL)			
Level 1 (<3.5)	254/2150 (11.8)	148/1072 (13.8)	-2.0 (-4.5, 0.4)
Level 2 (<3)	113/2150 (5.3)	63/1072 (5.9)	-0.6 (-2.4, 1.0)
Level 3 (<1)	0/2150 (0)	0/1072 (0)	0.0 (-0.4, 0.2)
WBC, high (10^3 cells/μL)			
Level 1 (>10.8)	175/2150 (8.1)	67/1072 (6.2)	1.9 (-0.0, 3.7)
Level 2 (>13)	57/2150 (2.7)	26/1072 (2.4)	0.2 (-1.0, 1.3)
Level 3 (>15)	27/2150 (1.3)	5/1072 (0.5)	0.8 (0.1, 1.4) *
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	280/2139 (13.1)	121/1065 (11.4)	1.7 (-0.7, 4.1)
Level 3 (>2 g/dL dec. from baseline)	99/2139 (4.6)	45/1065 (4.2)	0.4 (-1.2, 1.8)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	97/2139 (4.5)	44/1065 (4.1)	0.4 (-1.2, 1.8)
Level 3 (>3 g/dL inc. from baseline)	15/2139 (0.7)	6/1065 (0.6)	0.1 (-0.6, 0.7)
Platelets, low (10^3 cells/μL)			
Level 1 (<140)	63/2148 (2.9)	30/1071 (2.8)	0.1 (-1.2, 1.3)
Level 2 (<125)	37/2148 (1.7)	14/1071 (1.3)	0.4 (-0.6, 1.3)
Level 3 (<100)	10/2148 (0.5)	2/1071 (0.2)	0.3 (-0.2, 0.7)

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
WBC differential			
Lymphocytes, low (10^3 cells/µL)			
Level 1 (<1)	189/2150 (8.8)	125/1072 (11.7)	-2.9 (-5.2, -0.7) *
Level 2 (<0.75)	43/2150 (2.0)	26/1072 (2.4)	-0.4 (-1.6, 0.6)
Level 3 (<0.5)	7/2150 (0.3)	4/1072 (0.4)	-0.0 (-0.7, 0.4)
Lymphocytes, high (10^3 cells/µL)			
Level 1 (>4)	27/2150 (1.3)	20/1072 (1.9)	-0.6 (-1.7, 0.3)
Level 2 (>10)	0/2150 (0)	0/1072 (0)	0.0 (-0.4, 0.2)
Level 3 (>20)	0/2150 (0)	0/1072 (0)	0.0 (-0.4, 0.2)
Neutrophils, low (10^3 cells/µL)			
Level 1 (<2)	501/2150 (23.3)	268/1072 (25.0)	-1.7 (-4.9, 1.4)
Level 2 (<1)	40/2150 (1.9)	32/1072 (3.0)	-1.1 (-2.4, -0.0) *
Level 3 (<0.5)	1/2150	0/1072 (0)	0.0 (-0.3, 0.3)
Eosinophils, high (10^3 cells/µL)			
Level 1 (>0.65)	83/2150 (3.9)	29/1072 (2.7)	1.2 (-0.2, 2.4)
Level 2 (>1.5)	15/2150 (0.7)	4/1072 (0.4)	0.3 (-0.3, 0.8)
Level 3 (>5)	0/2150 (0)	0/1072 (0)	0.0 (-0.4, 0.2)

Source: [Clinical Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; dec., decrease; F/TDF, emtricitabine/tenofovir disoproxil fumarate; inc., increase; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; NA, not applicable; N_w, number of participants with data; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells.

Figure 57. Mean Change From Baseline, Leukocytes, Safety Population, PURPOSE 2



Source: [Clinical Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir.

Table 105. Participants With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 2

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	13/2153 (0.6)	11/1073 (1.0)	-0.4 (-1.3, 0.2)
Level 2 (≥2× baseline)	0/2153 (0)	2/1073 (0.2)	-0.2 (-0.7, -0.0) *
Level 3 (≥3× baseline)	0/2153 (0)	1/1073 (0.1)	-0.1 (-0.5, 0.1)
eGFR, low (mL/min/1.73 m^2)			
Level 1 (≥25% decrease)	66/1972 (3.3)	63/995 (6.3)	-3.0 (-4.8, -1.4) *
Level 2 (≥50% decrease)	0/1972 (0)	2/995 (0.2)	-0.2 (-0.7, -0.0) *
Level 3 (≥75% decrease)	0/1972 (0)	1/995 (0.1)	-0.1 (-0.6, 0.1)

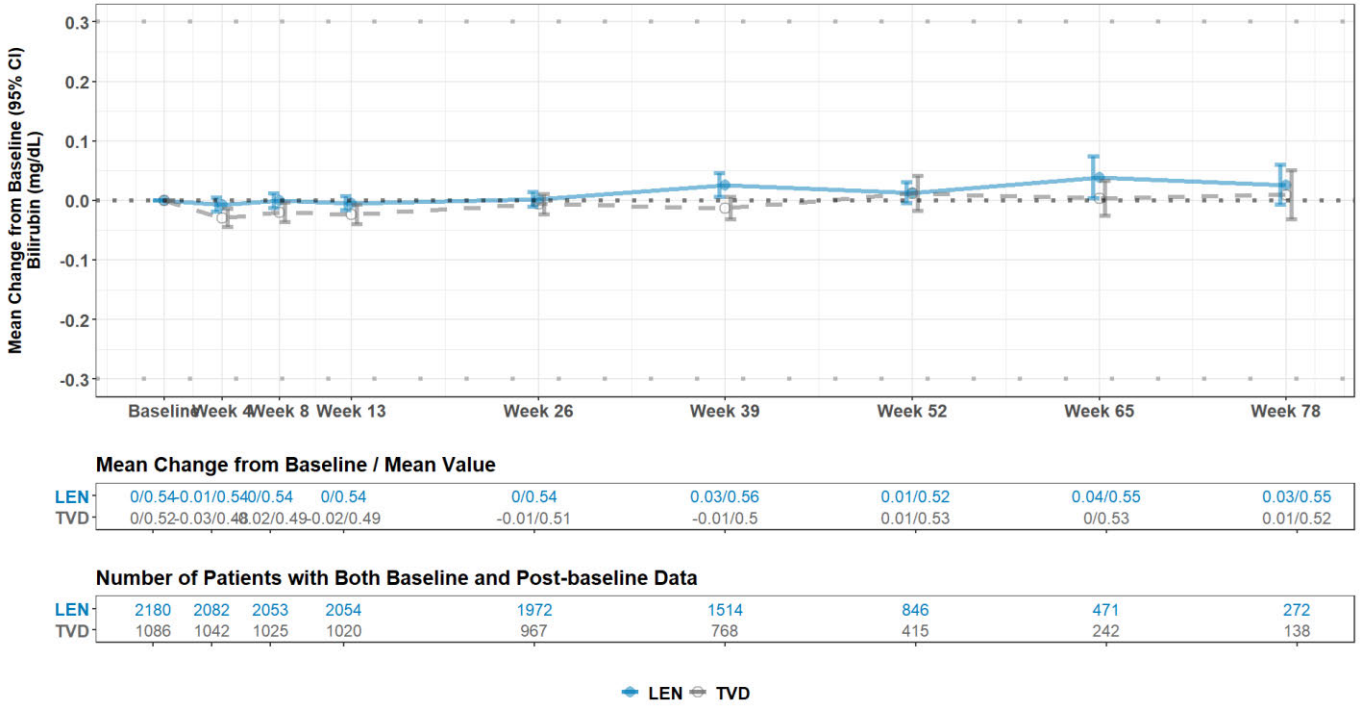
Source: [Clinical Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data.

Table 106. Participants With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, PURPOSE 2

Laboratory Parameter	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)	LEN vs. F/TDF Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5× ULN)	21/2153 (1.0)	12/1073 (1.1)	-0.1 (-1.0, 0.6)
Level 2 (>2× ULN)	5/2153 (0.2)	3/1073 (0.3)	-0.0 (-0.6, 0.3)
Level 3 (>3× ULN)	1/2153 (0.0)	1/1073 (0.1)	-0.0 (-0.5, 0.2)
Alanine aminotransferase, high (U/L)			
Level 1 (>3× ULN)	54/2151 (2.5)	30/1073 (2.8)	-0.3 (-1.6, 0.8)
Level 2 (>5× ULN)	18/2151 (0.8)	8/1073 (0.7)	0.1 (-0.7, 0.7)
Level 3 (>10× ULN)	9/2151 (0.4)	1/1073 (0.1)	0.3 (-0.1, 0.7)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3× ULN)	61/2153 (2.8)	30/1073 (2.8)	0.0 (-1.3, 1.2)
Level 2 (>5× ULN)	24/2153 (1.1)	10/1073 (0.9)	0.2 (-0.7, 0.9)
Level 3 (>10× ULN)	9/2153 (0.4)	2/1073 (0.2)	0.2 (-0.3, 0.6)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5× ULN)	64/2153 (3.0)	18/1073 (1.7)	1.3 (0.2, 2.3) *
Level 2 (>2× ULN)	26/2153 (1.2)	10/1073 (0.9)	0.3 (-0.6, 1.0)
Level 3 (>3× ULN)	7/2153 (0.3)	2/1073 (0.2)	0.1 (-0.4, 0.5)

Source: [Data Scientist] adlb.xpt; Software: R.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide (FDA 2022b).
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot.” and “Cholestatic Drug-Induced Liver Injury Screening Plot.” and the tables “Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot.” and “Patients in Each Quadrant for Cholestatic DILI Screening Plot…”
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

Figure 58. Mean Change from Baseline, Bilirubin, Safety Population, PURPOSE 2



Source: [Data Scientist] adlb.xpt; Software: R.
Figures do not include time points with data from fewer than 10% of randomized/enrolled participants in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir.

17.2.4. Assessment of Drug-Induced Liver Injury, PURPOSE 2

Details of the assessment of drug-induced liver injury can be found in Section 7.6.2.7. In addition to the referenced findings, the incidence of cholestatic DILI screening labs was also similar between study groups as seen in Table 107 below.

Table 107. Participants in Each Quadrant for Cholestatic DILI Screening Plot, Safety Population, PURPOSE 2

Quadrant	LEN N=2183 n/N_w (%)	F/TDF N=1088 n/N_w (%)
Bilirubin ≥2× ULN and ALP ≥2× ULN (right upper)	2/2153 (0.1)	1/1073 (0.1)
Bilirubin ≥2× ULN and ALP <2× ULN (left upper)	27/2153 (1.3)	11/1073 (1)
Bilirubin <2× ULN and ALP ≥2× ULN (right lower)	3/2153 (0.1)	2/1073 (0.2)
Total	32/2153 (1.5)	14/1073 (1.3)

Source: [Clinical Scientist] adlb.xpt; Software: R.
A potential cholestatic DILI case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2× ULN within 30 days after postbaseline ALP became equal to or exceeding 2× ULN. The within 30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; DILI, drug-induced liver injury; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

17.3. Pooled Analyses, PURPOSE 1 and PURPOSE 2

17.3.1. Overview of Treatment-Emergent Adverse Events, Pooled Analyses, PURPOSE 1 and PURPOSE 2

An overall assessment of the safety results from the pooled analyses of PURPOSE 1 and PURPOSE 2 are discussed in Section 7.6.3. An overview of TEAEs for the pooled Phase 3 studies, PURPOSE 1 and PURPOSE 2, are provided in Table 108, there were similar rates of SAEs between groups. The rates of AEs leading to discontinuation of study drug are overall low across groups. The majority of AEs were mild to moderate in severity and also with similar incidence across groups. The clinical review team does not find concerning safety signals in the pooled analyses.

Table 108. Overview of Adverse Events, Safety Population, PURPOSE 1 and PURPOSE 2

Event Category	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
SAE	130 (3.0)	78 (3.6)	-0.6 (-1.6, 0.3)
SAEs with fatal outcome	4 (0.1)	1 (0.0)	0.0 (-0.2, 0.2)
Life-threatening SAEs	22 (0.5)	11 (0.5)	-0.0 (-0.4, 0.3)
SAEs requiring hospitalization	106 (2.5)	66 (3.1)	-0.6 (-1.5, 0.2)
SAEs resulting in substantial disruption of normal life functions	19 (0.4)	8 (0.4)	0.1 (-0.3, 0.4)
AE leading to permanent discontinuation of study drug	41 (0.9)	10 (0.5)	0.5 (0.0, 0.9) *
AE leading to dose modification of study drug	49 (1.1)	29 (1.3)	-0.2 (-0.9, 0.3)
AE leading to interruption of study drug	49 (1.1)	29 (1.3)	-0.2 (-0.9, 0.3)
AE leading to reduction of study drug	0	0	0.0 (-0.2, 0.1)
AE leading to dose delay of study drug	0	0	0.0 (-0.2, 0.1)
Any AE	3922 (90.7)	1857 (86.1)	4.7 (3.0, 6.4) *
Severe and worse	196 (4.5)	118 (5.5)	-0.9 (-2.1, 0.2)
Moderate	2337 (54.1)	1087 (50.4)	3.7 (1.1, 6.3) *
Mild	1389 (32.1)	652 (30.2)	1.9 (-0.5, 4.3)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event.

17.3.2. Deaths, Pooled Analyses, PURPOSE 1 and PURPOSE 2

Deaths were not included in a pooled analyses as there were few deaths in the LEN group overall, and no death was considered related to study drug. Please see Sections 7.6.1.2 and 7.6.2.2 for more details.

17.3.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, PURPOSE 1 and PURPOSE 2

In the pooled analyses, SAE incidence was similar between groups. Table 109 displays the pooled analyses of SAEs occurring in more than 0.1% of participants in either group. Additionally, the SOC of pregnancy, puerperium and perinatal conditions have been removed as there were no pregnancies in PURPOSE 2. The clinical review team does not find concerning safety signals in the pooled analyses of SAEs.

Table 109. Participants With Serious Adverse Events by Preferred Term Occurring in at Least 0.1% of Participants in Either Group, Safety Population, PURPOSE 1 and PURPOSE 2

System Organ Class Preferred Term	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Any SAE	130 (3.0)	78 (3.6)	-0.6 (-1.6, 0.3)
Gastritis	0	2 (0.1)	-0.1 (-0.3, -0.0) *
Abscess limb	3 (0.1)	0	0.1 (-0.1, 0.2)
Malaria	3 (0.1)	0	0.1 (-0.1, 0.2)
Hepatitis A	3 (0.1)	2 (0.1)	-0.0 (-0.3, 0.1)
Appendicitis	8 (0.2)	7 (0.3)	-0.1 (-0.5, 0.1)
Ankle fracture	3 (0.1)	0	0.1 (-0.1, 0.2)
Overdose	3 (0.1)	0	0.1 (-0.1, 0.2)
Road traffic accident	3 (0.1)	1 (0.0)	0.0 (-0.2, 0.2)
Humerus fracture	0	2 (0.1)	-0.1 (-0.3, -0.0) *
Lower limb fracture	0	2 (0.1)	-0.1 (-0.3, -0.0) *
Suicide attempt	9 (0.2)	3 (0.1)	0.1 (-0.2, 0.3)
Depression	4 (0.1)	1 (0.0)	0.0 (-0.2, 0.2)
Major depression	1 (0.0)	2 (0.1)	-0.1 (-0.3, 0.1)
Anxiety	0	2 (0.1)	-0.1 (-0.3, -0.0) *
Suicidal ideation	3 (0.1)	4 (0.2)	-0.1 (-0.4, 0.1)
Asthma	0	4 (0.2)	-0.2 (-0.5, -0.1) *

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class.

17.3.4. Adverse Events and OND Custom Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, PURPOSE 1 and PURPOSE 2

The pooled analyses of PURPOSE 1 and PURPOSE 2 show that AEs leading to discontinuation of study drug are overall rare and continue to be primarily ISR-related. Table 110 displays the AEs leading to study drug discontinuation. The clinical review team does not find safety signals in the pooled analyses of AEs leading to treatment discontinuation not already identified in the analyses of the individual studies.

Table 110. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, PURPOSE 1 and PURPOSE 2

System Organ Class Preferred Term	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Any AE leading to discontinuation	41 (0.9)	10 (0.5)	0.5 (0.0, 0.9) *
Gastrointestinal disorders (SOC)	2 (0.0)	3 (0.1)	-0.1 (-0.4, 0.1)
Nausea	2 (0.0)	1 (0.0)	-0.0 (-0.2, 0.1)
Abdominal pain	1 (0.0)	1 (0.0)	-0.0 (-0.2, 0.1)
Abdominal pain upper	0	1 (0.0)	-0.0 (-0.3, 0.0)
Diarrhoea	0	1 (0.0)	-0.0 (-0.3, 0.0)
General disorders and administration site conditions (SOC)	31 (0.7)	4 (0.2)	0.5 (0.2, 0.9) *
Injection site nodule	21 (0.5)	0	0.5 (0.3, 0.7) *
Injection site pain	9 (0.2)	2 (0.1)	0.1 (-0.1, 0.3)
Injection site induration	2 (0.0)	0	0.0 (-0.1, 0.2)
Injection site granuloma	1 (0.0)	0	0.0 (-0.2, 0.1)
Injection site ulcer	1 (0.0)	0	0.0 (-0.2, 0.1)
Oedema peripheral	1 (0.0)	0	0.0 (-0.2, 0.1)
Injection site mass	0	1 (0.0)	-0.0 (-0.3, 0.0)
Malaise	0	1 (0.0)	-0.0 (-0.3, 0.0)
Infections and infestations (SOC)	2 (0.0)	0	0.0 (-0.1, 0.2)
Gastroenteritis	1 (0.0)	0	0.0 (-0.2, 0.1)
Onychomycosis	1 (0.0)	0	0.0 (-0.2, 0.1)
Investigations (SOC)	2 (0.0)	2 (0.1)	-0.0 (-0.3, 0.1)
Hepatic enzyme increased	1 (0.0)	0	0.0 (-0.2, 0.1)
Creatinine renal clearance decreased	1 (0.0)	2 (0.1)	-0.1 (-0.3, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.0)	0	0.0 (-0.2, 0.1)
Brain neoplasm	1 (0.0)	0	0.0 (-0.2, 0.1)
Nervous system disorders (SOC)	0	1 (0.0)	-0.0 (-0.3, 0.0)
Headache	0	1 (0.0)	-0.0 (-0.3, 0.0)
Pregnancy, puerperium and perinatal conditions (SOC)	1 (0.0)	0	0.0 (-0.2, 0.1)
Abortion spontaneous	1 (0.0)	0	0.0 (-0.2, 0.1)
Psychiatric disorders (SOC)	1 (0.0)	0	0.0 (-0.2, 0.1)
Major depression	1 (0.0)	0	0.0 (-0.2, 0.1)
Suicide attempt	1 (0.0)	0	0.0 (-0.2, 0.1)
Renal and urinary disorders (SOC)	0	1 (0.0)	-0.0 (-0.3, 0.0)
Nephropathy	0	1 (0.0)	-0.0 (-0.3, 0.0)

System Organ Class Preferred Term	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Skin and subcutaneous tissue disorders (SOC)	3 (0.1)	0	0.1 (-0.1, 0.2)
Rash	1 (0.0)	0	0.0 (-0.2, 0.1)
Urticaria	1 (0.0)	0	0.0 (-0.2, 0.1)
Vasculitic rash	1 (0.0)	0	0.0 (-0.2, 0.1)

Source:[Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

17.3.5. Treatment-Emergent Adverse Events, Pooled Analyses, PURPOSE 1 and PURPOSE 2

In the pooled analysis, the three most commonly reported AEs in each treatment group were related to ISRs, where participants in the LEN group have higher incidence of injection site nodule, pain, and induration than participants in the F/TDF group. Additionally, LEN continues to have less nausea and vomiting than F/TDF. Table 111 displays the most common TEAEs occurring in at least 2% of participants in either group. The clinical review team does not find any new safety signals in the pooled analyses of TEAEs not already identified in the analyses of the individual studies.

Table 111. Participants With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, PURPOSE 1 and PURPOSE 2

Preferred Term	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Any AE	3922 (90.7)	1857 (86.1)	4.7 (3.0, 6.4) *
Injection site nodule	2748 (63.6)	610 (28.3)	35.3 (32.9, 37.7) *
Injection site pain	1900 (44.0)	818 (37.9)	6.0 (3.5, 8.6) *
Injection site induration	433 (10.0)	120 (5.6)	4.5 (3.1, 5.8) *
Genitourinary chlamydia infection	354 (8.2)	151 (7.0)	1.2 (−0.2, 2.5)
Oropharyngeal gonococcal infection	283 (6.5)	119 (5.5)	1.0 (−0.2, 2.2)
Injection site pruritus	124 (2.9)	43 (2.0)	0.9 (0.1, 1.6) *
Anal gonococcal infection	233 (5.4)	99 (4.6)	0.8 (−0.4, 1.9)
Anal chlamydia infection	289 (6.7)	128 (5.9)	0.8 (−0.5, 2.0)
Latent syphilis	132 (3.1)	53 (2.5)	0.6 (−0.3, 1.4)
Upper respiratory tract infection	419 (9.7)	198 (9.2)	0.5 (−1.0, 2.0)
Back pain	90 (2.1)	36 (1.7)	0.4 (−0.3, 1.1)
Syphilis	116 (2.7)	49 (2.3)	0.4 (−0.4, 1.2)
Vulvovaginal candidiasis	146 (3.4)	70 (3.2)	0.1 (−0.8, 1.0)
Nasopharyngitis	112 (2.6)	55 (2.5)	0.0 (−0.8, 0.8)
Genitourinary tract gonococcal infection	167 (3.9)	83 (3.8)	0.0 (−1.0, 1.0)
Influenza like illness	89 (2.1)	45 (2.1)	-0.0 (−0.8, 0.7)
Influenza	185 (4.3)	94 (4.4)	-0.1 (−1.2, 0.9)
Diarrhoea	279 (6.5)	142 (6.6)	-0.1 (−1.4, 1.1)
Gastroenteritis	116 (2.7)	62 (2.9)	-0.2 (−1.1, 0.6)

Preferred Term	LEN N=4323 n (%)	F/TDF N=2158 n (%)	LEN vs. F/TDF Risk Difference (%) (95% CI)
Vaginal discharge	168 (3.9)	88 (4.1)	-0.2 (−1.3, 0.8)
Injection site bruising	74 (1.7)	45 (2.1)	-0.4 (−1.1, 0.3)
Urinary tract infection	340 (7.9)	179 (8.3)	-0.4 (−1.9, 0.9)
COVID-19	69 (1.6)	44 (2.0)	-0.4 (−1.2, 0.2)
Abnormal uterine bleeding	71 (1.6)	45 (2.1)	-0.4 (−1.2, 0.2)
Abdominal pain	71 (1.6)	48 (2.2)	-0.6 (−1.4, 0.1)
Dizziness	155 (3.6)	98 (4.5)	-1.0 (−2.0, 0.0)
Injection site erythema	401 (9.3)	222 (10.3)	-1.0 (−2.6, 0.5)
Headache	404 (9.3)	231 (10.7)	-1.4 (−3.0, 0.2)
Injection site swelling	245 (5.7)	154 (7.1)	-1.5 (−2.8, −0.2) *
Vomiting	161 (3.7)	125 (5.8)	-2.1 (−3.3, −1.0) *
Nausea	233 (5.4)	209 (9.7)	-4.3 (−5.8, −2.9) *

Source:[Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous.

17.3.6. Laboratory Findings, Pooled Analyses, PURPOSE 1 and PURPOSE 2

An analysis of pooled laboratory findings from PURPOSE 1 and PURPOSE 2 did not identify any imbalances not previously noted in the analyses of the separate trials.

17.4. Safety Analyses in Adolescents, PURPOSE 1 and PURPOSE 2

As stated, there were 124 adolescent participants in PURPOSE 1 and 4 adolescent participants in PURPOSE 2. Therefore, the overall safety data in adolescent participants for Table 112 below is taken from PURPOSE 1 for this section.

Please see Section 8.3 for additional details. Overall, there are no safety concerns specific to adolescents in PURPOSE 1 or PURPOSE 2, and findings are consistent with those in the general participant groups. The SAEs in adolescent participants who received LEN are PTs of food poisoning and pyelonephritis. Related AEs in the adolescent participants who received LEN include ISRs, headache, dizziness, and one episode of rash which was attributed to the pill placebo. There were no SAEs among adolescents in PURPOSE 2.

Table 112. Adolescent Safety Data, PURPOSE 1

Adverse Event Type	LEN N=2140 n (%)	F/TDF N=1070 n (%)	F/TAF N=2135 n (%)	LEN <18 N=56 n (%)	F/TDF <18 N=23 n (%)	F/TAF <18 N=45 n (%)
Any AE	1893 (88.5)	881 (82.3)	1779 (83.3)	53 (94.6)	21 (91.3)	39 (86.7)
TEAE, Grade 3 or higher	92 (4.3)	52 (4.9)	97 (4.5)	5 (8.9)	0	3 (6.7)
TEAE, related	1377 (64.3)	513 (47.9)	987 (46.2)	40 (71.4)	11 (47.8)	25 (55.6)
TEAE, serious	59 (2.8)	35 (3.3)	85 (4.0)	2 (3.6)	0	3 (6.7)
TEAE, discontinuation	9 (0.4)	0	2 (<0.1)	0	0	0
ISRs	1472 (68.8)	363 (33.9)	753 (35.3)	44 (78.6)	7 (30.4)	17 (37.8)
IS Nodule	1365 (63.8)	183 (17.1)	347 (16.3)	42 (75)	4 (17.4)	8 (17.8)
IS pain	669 (31.3)	237 (22.1)	521 (24.4)	18 (32.1)	4 (17.4)	12 (26.7)
IS swelling	91 (4.3)	10 (0.9)	22 (1.0)	2 (3.5)	1 (4.3)	3 (6.7)
Nausea	144 (6.7)	142 (13.3)	234 (11)	0	1 (4.3)	7 (15.6)
Vomiting	125 (5.8)	107 (10)	235 (11)	3 (5.3)	3 (13)	6 (13.3)

Source: Clinical Reviewer analysis. adae.xpt; JMP Analysis.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; ISR, injection site reaction; IS, injection site; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with at least one event; SAE, serious adverse event; SC, subcutaneous; TEAE, treatment-emergent adverse event.

17.5. Pregnancy Safety Analyses , PURPOSE 1

As there were more than 500 pregnancies in PURPOSE 1, safety in pregnancy was assessed as a subgroup. Please see Section 8.4 for additional details. Overall, there was a similar percentage of SAEs and any AEs between groups. Table 113 below displays SAEs by SOC and PT in the pregnant population across groups, as well as the general population. General AEs occurring in at least 1.5% of participants in any group were also examined in the pregnant population and displayed in Table 114. Imbalances of general AEs between groups for pregnant participants are consistent with those in overall participants, with higher incidence of ISRs in the LEN group, and lower incidence of nausea and vomiting in the LEN group. There are no major imbalances of TEAEs for pregnancy-associated PTs between groups of pregnant participants who do not favor LEN (i.e., morning sickness rates are higher in the F/TDF group [6.1%] compared to LEN [1%]).

Table 113. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population With Pregnancy, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Any SAE	59 (2.8)	85 (4.0)	35 (3.3)	34 (17.8)	43 (20.5)	20 (20.8)
Blood and lymphatic system disorders (SOC)	2 (0.1)	1 (0.0)	0	1 (0.5)	1 (0.5)	0
Hypochromic anaemia	2 (0.1)	0	0	1 (0.5)	0	0
Anaemia	0	1 (0.0)	0	0	1 (0.5)	0
Cardiac disorders (SOC)	0	2 (0.1)	0	0	1 (0.5)	0
Ischaemic cardiomyopathy	0	1 (0.0)	0	0	0	0
Nonreassuring foetal heart rate pattern	0	1 (0.0)	0	0	1 (0.5)	0
Eye disorders (SOC)	0	1 (0.0)	0	0	0	0
Cataract	0	1 (0.0)	0	0	0	0
Gastrointestinal disorders (SOC)	0	2 (0.1)	3 (0.3)	0	0	0
Abdominal pain lower	0	0	1 (0.1)	0	0	0
Gastritis	0	0	2 (0.2)	0	0	0
Haematemesis	0	1 (0.0)	0	0	0	0
Peptic ulcer	0	1 (0.0)	0	0	0	0
Hepatobiliary disorders (SOC)	0	1 (0.0)	0	0	0	0
Cholelithiasis	0	1 (0.0)	0	0	0	0
Infections and infestations (SOC)	12 (0.6)	16 (0.7)	3 (0.3)	4 (2.1)	6 (2.9)	0
Malaria	3 (0.1)	5 (0.2)	0	2 (1.0)	3 (1.4)	0
Appendicitis	1 (0.0)	1 (0.0)	1 (0.1)	0	0	0
Brain empyema	1 (0.0)	0	0	0	0	0
Gastroenteritis	1 (0.0)	0	0	0	0	0
Helicobacter infection	1 (0.0)	0	0	0	0	0
Pyelonephritis	1 (0.0)	0	0	0	0	0
Pyelonephritis acute	1 (0.0)	0	0	1 (0.5)	0	0
Sinusitis	1 (0.0)	0	0	0	0	0
Subcutaneous abscess	1 (0.0)	0	0	0	0	0
Tonsillitis	1 (0.0)	0	0	0	0	0
Urinary tract infection	1 (0.0)	3 (0.1)	0	1 (0.5)	2 (1.0)	0
Hepatitis A	0	1 (0.0)	1 (0.1)	0	0	0
Injection site abscess	0	1 (0.0)	0	0	0	0
Lower respiratory tract infection	0	1 (0.0)	0	0	0	0
Pelvic inflammatory disease	0	1 (0.0)	0	0	0	0
Peritonitis	0	1 (0.0)	0	0	0	0
Pneumonia	0	1 (0.0)	0	0	0	0

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Postoperative wound infection	0	1 (0.0)	0	0	1 (0.5)	0
Salpingitis	0	0	1 (0.1)	0	0	0
Sepsis	0	1 (0.0)	0	0	0	0
Injury, poisoning and procedural complications (SOC)	9 (0.4)	13 (0.6)	5 (0.5)	2 (1.0)	1 (0.5)	1 (1.0)
Overdose	3 (0.1)	1 (0.0)	0	1 (0.5)	0	0
Ankle fracture	2 (0.1)	0	0	0	0	0
Foot fracture	1 (0.0)	0	0	1 (0.5)	0	0
Limb injury	1 (0.0)	0	0	0	0	0
Road traffic accident	1 (0.0)	2 (0.1)	0	0	0	0
Thermal burn	1 (0.0)	1 (0.0)	0	0	0	0
Anaemia postoperative	0	0	1 (0.1)	0	0	1 (1.0)
Animal bite	0	0	1 (0.1)	0	0	0
Eye injury	0	1 (0.0)	0	0	0	0
Gun shot wound	0	1 (0.0)	0	0	0	0
Humerus fracture	0	0	2 (0.2)	0	0	0
Lower limb fracture	0	0	2 (0.2)	0	0	0
Pelvic fracture	0	1 (0.0)	0	0	0	0
Radius fracture	0	1 (0.0)	0	0	0	0
Rib fracture	0	1 (0.0)	0	0	1 (0.5)	0
Stab wound	0	2 (0.1)	0	0	0	0
Tendon injury	0	1 (0.0)	0	0	0	0
Tibia fracture	0	1 (0.0)	0	0	0	0
Toxicity to various agents	0	1 (0.0)	0	0	0	0
Investigations (SOC)	1 (0.0)	0	0	0	0	0
Blood pressure increased	1 (0.0)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (0.0)	0	0	0	0
Ovarian cancer	0	1 (0.0)	0	0	0	0
Nervous system disorders (SOC)	4 (0.2)	3 (0.1)	1 (0.1)	1 (0.5)	0	0
Syncope	2 (0.1)	1 (0.0)	0	1 (0.5)	0	0
Monoparesis	1 (0.0)	0	0	0	0	0
Seizure	1 (0.0)	0	0	0	0	0
Headache	0	2 (0.1)	0	0	0	0
Neuromyelitis optica spectrum disorder	0	0	1 (0.1)	0	0	0
Pregnancy, puerperium and perinatal conditions (SOC)	30 (1.4)	37 (1.7)	17 (1.6)	29 (15.2)	37 (17.6)	17 (17.7)
Abortion spontaneous	15 (0.7)	28 (1.3)	9 (0.8)	14 (7.3)	28 (13.3)	9 (9.4)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Foetal death	3 (0.1)	0	0	3 (1.6)	0	0
Abortion missed	2 (0.1)	2 (0.1)	0	2 (1.0)	2 (1.0)	0
Cephalo-pelvic disproportion	2 (0.1)	1 (0.0)	1 (0.1)	2 (1.0)	1 (0.5)	1 (1.0)
Gestational hypertension	2 (0.1)	1 (0.0)	1 (0.1)	2 (1.0)	1 (0.5)	1 (1.0)
Abortion spontaneous complete	1 (0.0)	0	0	1 (0.5)	0	0
Abortion spontaneous incomplete	1 (0.0)	0	0	1 (0.5)	0	0
Foetal distress syndrome	1 (0.0)	0	1 (0.1)	1 (0.5)	0	1 (1.0)
Hyperemesis gravidarum	1 (0.0)	0	0	1 (0.5)	0	0
Polyhydramnios	1 (0.0)	0	0	1 (0.5)	0	0
Retained products of conception	1 (0.0)	0	0	1 (0.5)	0	0
Ruptured ectopic pregnancy	1 (0.0)	2 (0.1)	0	1 (0.5)	2 (1.0)	0
Abortion incomplete	0	1 (0.0)	1 (0.1)	0	1 (0.5)	1 (1.0)
Abortion of ectopic pregnancy	0	0	1 (0.1)	0	0	1 (1.0)
Abortion threatened	0	1 (0.0)	0	0	1 (0.5)	0
Anembryonic gestation	0	2 (0.1)	0	0	2 (1.0)	0
Ectopic pregnancy	0	1 (0.0)	0	0	1 (0.5)	0
Haemorrhage in pregnancy	0	1 (0.0)	0	0	1 (0.5)	0
Obstructed labour	0	0	2 (0.2)	0	0	2 (2.1)
Pre-eclampsia	0	1 (0.0)	0	0	1 (0.5)	0
Prolonged labour	0	1 (0.0)	0	0	1 (0.5)	0
Stillbirth	0	1 (0.0)	1 (0.1)	0	1 (0.5)	1 (1.0)
Product issues (SOC)	1 (0.0)	0	0	1 (0.5)	0	0
Device dislocation	1 (0.0)	0	0	1 (0.5)	0	0
Psychiatric disorders (SOC)	6 (0.3)	8 (0.4)	0	0	0	0
Intentional self-injury	2 (0.1)	4 (0.2)	0	0	0	0
Suicide attempt	2 (0.1)	3 (0.1)	0	0	0	0
Depression	1 (0.0)	0	0	0	0	0
Psychotic disorder	1 (0.0)	0	0	0	0	0
Suicidal ideation	0	1 (0.0)	0	0	0	0
Renal and urinary disorders (SOC)	0	0	1 (0.1)	0	0	0
Proteinuria	0	0	1 (0.1)	0	0	0
Reproductive system and breast disorders (SOC)	0	2 (0.1)	0	0	1 (0.5)	0
Abnormal uterine bleeding	0	1 (0.0)	0	0	0	0
Threatened uterine rupture	0	1 (0.0)	0	0	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders (SOC)	0	2 (0.1)	4 (0.4)	0	0	1 (1.0)
Asphyxia	0	1 (0.0)	0	0	0	0

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Asthma	0	1 (0.0)	4 (0.4)	0	0	1 (1.0)
Social circumstances (SOC)	1 (0.0)	2 (0.1)	1 (0.1)	1 (0.5)	0	1 (1.0)
Victim of sexual abuse	1 (0.0)	0	1 (0.1)	1 (0.5)	0	1 (1.0)
Victim of homicide	0	2 (0.1)	0	0	0	0
Vascular disorders (SOC)	0	3 (0.1)	0	0	1 (0.5)	0
Haemorrhage	0	1 (0.0)	0	0	0	0
Hypertension	0	1 (0.0)	0	0	0	0
Superficial vein thrombosis	0	1 (0.0)	0	0	1 (0.5)	0

Source: adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; incl, including; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class.

Table 114. Participants With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 1.5% of Participants in Any Group, Safety Population, With Pregnancy, PURPOSE 1

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Any AE	1893 (88.5)	1779 (83.3)	881 (82.3)	176 (92.1)	181 (86.2)	84 (87.5)
Blood and lymphatic system disorders (SOC)	68 (3.2)	54 (2.5)	43 (4.0)	14 (7.3)	11 (5.2)	10 (10.4)
Anaemia	48 (2.2)	44 (2.1)	36 (3.4)	10 (5.2)	9 (4.3)	7 (7.3)
Eye disorders (SOC)	26 (1.2)	28 (1.3)	16 (1.5)	2 (1.0)	4 (1.9)	4 (4.2)
Conjunctivitis allergic	12 (0.6)	9 (0.4)	6 (0.6)	1 (0.5)	0	3 (3.1)
Gastrointestinal disorders (SOC)	492 (23.0)	651 (30.5)	336 (31.4)	51 (26.7)	71 (33.8)	39 (40.6)
Nausea	144 (6.7)	234 (11.0)	142 (13.3)	9 (4.7)	20 (9.5)	17 (17.7)
Diarrhoea	133 (6.2)	161 (7.5)	67 (6.3)	16 (8.4)	9 (4.3)	1 (1.0)
Vomiting	125 (5.8)	235 (11.0)	107 (10.0)	10 (5.2)	29 (13.8)	12 (12.5)
Gastritis	51 (2.4)	60 (2.8)	27 (2.5)	11 (5.8)	7 (3.3)	9 (9.4)
Abdominal pain	45 (2.1)	61 (2.9)	25 (2.3)	6 (3.1)	9 (4.3)	4 (4.2)
Abdominal pain lower	25 (1.2)	30 (1.4)	15 (1.4)	6 (3.1)	7 (3.3)	3 (3.1)
Toothache	23 (1.1)	27 (1.3)	18 (1.7)	4 (2.1)	5 (2.4)	1 (1.0)
Abdominal pain upper	17 (0.8)	22 (1.0)	11 (1.0)	1 (0.5)	2 (1.0)	2 (2.1)
Peptic ulcer	16 (0.7)	12 (0.6)	5 (0.5)	4 (2.1)	2 (1.0)	1 (1.0)
Dyspepsia	11 (0.5)	10 (0.5)	6 (0.6)	1 (0.5)	2 (1.0)	2 (2.1)
General disorders and administration site conditions (SOC)	1503 (70.2)	835 (39.1)	410 (38.3)	128 (67.0)	77 (36.7)	35 (36.5)
Injection site nodule	1365 (63.8)	347 (16.3)	183 (17.1)	113 (59.2)	32 (15.2)	7 (7.3)
Injection site pain	669 (31.3)	521 (24.4)	237 (22.1)	58 (30.4)	41 (19.5)	23 (24.0)
Injection site swelling	96 (4.5)	121 (5.7)	50 (4.7)	16 (8.4)	7 (3.3)	4 (4.2)
Injection site induration	91 (4.3)	22 (1.0)	10 (0.9)	8 (4.2)	1 (0.5)	2 (2.1)
Influenza like illness	74 (3.5)	68 (3.2)	39 (3.6)	3 (1.6)	3 (1.4)	2 (2.1)
Injection site pruritus	50 (2.3)	25 (1.2)	13 (1.2)	2 (1.0)	0	0
Fatigue	31 (1.4)	33 (1.5)	19 (1.8)	2 (1.0)	5 (2.4)	1 (1.0)
Injection site erythema	24 (1.1)	29 (1.4)	11 (1.0)	5 (2.6)	2 (1.0)	0
Pyrexia	24 (1.1)	22 (1.0)	13 (1.2)	2 (1.0)	4 (1.9)	6 (6.2)
Asthenia	4 (0.2)	8 (0.4)	7 (0.7)	0	2 (1.0)	3 (3.1)
Infections and infestations (SOC)	1191 (55.7)	1171 (54.8)	578 (54.0)	128 (67.0)	127 (60.5)	67 (69.8)
Urinary tract infection	307 (14.3)	305 (14.3)	163 (15.2)	51 (26.7)	56 (26.7)	36 (37.5)
Genitourinary chlamydia infection	300 (14.0)	317 (14.8)	129 (12.1)	23 (12.0)	22 (10.5)	10 (10.4)
Upper respiratory tract infection	271 (12.7)	274 (12.8)	121 (11.3)	42 (22.0)	33 (15.7)	23 (24.0)
Vulvovaginal candidiasis	146 (6.8)	172 (8.1)	67 (6.3)	29 (15.2)	36 (17.1)	21 (21.9)
Genitourinary tract gonococcal infection	141 (6.6)	157 (7.4)	66 (6.2)	17 (8.9)	10 (4.8)	2 (2.1)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Influenza	65 (3.0)	55 (2.6)	28 (2.6)	5 (2.6)	10 (4.8)	7 (7.3)
Malaria	61 (2.9)	71 (3.3)	21 (2.0)	16 (8.4)	20 (9.5)	7 (7.3)
Trichomoniasis	52 (2.4)	73 (3.4)	29 (2.7)	7 (3.7)	16 (7.6)	3 (3.1)
Gastroenteritis	50 (2.3)	70 (3.3)	31 (2.9)	4 (2.1)	6 (2.9)	3 (3.1)
Syphilis	45 (2.1)	48 (2.2)	15 (1.4)	6 (3.1)	7 (3.3)	3 (3.1)
Nasopharyngitis	43 (2.0)	55 (2.6)	16 (1.5)	15 (7.9)	13 (6.2)	5 (5.2)
Vulvovaginitis chlamydial	40 (1.9)	39 (1.8)	24 (2.2)	1 (0.5)	2 (1.0)	0
Urogenital trichomoniasis	38 (1.8)	45 (2.1)	15 (1.4)	6 (3.1)	5 (2.4)	3 (3.1)
Pelvic inflammatory disease	35 (1.6)	39 (1.8)	22 (2.1)	7 (3.7)	5 (2.4)	9 (9.4)
Tonsillitis	35 (1.6)	29 (1.4)	17 (1.6)	2 (1.0)	1 (0.5)	1 (1.0)
Vulvovaginitis trichomonal	34 (1.6)	26 (1.2)	27 (2.5)	3 (1.6)	1 (0.5)	4 (4.2)
Lower respiratory tract infection	30 (1.4)	16 (0.7)	9 (0.8)	2 (1.0)	0	2 (2.1)
Gynaecological chlamydia infection	26 (1.2)	19 (0.9)	8 (0.7)	3 (1.6)	1 (0.5)	1 (1.0)
Vaginitis chlamydial	23 (1.1)	23 (1.1)	17 (1.6)	3 (1.6)	4 (1.9)	5 (5.2)
Tinea versicolour	20 (0.9)	14 (0.7)	9 (0.8)	5 (2.6)	4 (1.9)	2 (2.1)
Helicobacter infection	19 (0.9)	28 (1.3)	9 (0.8)	4 (2.1)	10 (4.8)	3 (3.1)
Vulvovaginitis gonococcal	18 (0.8)	20 (0.9)	12 (1.1)	0	4 (1.9)	2 (2.1)
Bacterial vaginosis	14 (0.7)	11 (0.5)	4 (0.4)	3 (1.6)	1 (0.5)	1 (1.0)
Pharyngitis	12 (0.6)	10 (0.5)	4 (0.4)	3 (1.6)	1 (0.5)	0
Subcutaneous abscess	12 (0.6)	15 (0.7)	7 (0.7)	1 (0.5)	1 (0.5)	2 (2.1)
Typhoid fever	12 (0.6)	18 (0.8)	5 (0.5)	2 (1.0)	3 (1.4)	2 (2.1)
Cystitis	11 (0.5)	7 (0.3)	4 (0.4)	2 (1.0)	0	2 (2.1)
Respiratory tract infection	10 (0.5)	14 (0.7)	4 (0.4)	3 (1.6)	3 (1.4)	1 (1.0)
Cervicitis	7 (0.3)	4 (0.2)	4 (0.4)	3 (1.6)	0	0
Conjunctivitis bacterial	3 (0.1)	4 (0.2)	4 (0.4)	0	0	2 (2.1)
Pregnancy related infection	3 (0.1)	3 (0.1)	1 (0.1)	3 (1.6)	3 (1.4)	1 (1.0)
Metabolism and nutrition disorders (SOC)	78 (3.6)	92 (4.3)	47 (4.4)	8 (4.2)	6 (2.9)	5 (5.2)
Decreased appetite	27 (1.3)	48 (2.2)	28 (2.6)	3 (1.6)	3 (1.4)	2 (2.1)
Abnormal loss of weight	18 (0.8)	7 (0.3)	8 (0.7)	1 (0.5)	0	2 (2.1)
Musculoskeletal and connective tissue disorders (SOC)	87 (4.1)	71 (3.3)	41 (3.8)	8 (4.2)	8 (3.8)	4 (4.2)
Back pain	44 (2.1)	25 (1.2)	16 (1.5)	2 (1.0)	3 (1.4)	2 (2.1)
Myalgia	11 (0.5)	3 (0.1)	1 (0.1)	3 (1.6)	1 (0.5)	0
Nervous system disorders (SOC)	378 (17.7)	450 (21.1)	220 (20.6)	34 (17.8)	54 (25.7)	22 (22.9)
Headache	285 (13.3)	352 (16.5)	155 (14.5)	26 (13.6)	44 (21.0)	15 (15.6)
Dizziness	120 (5.6)	141 (6.6)	79 (7.4)	10 (5.2)	14 (6.7)	9 (9.4)

System Organ Class Preferred Term	LEN N=2140 n (%)	F/TAF N=2135 n (%)	F/TDF N=1070 n (%)	LEN (Pregnancy) N=191 n (%)	F/TAF (Pregnancy) N=210 n (%)	F/TDF (Pregnancy) N=96 n (%)
Pregnancy, puerperium and perinatal conditions (SOC)	40 (1.9)	50 (2.3)	22 (2.1)	39 (20.4)	50 (23.8)	22 (22.9)
Abortion spontaneous	15 (0.7)	28 (1.3)	9 (0.8)	14 (7.3)	28 (13.3)	9 (9.4)
Abortion threatened	4 (0.2)	2 (0.1)	2 (0.2)	4 (2.1)	2 (1.0)	2 (2.1)
Foetal death	3 (0.1)	0	0	3 (1.6)	0	0
Gestational hypertension	3 (0.1)	2 (0.1)	2 (0.2)	3 (1.6)	2 (1.0)	2 (2.1)
Haemorrhage in pregnancy	3 (0.1)	2 (0.1)	0	3 (1.6)	2 (1.0)	0
Hyperemesis gravidarum	3 (0.1)	2 (0.1)	0	3 (1.6)	2 (1.0)	0
Morning sickness	2 (0.1)	4 (0.2)	6 (0.6)	2 (1.0)	4 (1.9)	6 (6.2)
Obstructed labour	0	0	2 (0.2)	0	0	2 (2.1)
Reproductive system and breast disorders (SOC)	391 (18.3)	401 (18.8)	210 (19.6)	41 (21.5)	43 (20.5)	23 (24.0)
Vaginal discharge	166 (7.8)	191 (8.9)	87 (8.1)	20 (10.5)	22 (10.5)	14 (14.6)
Abnormal uterine bleeding	70 (3.3)	60 (2.8)	45 (4.2)	1 (0.5)	3 (1.4)	3 (3.1)
Heavy menstrual bleeding	65 (3.0)	78 (3.7)	38 (3.6)	8 (4.2)	7 (3.3)	2 (2.1)
Intermenstrual bleeding	26 (1.2)	27 (1.3)	14 (1.3)	5 (2.6)	0	0
Dysmenorrhoea	24 (1.1)	28 (1.3)	17 (1.6)	2 (1.0)	3 (1.4)	2 (2.1)
Vulvovaginal pruritus	23 (1.1)	25 (1.2)	7 (0.7)	1 (0.5)	4 (1.9)	0
Vaginal haemorrhage	17 (0.8)	17 (0.8)	3 (0.3)	4 (2.1)	7 (3.3)	1 (1.0)
Respiratory, thoracic and mediastinal disorders (SOC)	76 (3.6)	79 (3.7)	41 (3.8)	8 (4.2)	6 (2.9)	4 (4.2)
Cough	31 (1.4)	27 (1.3)	17 (1.6)	6 (3.1)	2 (1.0)	3 (3.1)
Skin and subcutaneous tissue disorders (SOC)	130 (6.1)	119 (5.6)	56 (5.2)	13 (6.8)	13 (6.2)	8 (8.3)
Rash	34 (1.6)	33 (1.5)	21 (2.0)	5 (2.6)	2 (1.0)	0
Pruritus	13 (0.6)	20 (0.9)	6 (0.6)	1 (0.5)	4 (1.9)	3 (3.1)
Dermatitis	11 (0.5)	10 (0.5)	4 (0.4)	3 (1.6)	2 (1.0)	2 (2.1)

Source: [Data Scientist] adae.xpt; Software: R.
Treatment-emergent adverse events defined as adverse events that began on or after study drug first dose date up through last exposure date for the study Phase after permanent discontinuation of study drug or led to premature study drug discontinuation. Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HLT, high-level term; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event; SC, subcutaneous; SOC, system organ class.

17.6. Injection Site Reactions Supplemental Information

The type, severity, and frequency of ISRs are summarized with the overall assessment of ISRs in Section 7.6.4. See Table 115 and Table 116 for the specific ISR preferred terms reported in each trial.

Table 115. Injection Site Reactions by Preferred Term, Injection Safety Population, PURPOSE 1

Preferred Term	LEN N=2140 n (%)	F/TDF+F/TAF[a] N=3205 n (%)	LEN vs. F/TDF+F/TAF[a] Risk Difference[b] (%) (95% CI)
Number of participants with ISRs	1472 (68.8)	1116 (34.8)	34.0 (31.4, 36.5)
Injection site nodule	1365 (63.8)	530 (16.5)	47.2 (44.8, 49.6)
Injection site pain	669 (31.3)	758 (23.7)	7.6 (5.2, 10.1)
Injection site swelling	96 (4.5)	171 (5.3)	-0.8 (−2.0, 0.4)
Injection site induration	91 (4.3)	32 (1.0)	3.3 (2.4, 4.2)
Injection site pruritus	50 (2.3)	38 (1.2)	1.2 (0.4, 2.0)
Injection site erythema	24 (1.1)	40 (1.2)	-0.1 (−0.7, 0.5)
Injection site discolouration	22 (1.0)	9 (0.3)	0.7 (0.3, 1.3)
Injection site bruising	7 (0.3)	8 (0.2)	0.1 (−0.2, 0.4)
Injection site ulcer	3 (0.1)	4 (0.1)	0.0 (−0.2, 0.3)
Injection site granuloma	2 (<0.1)	1 (<0.1)	0.1 (−0.1, 0.3)
Injection site reaction	2 (<0.1)	2 (<0.1)	0.0 (−0.1, 0.3)
Injection site warmth	2 (<0.1)	3 (<0.1)	-0.0 (−0.2, 0.3)
Injection site haematoma	1 (<0.1)	0	0.0 (−0.1, 0.3)
Injection site haemorrhage	1 (<0.1)	0	0.0 (−0.1, 0.3)
Injection site rash	1 (<0.1)	2 (<0.1)	-0.0 (−0.2, 0.2)
Injection site scab	1 (<0.1)	0	0.0 (−0.1, 0.3)
Injection site scar	1 (<0.1)	1 (<0.1)	0.0 (−0.1, 0.2)
Injection site hypoaesthesia	0	2 (<0.1)	-0.1 (−0.2, 0.1)
Injection site necrosis	0	2 (<0.1)	-0.1 (−0.2, 0.1)
Injection site discharge	0	1 (<0.1)	-0.0 (−0.2, 0.1)
Injection site erosion	0	1 (<0.1)	-0.0 (−0.2, 0.1)
Injection site oedema	0	1 (<0.1)	-0.0 (−0.2, 0.1)
Injection site pallor	0	1 (<0.1)	-0.0 (−0.2, 0.1)
Injection site vesicles	0	1 (<0.1)	-0.0 (−0.2, 0.1)

Source: Clinical Reviewer and Clinical Data Scientist; adae.xpt; Software: R, JMP v17.2.0.
[a] Participants received subcutaneous placebo injections.
[b] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate (coformulated TRUVADA); F/TAF, emtricitabine/tenofovir alafenamide (coformulated DESCOVY); ISR, injection site reaction; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event.

Table 116. Injection Site Reactions by Preferred Term, Injection Safety Population, PURPOSE 2

Preferred Term	LEN N=2183 n (%)	F/TDF[a] N=1088 n (%)	LEN vs. F/TDF[a] Risk Difference[b] (%) (95% CI)
Participants with any ISR	1816 (83.2)	756 (69.5)	13.8 (10.7, 17.0)
Injection site nodule	1383 (63.4)	427 (39.2)	24.1 (20.5, 27.6)
Injection site pain	1231 (56.4)	581 (53.4)	3.0 (-0.6, 6.6)
Injection site erythema	377 (17.3)	211 (19.4)	-2.1 (-5.0, 0.7)
Injection site induration	342 (15.7)	110 (10.1)	5.6 (3.1, 7.9)
Injection site swelling	149 (6.8)	104 (9.6)	-2.7 (-4.9, -0.8)
Injection site pruritus	74 (3.4)	30 (2.8)	0.6 (-0.7, 1.8)
Injection site bruising	67 (3.1)	42 (3.9)	-0.8 (-2.3, 0.5)
Injection site warmth	51 (2.3)	24 (2.2)	0.1 (-1.1, 1.2)
Injection site oedema	17 (0.8)	10 (0.9)	-0.1 (-1.0, 0.5)
Injection site discolouration	15 (0.7)	4 (0.4)	0.3 (-0.3, 0.8)
Injection site ulcer	11 (0.5)	1 (<0.1)	0.4 (-0.0, 0.8)
Injection site hematoma	9 (0.4)	12 (1.1)	-0.7 (-1.5, -0.1)
Injection site haemorrhage	8 (0.4)	6 (0.6)	-0.2 (-0.9, 0.3)
Injection site discomfort	7 (0.3)	2 (0.2)	0.1 (-0.4, 0.5)
Injection site mass	5 (0.2)	2 (0.2)	0.0 (-0.5, 0.4)
Injection site paresthesia	5 (0.2)	3 (0.3)	-0.0 (-0.6, 0.3)
Injection site scar	4 (0.2)	1 (<0.1)	0.1 (-0.3, 0.4)
Injection site vesicles	4 (0.2)	3 (0.3)	-0.1 (-0.6, 0.2)
Injection site discharge	2 (<0.1)	0	0.1 (-0.3, 0.3)
Injection site hyperaesthesia	2 (<0.1)	0	0.1 (-0.3, 0.3)
Injection site inflammation	2 (<0.1)	1 (<0.1)	-0.0 (-0.4, 0.3)
Injection site rash	2 (<0.1)	0	0.1 (-0.3, 0.3)
Injection site reaction	2 (<0.1)	1 (<0.1)	-0.0 (-0.4, 0.3)
Injection site dermatitis	1 (<0.1)	0	0.0 (-0.3, 0.3)
Injection site granuloma	1 (<0.1)	0	0.0 (-0.3, 0.3)
Injection site hypersensitivity	1 (<0.1)	0	0.0 (-0.3, 0.3)
Injection site hypoaesthesia	1 (<0.1)	0	0.0 (-0.3, 0.3)
Injection site irritation	1 (<0.1)	1 (<0.1)	-0.0 (-0.5, 0.2)
Injection site papule	1 (<0.1)	0	0.0 (-0.3, 0.3)
Injection site scab	0	2 (0.2)	-0.2 (-0.7, -0.0)

Source: Clinical Reviewer and Clinical Data Scientist; adae.xpt; Software: R, JMP v17.2.0.
[a] Participants received subcutaneous placebo injections.
[b] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; F/TDF, emtricitabine/tenofovir disoproxil fumarate (coformulated TRUVADA); ISR, injection site reaction; LEN, lenacapavir; N, number of participants in treatment arm; n, number of participants with adverse event.

18. Clinical Virology

HIV-1 Diagnosis and Resistance in the F/TAF and F/TDF Comparator Arms

Key information for the HIV-1 infections among participants randomized to receive F/TAF or F/TDF for PrEP is presented in Table 117, including HIV-1 diagnostic assay results at each timepoint, tenofovir diphosphate (TFV-DP) concentrations in DBS, ART initiation time, and genotypic data (viral subtype and emtricitabine/tenofovir [F/TFV] RAS).

Adherence to oral F/TAF and F/TDF was assessed by analysis of TFV-DP concentrations in DBS, which have been correlated with the number of doses used per week to provide an objective measure of adherence (Grant et al. 2014; Anderson et al. 2018; Yager et al. 2020). The relationship between TFV-DP concentrations and the number of weekly doses are: F/TAF: <2 doses per week (<450 fmol/punch), 2 to 3 doses per week (≥450 to <950 fmol/punch), and ≥4 doses per week (≥950 fmol/punch); F/TDF: <2 doses per week (<350 fmol/punch), 2 to 3 doses per week (≥350 to <700 fmol/punch), and ≥4 doses per week (≥700 fmol/punch). Please see Sections 14.2.2 and 14.2.3 for more information on the adherence data in PURPOSE 1 and PURPOSE 2.

Resistance to F/TFV

Resistance data were reported for 70% (37/53) of PURPOSE 1 participants in the F/TAF group, 62% (16/26) of PURPOSE 1 participants in the F/TDF group, and 69% (9/13) of PURPOSE 2 participants in the F/TDF group who acquired HIV-1. Collectively, variants expressing M184I/V were detected among 6% (3/53) of participants who received F/TAF and among 8% (3/39) of participants who received F/TDF. The M184I-expressing variant isolated from a participant who received F/TAF (b) (6) also expressed K65R.

The low proportion of participants with resistance to F/TFV is consistent with low adherence near the time of virologic failure. It is also possible that additional cases of F/TFV resistance would have been observed among those participants with missing genotypic data or among those participants who had higher levels of adherence but only had early isolates analyzed (e.g., (b) (6), (b) (6)

Table 117. HIV-1 Infections in F/TAF and F/TDF Groups, PURPOSE 1 and PURPOSE 2

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
Prevalent											
PURPOSE 1											
F/TAF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	+	-	+	36,200,000	C	NR
		9	HIV Infection					+	191,000		
		41	30-Day FU					+	22,900	C	M184V
		52	Initiate ART								
		101	90-Day FU					-			
F/TDF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		+	47,500		
		7	Unscheduled		-	-		+	59,000		
		13	HIV Infection		+	+	+	+	187,000		
		96	90-Day FU					+	67,100		
		187	6 Month FU					+	37,600		
		291	9 Month FU					+	<20		
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	+	-	+	512,000	C	NR
		8	Initiate ART								
		15	Unscheduled					+	1,130		
		43	Unscheduled			+	+	+	62		
		49	30-Day FU					+	43		
		100	90-Day FU					-			
PURPOSE 2											
F/TDF	(b) (6)	-29	Screen		-	-		-			
		1	Injection 1		-	+	-	+	90,600,000	F1	NR
		20	Unscheduled					+	104,000		
		70	30-Day FU					+	93,000	F1	M184V
		117	Initiate ART					+	106,000	F1	NR
		209	6-Month FU					+	<20		
F/TDF	(b) (6)	-21	Screen		-	-		-			
		1	Injection 1		-	-		+	207	B	ND
		8	Unscheduled			-		+	1,710		
		23	Unscheduled			+	-	+	528		
		28	Initiate ART		-						
		56	30-Day FU					-			

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
Incident PURPOSE 1											
F/TAF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	BLQ	-	-					
		57	Week 8	BLQ	-	-					
		92	Week 13	BLQ	-	+	-	-			
		99	Unscheduled		-			-			
		183	Injection 2	46.0	-	-					
		277	Week 39	BLQ	-	-					
		366	Week 52	BLQ	-	-		-			
		450	Week 65	BLQ	-	-		-			
		542	Week 78	BLQ	+	+	+	+	10,600	A/D	NR
F/TAF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	136.4	-	-					
		55	Week 8	131.4	-	-		-			
		86	Week 13	63.6	-	-		+	627	D	NR
		176	Injection 2		+	+	+	+	33,400	D	NR
		177	Unscheduled								
F/TAF	(b) (6)	-14	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1150.3	-	-					
		56	Week 8	277.4	-	-					
		90	Week 13	58.6	-	-					
		176	Injection 2	BLQ	-	-		-			
		260	Week 39	294.0	-	-		-			
		355	Initiate ART	BLQ	+	+	+	+	95,700	A1	NR
		403	30-Day FU					+	606,000		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-25	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	63.5	-	-					
		56	Week 8	BLQ	-	-					
		91	Week 13	BLQ	-	-					
		179	Injection 2	BLQ	-	-					
		263	Week 39	BLQ	-	-		-			
		354	Week 52	BLQ	-	-		+	284,000		
		439	Initiate ART		+	+	+	+	38,100		
		469	30-Day FU					+	21		
		530	90-Day FU					+	86		
		619	6-Month FU					+	<20		
F/TAF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	365.6	-	-					
		56	Week 8	122.9	-	-		-			
		88	Week 13	BLQ	-	-		-			
		176	Initiate ART	BLQ	+	+	+	+	258,000	A1	NR
		239	30-Day FU					+	44,900		
		296	90-Day FU					+	23,300		
F/TAF	(b) (6)	-18	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4	1846.2	-	-					
		56	Week 8	2129.5	-	-					
		85	Week 13	1948.1	-	-		-			
		180	Injection 2	129.3	-	-		-			
		266	Week 39	129.3	-	+	-	+	2,320,000	A1	NR
		273	Unscheduled		+			+	11,600		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4	505.5	-	-					
		55	Week 8	174.0	-	-					
		85	Week 13	61.6	-	-					
		201	Injection 2	BLQ	-	-		-			
		285	Week 39	BLQ	-	-		+	335		
		376			+	+		+	338,000		
		386	Initiate ART								
		400						+	291		
		461						-	<20		
F/TAF	(b) (6)	-20	Screen		-	-		-			
		1	Injection 1		-	-		-			
		50	Week 4	BLQ	-	-					
		88	Week 13	BLQ	-	-		-			
		233	Discontinued	BLQ	+	+	+	+	761,000		
F/TAF	(b) (6)	-7	Screen		-	-		-			
		1	Injection 1		-	-		-			
		31	Week 4	572.1	-	-					
		57	Week 8	723.3	-	-		-			
		323	Injection 2	BLQ	+	+	+	+	132,000	C	NR
		351	30-Day FU			+	+				
		386	Initiate ART					+	56,800		
		410	90-Day FU					+	871		
		475	Initiate ART								
		494	6 Month FU					+	61		
		584	9 Month FU					-			
F/TAF	(b) (6)	-28	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	BLQ	-	-		+	1,790	C	NR
		57	Week 8		+	+	+				
		63	HIV Infection					+	92,900	C	NR
		91	30-Day FU					+	117,000		
		92	Initiate ART								
		148	90-Day FU					+	99,500		
		246	6 Month FU					+	29		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	182.5	-	-					
		57	Week 8	147.0	-	-					
		85	Unscheduled		-						
		92	Week 13	112.9	-	-		-			
		183	Injection 2	BLQ	-	-		-			
		274	Week 39	BLQ	+	+	+	+	1,700,000	C	NR
F/TAF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	601.4	-	-					
		56	Week 8	333.3	-	-		-			
		90	Week 13	144.6	-	-		-			
		181	Injection 2	BLQ	+	+	+	+	3,620,000	C	NR
		185	HIV Infection					+	4,480,000		
		219	30-Day FU					+	2,480,000		
		226	Initiate ART								
		274	90-Day FU					+	162		
F/TAF	(b) (6)	-14	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	697.1	-	-					
		55	Week 8	783.7	-	-					
		97	Week 13	941.6	-	-					
		176	Injection 2	61.8	-	-					
		286	Week 39	BLQ	-	-		-			
		357	Week 52	BLQ	+	+	+	+	611,000		
		366	Initiate ART					+	388,000		
		451	30-Day FU					+	26		
F/TAF	(b) (6)	-20	Screen		-	-		-			
		-3	Week 4		-						
		1	Injection 1		-	-		-			
		28	Week 4	1433.2		-					
		57	Week 8	1311.1	-	-					
		92	Week 13	777.1	-	-		-			
		176	Injection 2	215.4	-	-		-			
		271	Week 39	134.6	-	+	+	+	29,300	C	NR
		307	30-Day FU					+	87,100		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		32	Week 4	1040.7	-	-					
		58	Week 8	657.1	-	-		-			
		92	Week 13	527.1	-	-		-			
		184	Injection 2	211.4	+	+	+	+	71,800	C	NR
		192	Initiate ART								
		213	30-Day FU					+	1,760		
		283	90-Day FU					+	<20		
F/TAF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4	777.0	-	-					
		57	Week 8	743.6	-	-		-			
		85	Week 13	411.8	-	-		-			
		176	Injection 2	90.4	-	+	+	+	71,100		
		182	Initiate ART					+	86,200	C	NR
		217	30-Day FU					+	<20		
		273	90-Day FU					+	<20		
F/TAF	(b) (6)	-8	Screen		-						
		-7	Screen			-		-			
		1	Injection 1		-	-		-			
		27	Week 4	503.9	-	-					
		55	Week 8	352.1	-	-		-			
		86	Week 13	193.5	-	-		-			
		176	Initiate ART	BLQ	+	+	+	+	3,400,000	C	NR
		213	30-Day FU					+	43		
		308	90-Day FU					+	44		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-8	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	614.2	-	-					
		57	Week 8	1030.8	-	-					
		92	Week 13	947.5	-	-					
		183	Injection 2	223.5	-	-					
		276	Week 39	251.2	-	-		-			
		358	Week 52	234.3	-	-		-			
		449	Week 65	56.8	+	+	+	+	1,660,000		
		462	Initiate ART								
		479	30-Day FU					+	497		
		543	90-Day FU					+	<20		
F/TAF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	674.9	-	-					
		57	Week 8	806.6	-	-					
		92	Week 13	528.5	-	-		-			
		184	Injection 2	293.5	-	-		-			
		273	Week 39	76.7	-	+	-	+	1,770,000	C	NR
		281	HIV Infection					+	92,900		
		324	30-Day FU					+	17,900		
		368	90-Day FU					+	1,870		
F/TAF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1788.7	-	-					
		56	Week 8	1795.8	-	-					
		92	Unscheduled	2450.0		-		-			
		183	Injection 2	1346.9	-	+	±	+	1,160	C	NR
		191	HIV Infection					+	445		
		229	30-Day FU					+	1,590,000		
		348	90-Day FU					+	85,500		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	288.0	-	-					
		57	Week 8	189.2	-	-					
		87	Week 13	150.7	-	-					
		183	Injection 2	66.6	-	-		-			
		274	Week 39	BLQ	-	-		-			
		365	Week 52	BLQ	+	+	+	+	507,000		
		395	30-Day FU					+	63,500		
		410	Initiate ART								
		452	90-Day FU					+	<20		
F/TAF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1485.1	-	-					
		56	Week 8	1853.4	-	-					
		92	Week 13	1975.9	-	-					
		185	Injection 2	571.5	-	-					
		276	Week 39	1554.3	-	-					
		375	Week 52	2553.7	-	-		-			
		465	Week 65	128.3	-	-		-			
		555	Week 78	BLQ	+			+	539	C	NR
		561	Unscheduled		+			+	496		
		609	30-Day FU			+	+	+	1,750		
F/TAF	(b) (6)	-21	Screen		-	-		-			
		1	Injection 1		-	-		-			
		16	PK Tail Day 1	BLQ	-	-					
		103	PK Tail Week 13	BLQ	-	-					
		191	PK Tail Week 26	BLQ	-	-		-			
		282	PK Tail Week 39	BLQ	-	-		-			
		373	PK Tail Week 52		+	+	+	+	10,300		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-16	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	BLQ	-	-					
		55	Week 8	345.9	-	-		-			
		91	Week 13	185.7	-	-		-			
		181	Injection 2	55.4	-	+	+	+	45,800	C	ND
		189	Unscheduled		+			+	15,400		
		201	Initiate ART								
		229	30-Day FU			+	+	-			
		270	Unscheduled			+	+	+	<20		
F/TAF	(b) (6)	-18	Screen		-	-		-			
		1	Injection 1		-	-		-			
		30	Week 4	74.1	-	-					
		56	Week 8		-						
		57	Week 8	65.7		-					
		86	Week 13	34.9	-	-					
		176	Injection 2	BLQ	-	-					
		260	Week 39	BLQ	-	-					
		359	Week 52	BLQ	-	-		-			
		443	Unscheduled	BLQ	+			+	643,000		
		465	LEN OLE Day 1		+	+	+	+	13,800		
		497	30-Day FU					+	67		
		556	90-Day FU					+	37		
F/TAF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		42	Week 4	BLQ	-	-					
		127	Week 13	BLQ	-	-					
		255	Injection 2	BLQ	-	-		-			
		351	Week 39	38.4	-	-		-			
		443	LEN OLE Day 1		-	+	+	+	4,980,000		
		452	Unscheduled					+	336		
		504	30-Day FU					-			
		542	90-Day FU					-			

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	BLQ	-	-					
		57	Week 8	BLQ	-	-		-			
		106	Week 13	BLQ	-	-		+	218		
		208	Injection 2		+	+	+	+	2,220,000	A	NR
		218	Initiate ART								
		246	30-Day FU					+	184		
F/TAF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	855.0	-	-		-			
		58	Week 8	464.9	-	-		-			
		93	Week 13	534.7	-	-		+	74		
		156	Unscheduled								
		189	Unscheduled		-	+	+	-			
		198	Unscheduled			+	+	-			
		229	30-Day FU					-			
F/TAF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1794.6	-	-					
		56	Week 8	1153.1	-	-					
		92	Week 13	569.2	-	-					
		183	Injection 2	103.1	-	-		-			
		274	Week 39	55.1	-	-		-			
		369	Unscheduled	2.1	+	+	+	+	54,800	C	NR
		376	Initiate ART								
		401	30-Day FU			+	+	+	232		
		461	90-Day FU						48		
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1315.6	-	-		-			
		57	Week 8	1779.2	-	-	-	+	6,890	C	K65R, M184I
		92	Week 13		-	+	+	+	1,510	C	M184I
		103	Initiate ART			+					
		115	Discontinued		-	+	+	+	<20		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		35	Week 4	7782.0	-	-					
		57	Week 8	3259.9	-	-					
		91	Week 13	1137.5	-	-		-			
		211	Injection 2	150.6	-	-		-			
		306	Week 39	253.3	-	-		-			
		427	Week 52	BLQ	+	+	+	+	10,200	C	NR
F/TAF	(b) (6)	-14	Screen		-	-		-			
		1	Injection 1		-	-		-			
		30	Week 4	243.6	-	-					
		58	Week 8	114.9	-	-					
		85	Week 13	69.1	-	-		-			
		183	Injection 2	BLQ	-	-		-			
		267	Week 39	BLQ	+	+	+	+	5,930		
		365	90-Day FU	BLQ				+	6,600		
F/TAF	(b) (6)	-29	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4	1143.8	-	-					
		58	Week 8	868.4	-	-					
		85	Week 13	603.3	-	-					
		181	Injection 2	BLQ	-	-		-			
		267	Week 39	BLQ	-	-		-			
		363	Week 52	BLQ	+	+	+	+	2,950,000	C	NR
		372	Initiate ART								
		386	HIV Infection					+	2,560,000		
		449	30-Day FU					+	235,000		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-20	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	147.8	-	-					
		58	Week 8	144.6	-	-					
		93	Week 13	43.9	-	-					
		183	Injection 2	BLQ	-	-					
		274	Week 39	BLQ	-	-					
		365	Week 52	BLQ	-	-		+	72,500		
		456	Week 65	BLQ	+	+	+	+	226,000		
		492	30-Day FU	BLQ				+	37		
		556	90-Day FU	BLQ				+	<20		
F/TAF	(b) (6)	-26	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	290.7	-	-					
		57	Week 8	184.2	-	-					
		92	Week 13	80.1	-	-		-			
		183	Injection 2	BLQ	-	-		-			
		276	Week 39	BLQ	-	+	-	+	2,010,000	C	NR
		290	Initiate ART					+	517,000		
		312	30-Day FU					+	232		
F/TAF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	211.2	-	-					
		58	Week 8	104.5	-	-					
		93	Week 13	78.7	-	-					
		183	Injection 2	42.4	-	-					
		272	Week 39	BLQ	-	-					
		364	Week 52	BLQ	-	-					
		457	Week 65	119.0	+	+	+	+	526,000		
F/TAF	(b) (6)	-8	Screen		-	-		-			
		1	Injection 1		-	-		-			
		30	Week 4	179.5	-	-		-			
		58	Week 8	72.1	-	-		-			
		93	Week 13	BLQ	+	+	+	+	49,600	C	NR
		121	Initiate ART								
		126	30-Day FU					+	40,300	C	
		184	90-Day FU					-			

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	398.5	-	-					
		57	Week 8	768.0	-	-					
		92	Week 13	1089.8	-	-					
		178	Injection 2	84.1	-	-		-			
		262	Week 39	148.1	-	-		-			
		360	Week 52	87.9	-	+	-	+	17,700,000	C	NR
		373	Unscheduled					+	23,200,000		
		378	Initiate ART								
		395	30-Day FU			+	+	+	572		
		546	Unscheduled					+	46		
F/TAF	(b) (6)	-33	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1576.7	-	-					
		57	Week 8	1829.0	-	-					
		94	Week 13	556.6	-	-					
		183	Injection 2	BLQ	-	-		-			
		268	Week 39	BLQ	-	-		-			
		366	Week 52	187.6	+	+	+	+	4,820	C	NR
		374	HIV Infection					+	565	C	NR
		403	30-Day FU			+	+	+	284,000		
		436	Initiate ART								
		500	90-Day FU					+	21,000		
		599	6-Month FU					+	6,470		
		788	12-Month FU					+	3,830		
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		41	Week 4	BLQ	-	-					
		57	Week 8	81.8	-	-					
		91	Week 13	BLQ	-	-		-			
		183	Injection 2	BLQ	-	-		-			
		277	Week 39	BLQ	-	+	+	+	14,600	C	NR
		287	HIV Infection					+	1,480		
		298	Initiate ART								
		329	30-Day FU					-			
		407	90-Day FU					-			

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-18	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1212.0	-	-					
		57	Week 8	1282.4	-	-					
		92	Week 13	587.4	-	-		-			
		179	Injection 2			-		-			
		182	Injection 2	56.8	-						
		270	Week 39	34.3	+	+	+	+	4,960	C	NR
		290	Initiate ART								
		312	30-Day FU					+	<20		
		402	90-Day FU					-			
F/TAF	(b) (6)	-14	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	220.4	-	-					
		58	Week 8	137.1	-	-					
		92	Week 13	44.7	-	-					
		184	Injection 2	BLQ	-	-					
		288	Week 39	BLQ	-	-		-			
		364	Week 52	BLQ	-	-		-			
		450	Week 65	113.3	+	+	+	+	1,990		
		498	30-Day FU					+	<20		
		533	90-Day FU					+	<20		
F/TAF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	BLQ	-	-					
		56	Week 8	99.6	-	-					
		91	Week 13	94.6	-	-		-			
		178	Injection 2	68.5	-	-		-			
		280	Week 39	BLQ	+	+	+	+	33,900	C	NR
		317	30-Day FU					+	48		
		408	90-Day FU					+	<20		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1571.0	-	-					
		57	Week 8	1259.5	-	-		-			
		92	Week 13	429.6	-	-		-			
		183	Injection 2	53.5	-	+	+	+	20,000	C	NR
		190	Unscheduled					+	1,250		
		192	Initiate ART								
		226	30-Day FU					+	<20		
		274	90-Day FU					+	<20		
F/TAF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4		-	-					
		55	Week 8		-	-					
		86	Week 13		-	-		-			
		176	Injection 2		-	-		-			
		260	Week 39		+	+	+	+	853,000	C	NR
		302	30-Day FU					+	7,240		
		351	90-Day FU					+	6,270		
		435	6 Month FU					+	101,000		
F/TAF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	1344.6	-	-					
		55	Week 8		-	-		-			
		110	Week 13	360.4	-	-		-			
		176	Injection 2	39.8	-	+	-	+	27,000,000		
		183	Unscheduled		+	+	-	+	4,100,000	C	NR
		263	30-Day FU					+	576,000		
		273	Initiate ART								
		384	6 Month FU					+	257,000		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	176.7	-	-					
		57	Week 8	729.2	-	-					
		96	Week 13	991.2	-	-		-			
		189	Injection 2	404.8	-	-		+	4,500	C	M184I
		293	Unscheduled		+			+	752	C	NR
		293	Week 39		-	+	-	+	908		
		309	Unscheduled					+	42		
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	BLQ	-	-					
		56	Week 8	BLQ	-	-					
		90	Week 13	BLQ	-	-					
		182	Injection 2	BLQ	-	-					
		273	Week 39	BLQ	-	-					
		368	Week 52	BLQ	-	-					
		459	Week 65	BLQ	-	-		-			
		550	LEN OLE Day 1		-	+	+	+	23,600		
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	569.7	-	-					
		55	Week 8	1218.8	-	-					
		91	Week 13	1580.1	-	-					
		181	Injection 2	120.8	-	-		-			
		272	Week 39	62.6	-	-		-			
		363	Week 52	BLQ	-	+	+	+	638,000	C	NR
		369	Initiate ART								
		386	Unscheduled			+	+	+	978		
		396	30-Day FU					+	553		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TAF	(b) (6)	-29	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	307.6	-	-		-			
		57	Week 8	186.0	-	-		-			
		89	Discontinued	63.8	+	+	+	+	796,000	C	NR
		119	30-Day FU					+	17,800		
		120	Initiate ART								
		182	90-Day FU					-			
F/TAF	(b) (6)	-18	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	364.1	-	-					
		56	Week 8	215.1	-	-		-			
		85	Week 13	593.5	-	-		-			
		189	Injection 2	BLQ	+	+	+	+	1,290,000	C	NR
		225	30-Day FU	BLQ		+	+	+	1,710,000		
		235	Initiate ART								
		273	90-Day FU					+	1,420,000		
F/TAF	(b) (6)	-10	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	814.0	-	-		-			
		57	Week 8	422.9	-	-		+	210		
		92	Week 13		+	+	+	+	448	C	NR
		116	Initiate ART								
		123	30-Day FU					-			
F/TDF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	80.8	-	-					
		58	Week 8	BLQ	-	-					
		91	Week 13	BLQ	-	-					
		212	Injection 2	BLQ	-	-					
		301	Week 39	BLQ	-	-		-			
		402	Week 52	74.0	-	-		+	165		
		499	Week 65		-	+	+	+	21,600	C	NR
		521	30-Day FU					+	<20		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-42	Screen		-	-		-			
		-8	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	684.8	-	-					
		85	Week 13	374.0	-	-		-			
		181	Injection 2	612.8	-	-		-			
		272	Week 39	142.7	-	+	-	+	1,080,000	C	NR
		338	30-Day FU					+	<20		
		437	90-Day FU					+	<20		
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4		-	-					
		56	Week 8		-	-					
		85	Week 13		-	-					
		176	Injection 2		-	-					
		267	Week 39		-	-					
		351	Week 52		-	-		-			
		436	Week 65		-	-		-			
		533	LEN OLE Day 1		-	-		+	12,600	A1	
		559	LEN OLE Week 4		-	+	-	-			
		589	LEN OLE Week 8		-	+	-	-			
		618	LEN OLE Week 13		-	+	-	-			
		639	Unscheduled			+	-	-			
		717	LEN OLE Week 26		-	+	-	-			
F/TDF	(b) (6)	-17	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	312.7	-	-					
		56	Week 8	150.8	-	-		-			
		92	Week 13	299.5	-	-		+	1,620	A1	NR
		179	Injection 2	41.8	+	+	+	+	777,000	A1	NR
		194	HIV Infection					+	1,880,000		
		222	Initiate ART					+	52,200		
		284	90-Day FU					+	<20		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4		-	-					
		55	Week 8		-	-					
		85	Week 13		-	-					
		183	Injection 2		-	-		-			
		267	Week 39		-	-		-			
		371	LEN OLE Day 1		+	+	+	+	75,000		
		398	30-Day FU					+	33		
		465	90-Day FU					+	<20		
F/TDF	(b) (6)	-16	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	367.8	-	-					
		57	Week 8	757.0	-	-					
		92	Week 13	1026.4	-	-					
		182	Injection 2	809.5	-	-		-			
		272	Week 39	63.1	-	-		-			
		364	Week 52	81.2	+	+	+	+	1,200,000	A/C	NR
		408	30-Day FU					+	313		
F/TDF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1199.1	-	-					
		63	Week 8	566.2	-	-		-			
		90	Week 13	307.6	-	-		-			
		209	Injection 2	BLQ	-	+	+	+	5,330	C	NR
		252	30-Day FU					+	4,280		
		299	90-Day FU					+	13,000		
		400	6-Month FU					+	13,900		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-25	Screen		-	-		-			
		1	Injection 1		-	-		-			
		30	Week 4	133.1	-	-					
		60	Week 8	366.4	-	-					
		97	Week 13	224.3	-	-		-			
		176	Injection 2	66.0	-	-		+	38,200	C	NR
		268	Week 39		+	+	+	+	108,000	C	M184I/V
		282	Initiate ART								
		310	30-Day FU					+	112,000		
		365	90-Day FU					+	165,000		
		463	6 Month FU					+	<20		
F/TDF	(b) (6)	-11	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1002.0	-	-					
		57	Week 8	1578.2	-	-					
		92	Week 13	764.0	-	-					
		180	Injection 2	644.1	-	-					
		271	Week 39	626.1	-	-					
		369	Week 52	BLQ	-	-		-			
		453	Week 65	BLQ	-	-		-			
		550	Week 78	BLQ	+	+	±	+	23,100	C	NR
		560	HIV Infection					+	509		
		581	30-Day FU					+	306		
		584	Initiate ART								
		640	90-Day FU					-			
F/TDF	(b) (6)	-25	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	1043.8	-	-					
		58	Week 8	1122.2	-	-		-			
		85	Week 13	1431.5	-	-		-			
		176	Injection 2	220.8	+	+	+	+	147,000	C	NR
		199	30-Day FU					+	113		
		270	90-Day FU					-			

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4		-	-					
		57	Week 8		-	-					
		96	Week 13		-	-					
		183	Injection 2		-	-					
		277	Week 39		-	-		-			
		366	Week 52		-	-		-			
		457	Week 65		-	-		+	150,000		
		548	LEN OLE Day 1		+	+	+	+	1,540		
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		85	Week 13		+	+	+	+	73,800	A1	NR
		85	Initiate ART			+	+	+	1,200,000		
		93	Unscheduled		+						
		115	30-Day FU					+	165		
		210	90-Day FU					+	<20		
F/TDF	(b) (6)	-8	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	380.5	-	-					
		57	Week 8	658.0	-	-					
		89	Week 13	468.2	-	-					
		182	Injection 2	361.0	-	-		-			
		274	Week 39	86.0	-	-		-			
		364	Week 52	67.2	+	+	+	+	8,370	C	NR
		370	Initiate ART								
		393	30-Day FU					+	37		
		454	90-Day FU					-			

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4		-	-					
		55	Week 8		-	-					
		94	Week 13		-	-					
		185	Injection 2		-	-					
		296	Unscheduled			-		-			
		365	Week 52		-	-		-			
		457	Week 65		-	-		-			
		542	LEN OLE Day 1		+	+	+	+	236,000		
		577	30-Day FU					+	281		
		636	90-Day FU					+	<20		
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		31	Week 4	264.0	-	-					
		58	Week 8	223.9	-	-					
		87	Week 13	329.2	-	-		-			
		184	Injection 2	100.2	-	-		-			
		274	Week 39	284.0	+	+	+	+	310,000	C	NR
		302	Initiate ART								
		304	30-Day FU					+	44		
F/TDF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	121.1	-	-					
		58	Week 8	50.7	-	-					
		93	Week 13	BLQ	-	-					
		183	Injection 2	BLQ	-	-		-			
		274	Week 39	BLQ	-	-		-			
		365	LEN OLE Day 1	BLQ	+	+	+	+	194,000		
		400	30-Day FU					+	71,700		
		457	90-Day FU					+	16,900		
		468	Unscheduled					+	21,300		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-8	Screen		-	-		-			
		1	Injection 1		-	-		-			
		33	Week 4	670.9	-	-					
		56	Week 8	1048.0	-	-					
		91	Week 13	1266.8	-	-					
		215	Injection 2	817.7	-	-		-			
		301	Week 39	566.1	-	-		-			
		307	Unscheduled			-					
		397	Week 52	815.6	+	+	+	+	2,660	C	ND
		404	HIV Infection					+	3,660		
		434	30-Day FU					+	22,000		
F/TDF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	367.8	-	-					
		58	Week 8	587.3	-	-					
		92	Week 13	163.3	-	-					
		183	Injection 2	50.1	-	-		-			
		268	Week 39	BLQ	-	-		-			
		361	LEN OLE Day 1	BLQ	-	+	+	+	1,210		
		396	30-Day FU			+	+	+	<20		
		493	90-Day FU					-			
F/TDF	(b) (6)	-9	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4		-	-					
		55	Week 8		-	-					
		110	Week 13		-	-		-			
		176	Injection 2		-	-		-			
		260	Week 39		+	+	+	+	2,230	C	NR
		265	Unscheduled					+	153		
		275	Initiate ART								
		288	30-Day FU					+	<20		
		343	90-Day FU					-			

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	876.5	-	-					
		58	Week 8	388.9	-	-					
		91	Week 13	217.4	-	-		-			
		206	Injection 2	BLQ	-	-		-			
		301	Week 39	BLQ	+	+	+	+	14,200	C	NR
		309	Unscheduled					+	5,020		
		381	Initiate ART								
		409	Unscheduled		+						
		470	90-Day FU					-			
F/TDF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	47.9	-	-					
		56	Week 8	84.5	-	-					
		92	Week 13	47.3	-	-		-			
		176	Injection 2	BLQ	-	-		-			
		260	Week 39	BLQ	+	+	+	+	13,600	C	NR
		269	Unscheduled					+	3,840		
		287	30-Day FU					+	5,490		
		354	Unscheduled					+	4,270		
F/TDF	(b) (6)	-16	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4		-	-					
		55	Week 8		-	-					
		89	Week 13		-	-		-			
		183	Injection 2		-	-		+	272,000		
		275	Week 39		+	+	+	+	19,400,000		
		289	Unscheduled					+	7,210,000		
		328	Unscheduled					+	7,240		
		383	90-Day FU					+	17,600		
		474	6-Month FU					+	2,890		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local	Central				HIV-1 Subtype	F/TFV RAS
					Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL		
F/TDF	(b) (6)	-28	Screen		-	-		-			
		1	Injection 1		-	-		-			
		31	Week 4		-						
		36	Unscheduled		-						
		36	Week 4			-					
		57	Week 8		-	-					
		85	Week 13		-	-		-			
		186	Injection 2		-	-		-			
		270	Week 39		-	+	+	+	35,400	C	
		279	Unscheduled		+			+	12,600		
		309	30-Day FU					-			
		372	90-Day FU					-			
F/TDF	(b) (6)	-11	Screen			-		-			
		-8	Screen		-						
		1	Injection 1		-	-		-			
		29	Week 4	292.3	-	-					
		57	Week 8	633.0	-	-		-			
		94	Week 13	184.1	-	-		-			
		183	Injection 2	BLQ	+	+	+	+	12,000	C	NR
		222	Initiate ART								
		249	30-Day FU			+	+	-			
		274	90-Day FU					+	<20		
PURPOSE 2											
F/TDF	(b) (6)	-12	Screen		-	-		-			
		1	Injection 1		-	-		-			
		88	PK Tail Day 1		-	+	-	+	32,800,000		
		95	Initiate ART		+			+	644,000	B	NR
		107	30-Day FU					+	850		
F/TDF	(b) (6)	-16	Screen		-	-		-			
		1	Injection 1		-	-		-			
		34	Week 4	367.0	-	-					
		69	Week 8	363.8	-	-					
		92	Week 13	467.6	-	-					
		190	Injection 2	343.5	-	-		-			
		323	Week 39	51.2	+	+	+	+	789,000	B	NR
		341	Initiate ART					+	74,200		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4		-	-					
		57	Week 8		-	-					
		91	Week 13		-	-					
		190	Injection 2		-	-					
		274	Week 39		-	-		-			
		370	LEN OLE Day 1		-	+		+	2,120,000		
		412	30-Day FU					+	9,230		
		470	90-Day FU					+	67		
F/TDF	(b) (6)	-13	Screen		-	-		-			
		1	Injection 1		-	-		-			
		62	Week 8	BLQ	-	-					
		94	Week 13	276.2	-	-		-			
		183	Injection 2	86.7	-	-		+	209,000	C	NR
		283	Week 39		+	+	+	+	159,000	C	M184V
		297	Initiate ART								
		311	30-Day FU					+	185		
F/TDF	(b) (6)	-29	Screen		-	-		-			
		1	Injection 1		-	-		-			
		27	Week 4	624.9	-	-					
		55	Week 8	950.3	-	-					
		86	Week 13	909.1	-	-					
		211	Injection 2	200.5	-	-		-			
		308	Week 39	BLQ	+	+	+	+	35,500,000	B	NR
		309	Initiate ART								
		342	30-Day FU					+	111		
F/TDF	(b) (6)	-15	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	83.6	-	-					
		56	Week 8	57.8	-	-					
		95	Week 13	BLQ	-	-		-			
		184	Injection 2	BLQ	-	+	+	+	3,180,000		
		193	Initiate ART					+	3,130,000	B	NR
		226	30-Day FU					+	396		
		275	90-Day FU					+	52		

					Local	Central					
Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Rapid Ag/Ab	Lab Ag/Ab	HIV-1/2 Ab	RNA	copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-22	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	829.0	-	-					
		55	Week 8	772.1	-	-					
		104	Week 13	300.2	-	-					
		182	Injection 2	BLQ	-	-		-			
		281	Week 39	BLQ	-	+	+	+	3,440,000		
		285	Unscheduled		+			+	2,530,000	C	NR
F/TDF	(b) (6)	-21	Screen		-	-		-			
		1	Injection 1		-	-		-			
		33	Week 4	41.1	-	-		-			
		57	Week 8	BLQ	-	-		+	639		
		95	Week 13		+	+	+				
		103	HIV Infection					+	58,300	C	NR
		169	30-Day FU					+	121,000		
		208	Unscheduled					+	144,000		
		301	6-Month FU					+	66,500		
		313	Discontinued			+	+	+	72,800		
F/TDF	(b) (6)	-18	Screen		-	-		-			
		1	Injection 1		-	-		-			
		29	Week 4	918.3	-	-					
		58	Week 8	768.0	-	-					
		93	Week 13	200.7	-	-		-			
		238	Injection 2	BLQ	+	+	+	+	6,860,000	C	
F/TDF	(b) (6)	-14	Screen		-	-		-			
		1	Injection 1		-	-		-			
		28	Week 4	201.0	-	-					
		57	Week 8	312.8	-	-					
		91	Week 13	192.2	-	-					
		183	Injection 2	79.6	-	-					
		274	Week 39	BLQ	-	-					
		362	Week 52	BLQ	-	-		-			
		449	Week 65	BLQ	-	+	-	+	344,000		
		456	Unscheduled					+	116,000	C	NR
		476	Discontinued			+	±	+	27,300		

Arm	ID	DAY	VISIT	[TFV-DP][1] (fmol/punch)	Local Rapid Ag/Ab	Central Lab Ag/Ab	Central HIV-1/2 Ab	Central RNA	Central copies/mL	HIV-1 Subtype	F/TFV RAS
F/TDF	(b) (6)	-24	Screen		-	-		-			
		1	Injection 1		-	-		-			
		31	Week 4	238.9	-	-					
		57	Week 8	202.5	-	-					
		92	Week 13	71.4	-	-					
		185	Injection 2	BLQ	-	-					
		278	Week 39		-	-		-			
		362	LEN OLE Day 1	BLQ	+	+	+	+	5,670		

Source: adcm.xpt datasets for PURPOSE 1 (Gilead Sciences 2024a) and PURPOSE 2 (Gilead Sciences 2024d), adsl.xpt datasets for PURPOSE 1 (Gilead Sciences 2024b) and PURPOSE 2 (Gilead Sciences 2024e); lb.xpt datasets for PURPOSE 1 (Gilead Sciences 2024c) and PURPOSE 2 (Gilead Sciences 2024f); PC-412-2006 (Gilead Sciences 2024g) and PC-528-2004 (Gilead Sciences 2024h), 90-Day Safety Update Narratives for PURPOSE 1 (Gilead Sciences 2025a) and PURPOSE 2 (Gilead Sciences 2025b).

[1] Tenofovir diphosphate, the active moiety of both TAF and TDF, concentrations in red blood cells collected in dried blood spots.

Abbreviations: Ab, HIV antibody test; Ag/Ab, HIV antigen/antibody test; ART, time of initiating antiretroviral therapy (dolutegravir, lamivudine, and tenofovir disoproxil fumarate); BLQ, below the assay's limit of quantification (25 fmol/punch); F/TDF, emtricitabine/tenofovir disoproxil fumarate (Truvada); F/TFV, emtricitabine/tenofovir; FU, post-HIV-1 infection follow-up visit; HIV, human immunodeficiency virus; ID, participant identifier; Lab, laboratory-based assay; LEN, lenacapavir; ND, no data; NR, no resistance associated substitutions detected; OLE, Open-Label Extension; RNA, ribonucleic acid; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate; +, positive assay result, -, negative assay result, ±, indeterminate assay result.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Lenacapavir is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Surface plasmon resonance sensorgrams showed dose-dependent and saturable binding of lenacapavir to cross-linked wild-type capsid hexamer with an equilibrium binding constant (K_D) of 1.4nM. Lenacapavir inhibits HIV-1 replication by interfering with multiple essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of capsid protein subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids). Refer to the Integrated Review of NDA 215973/215974 dated February 28, 2022, for a summary of the supporting data (FDA 2022a).

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section 10.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 118). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 118. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	The following Boxed Warning was added to alert healthcare providers of the risk of drug resistance of YEZTUYGO for HIV-1 PrEP in those with undiagnosed HIV-1 infection. See Section 7.7.1 for additional detail. **WARNING: RISK OF DRUG RESISTANCE WITH USE OF YEZTUGO FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED HIV-1 INFECTION** Individuals must be tested for HIV-1 infection prior to initiating YEZTUGO, and with each subsequent injection of YEZTUGO, using a test approved or cleared by the FDA for the diagnosis of acute or primary HIV-1 infection. Drug-resistant HIV-1 variants have been identified with use of YEZTUGO by individuals with undiagnosed HIV-1 infection. Do not initiate YEZTUGO unless negative infection status is confirmed. Individuals who acquire HIV-1 while receiving YEZTUGO must transition to a complete HIV-1 treatment regimen *[see Dosage and Administration (2.1), Contraindications (4), Warnings and Precautions (5.1, 5.2)].*
1 INDICATIONS AND USAGE	Indications statement was modified to add change "prevent" to "reduce the risk of" and to add "who are at risk for HIV-1 acquisition" to be consistent with other PrEP labels.
2 DOSAGE AND ADMINISTRATION	2.1 HIV-1 Screening for Individuals Receiving YEZTUGO for HIV-1 Pre-Exposure Prophylaxis Added recommended to confirm negative antigen/antibody-specific HIV-1 test results with RNA-specific assay. See Section 7.7.1 for additional detail. 2.4 Dosing Schedule for Missed Dose Added instructions on what to do for missed oral initiation dose at the beginning of the subsection. Made edits to provide additional clarity on the types of missed doses including changing planned missed dose to anticipated delayed injection and to change maintenance dosing to continuation dosing.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	2.5 Dosage Modifications for co-administration with Strong or Moderate CYP3A Inducers Added Table 4 Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Strong CYP3A Inducers and Table 5 Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Moderate CYP3A Inducers to provide detailed information on dose modification of YEZTUGO when taken with strong or moderate CYP3A inducers. See Sections 7.7.3 and 14.5 for additional detail. 2.6 Preparation and Administration of Subcutaneous Injection Removed [redacted (b) (4)] revised the thigh as a recommended site to an alternative injection site, and revised the 2nd injection site recommendation to be at least 4 inches from first injection site. See Section 7.7.2 for additional detail. Removed the following statement [redacted (b) (4)]
4 CONTRAINDICATIONS	Specified that YEZTUGO is contraindicated in individuals with unknown "or positive" HIV-1 status. Removed [redacted (b) (4)] as instructions on dosage modification was added to subsection 2.5. See Sections 7.7.3 and 14.5 for additional detail.
5 WARNINGS AND PRECAUTIONS	5.1 Comprehensive Management to Reduce the Risk of HIV-1 Infection and Other Sexually Acquired Infections Additional information on comprehensive management to reduce HIV-1 infection and other sexually acquired infections were added to align with other HIV-1 PrEP labeling. 5.2 Potential Risk of Resistance with YEZTUGO Additional information on how to minimize risk of resistance to YEZTUGO (e.g., confirm HIV-1 status) and recommendations on alternative forms of PrEP following discontinuation of YEZTUGO was added to align with other HIV-1 PrEP labeling. See Section 7.7.1 for additional detail. 5.3 Long-Acting Properties and Potential Associated Risks with YEZTUGO Recommendation for provider on selection due to those individuals who agree to the required every 6-month injection was added along with risk of increased exposure when YEZTUGO is coadministered with CYP3A substrates was added. See Section 5.2 for additional detail.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience In addition to the injection site reactions, all adverse reactions (all grades) reported in at least 2% of participants receiving YEZTUGO in either PURPOSE 1 or PURPOSE 2 were added to the main safety table (Table 6) and both PURPOSE 1 and PURPOSE 2 used TRUVADA as a comparator. See Sections 7.6.1.5 and 7.6.2.5 for additional detail. Table 7 with types of injection site reactions (all grades) in ≥2% of participants receiving YEZTUGO in PURPOSE 1 or PURPOSE 2 was added. See Section 7.6.4 for additional detail. Summary of nodules and indurations from CAPELLA was added from HIV-1 treatment trial data.
7 DRUG INTERACTIONS	7.1 Effects of Other Drugs on YEZTUGO Removed [redacted] (b) (4) and added recommendation that dosage modifications (supplemental doses) of YEZTUGO are recommended when initiating strong or moderate CYP3A inducers. See Sections 7.7.3 and 14.5 for additional detail. 7.2 Effect of YEZTUGO on Other Drugs The co-administration of YEZTUGO with substrates of CYP3A or P-gp may increase the concentrations of these substrates and result in the increased risk of their adverse events. See the prescribing information of these substrates for dosing recommendations or appropriate monitoring of safety. See Section 14.5 for additional detail. [redacted] (b) (4) 7.4 Drugs without Clinically Significant Interactions with YEZTUGO Removed [redacted] (b) (4) from this list. See Sections 8.2 and 14.2 for additional detail.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy The following was added to *Clinical Considerations*. See Section 8.4 for additional details. *Clinical Considerations* Disease-associated maternal and/or embryo/fetal risk Published studies indicate an increased risk of HIV-1 infection during pregnancy and an increased risk

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	of mother to child transmission during acute HIV-1 infection. In women at risk of acquiring HIV-1, consideration should be given to methods to prevent acquisition of HIV-1, including continuing or initiating YEZTUGO for HIV-1 PrEP, during pregnancy. **8.2 Lactation** The following benefit risk statement was added. See Section 8.4 for additional detail. In women without HIV-1 infection, the developmental and health benefits of breastfeeding and the mother's clinical need for YEZTUGO for HIV-1 PrEP should be considered along with any potential adverse effects on the breastfed child from YEZTUGO and the risk of HIV-1 acquisition due to nonadherence and subsequent mother to child transmission. **8.4 Pediatric Use** Safety and effectiveness data to support the use of YEZTUGO in adolescents weighing at least 35 kg was added along with recommendation for HIV-1 testing prior to initiating YEZTUGO. In addition, recommendation for additional counseling and appointment reminders in the adolescent population to support adherence to the dosing and testing schedule. See Section 8.3 for additional detail. **8.5 Geriatric Use** Statement on management of elderly individuals was added per 21 CFR 201.57(c)(9)(v)(A).
9 DRUG ABUSE AND DEPENDENCE	NA
10 OVERDOSAGE	NA
12 CLINICAL PHARMACOLOGY	12.4 Microbiology *In Clinical Trials* Description of incident infections and prevalent infections from PURPOSE 1 and PURPOSE 2 were added. See Section 7.7.1 for additional detail.
13 NONCLINICAL TOXICOLOGY	NA

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
14 CLINICAL STUDIES	Addition details of trial design including the population, site of injection and location of trials was added. The efficacy results for both PURPOSE 1 and PURPOSE 2 was modified to remove the background rate and to describe that efficacy was based on planned interim analysis following sequential HIV-1 incidence testing for YEZTUGO compared with background followed by YEZTUGO compared to TRUVADA at alpha level of 0.0026. See Sections 1.2, 6.2, 6.3.1, 15.1.4, 15.1.5, 15.2.5, and 16 for additional detail.
17 PATIENT COUNSELING INFORMATION	NA
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No major changes were made to the Product Quality Sections (i.e., 3 DOSAGE FORMS AND STRENGTHS, 11 DESCRIPTION, and 16 HOW SUPPLIED/STORAGE AND HANDLING) as the content of these sections for YEZTUGO PI is aligned with the previously approved PI for SUNLENCA.

Source: Reviewer-generated table.
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation: PI, Prescribing Information.

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- USPI
- Patient package insert (PPI)
- Instructions for use
- Carton and container labeling

24. Postmarketing Requirements and Commitments

There are no postmarketing requirements and one postmarketing commitment (PMC) associated with these applications.

PMC 4836-1 (NDA 220018) and 4837-1 (NDA 220020)

Conduct a study to determine the phenotype of LEN against the following HIV-1 capsids: 1) subtype A1 containing the P111T substitution; 2) subtype C containing the T54A, Q67R, I73V, and A105V substitutions, 3) subtype C containing the T54S and T107A substitutions, and 4) subtype D containing the L56M and L69V substitutions, assessed individually and in the context in which these were identified. In your study, use a wildtype control and known resistance-associated substitutions, such as a subtype B capsid with the K70N substitution (24-fold change in EC_{50} value) representing the range of reductions in susceptibility for comparison.

- Final Report Submission: 06/2026

25. Financial Disclosure

Table 119. Covered Clinical Studies: GS-US-412-5624 and GS-US-528-9023

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 883		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 875		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration.

The Applicant adequately disclosed financial interests/arrangements with clinic investigators as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators* (February 2013), and by 21 CFR 54.4. None of the 883 investigators for GS-US-412-5624 and GS-US-528-9023 are employed by the Applicant. Eight of the investigators (<1%) have financial interests or arrangements with the Applicant and all submitted information about financial disclosures. The remaining investigators (>99%) have no financial interests or arrangements with the Applicant, as defined in 21 CFR 54.2.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint (diagnosis of HIV-1 infection) is an objective laboratory measurement that is assessed centrally and not vulnerable to investigator bias. In addition, both trials were randomized, active-controlled, and double-blind, which would minimize the potential for investigator bias to play a role. Finally, <1% of investigators had financial interests or arrangements with the Applicant.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

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27. Review Team

Table 120. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Kevin Allen, MS
Nonclinical reviewer	Deacqunita Harris, PhD
Nonclinical team leader	Laine Peyton Myers, PhD, DABT
Virology reviewer(s)	Damon Deming, PhD Eric Donaldson, PhD
Virology Team Leader	Julian O'Rear, PhD
OCP reviewer(s)	Jomy George, PharmD Jiajun Liu, PharmD (Pharmacometrics) Yuching Yang, PhD (PBPK)
OCP team leader(s)	Su-Young Choi, PharmD, PhD Justin Earp, PhD (Pharmacometrics) Manuela Grimstein, PhD (PBPK)
Clinical reviewer (s)	Timothy Jancel, PharmD, MHS Ursula Levitov, MD
Clinical team leader	Stephanie Troy, MD
Biometrics reviewer	Yanming Yin, PhD
Biometrics team leader	Wen Zeng, PhD
Cross-discipline team leader	Stephanie Troy, MD
Associate Director for Labeling	Stacey Min, PharmD
Division director (pharm/tox)	Hanan Ghantous, PhD, DABT
Division director (OCP)	Kellie Reynolds, PharmD
Division director (OB)	Scott Komo, DrPH
Division director (clinical)	Wendy Carter, DO
Office director (or designated signatory authority)	Wendy Carter, DO

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology.

Table 121. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Hudson Roth, PhD (ATL) Akshata Nevrekar, PhD (Drug Product) Ruth Moore, PhD (OPMA) Kshitij Patkar, PhD (OPMA) Omolara Oyinlola-Adeyemi (RBPM)
Microbiology	Shannon Heine, PhD Neal Sweeney, PhD
OPDP	Wendy Lubarsky, PharmD
OSI	Elena Boley, MD, MBA, FCAP Phillip Kronstein, MD
DMPP	Maria Nguyen, MSHS, BSN, RN Barbara Fuller RN, MSN, WOCN (TL)
DPMH	Katie Kratz, MD Miriam Dinatale, DO (TL)
OSE/DMEPA	Melina Fanari, RPh Yevgeniya Kogan, PharmD (TL)
Other	
Medical Editor	Monika Deshpande, PhD (TL) Joseph Dorn, MPH, PMP Katherine Brophy
Clinical Data Scientist	William Quarles, PhD DeAngelo McKinley, PharmD, PhD (TL)

Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DPMH, Division of Pediatric and Maternal Health; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology

27.1. Reviewer Signatures

Table 27-122 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Karen Winestock ORO DROID	Sections: 12, 27	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Karen Winestock			**Digitally signed by Karen Winestock** **Date: 6/11/2025 1:52 PM EDT** **GUID: 2025611175232**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Tertiary Reviewer	David Claffey OPQAI DPQAIII	Sections: module 5 section 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: David Claffey			**Digitally signed by David Claffey** **Date: 6/11/2025 1:54 PM EDT** **GUID: 2025611175437**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Deacqunita Harris OID DPTID	Sections: 7.1 and 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Deacqunita Harris			**Digitally signed by Deacqunita Harris** **Date: 6/11/2025 1:56 PM EDT** **GUID: 2025611175657**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Virology Discipline Secondary Reviewer	Julian O Rear OID DAV	Sections: 18, 16, 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Julian O Rear			**Digitally signed by Julian O Rear** **Date: 6/11/2025 2:05 PM EDT** **GUID: 202561118518**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Scott Komo OB DBIV	Sections: 6, 15, 16	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Scott Komo			**Digitally signed by Scott Komo** **Date: 6/11/2025 2:05 PM EDT** **GUID: 202561118536**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	Akshata Nevrekar OPQAI DPQAIII	Sections: 9 (page 150)	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Akshata Nevrekar			**Digitally signed by Akshata Nevrekar** **Date: 6/11/2025 2:20 PM EDT** **GUID: 202561118209**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Wen Zeng OB DBIV	Sections: 6, 15, 16	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Wen Zeng			**Digitally signed by Wen Zeng** **Date: 6/11/2025 2:36 PM EDT** **GUID: 202561118366**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 5.2, 8.1, 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Justin Earp			**Digitally signed by Justin Earp** **Date: 6/11/2025 2:37 PM EDT** **GUID: 2025611183714**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Su-Young Choi OCP DIDP	Sections: 5,6,7,8, and 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Su-Young Choi			**Digitally signed by Su-Young Choi** **Date: 6/11/2025 2:39 PM EDT** **GUID: 2025611183928**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Hanan Ghantous OID DPTID	Sections: 7.1, 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hanan Ghantous			**Digitally signed by Hanan Ghantous** **Date: 6/11/2025 2:47 PM EDT** **GUID: 2025611184715**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Kevin Allen ORO DROID	Sections: 12, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Kevin Allen			**Digitally signed by Kevin Allen** **Date: 6/11/2025 3:00 PM EDT** **GUID: 20256111908**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Kellie Reynolds OCP DIDP	Sections: 5, 6, 7, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kellie Reynolds			**Digitally signed by Kellie Reynolds** **Date: 6/11/2025 3:02 PM EDT** **GUID: 20256111928**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Ursula Levitov OID DAV	Sections: 3, 7-8, 10, 17, 25	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Ursula Levitov			**Digitally signed by Ursula Levitov** **Date: 6/11/2025 3:08 PM EDT** **GUID: 20256111980**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Yanming Yin OB DBIV	Sections: 6, 15, and 16	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yanming Yin			**Digitally signed by Yanming Yin** **Date: 6/11/2025 3:08 PM EDT** **GUID: 202561119812**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Jomy George OCP DIDP	Sections: 5, 6, 7, 8, and 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Jomy George			**Digitally signed by Jomy George** **Date: 6/11/2025 3:20 PM EDT** **GUID: 2025611192033**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Secondary Reviewer	Manuela Grimstein OCP DPM	Sections: 14.5	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Manuela Grimstein			**Digitally signed by Manuela Grimstein** **Date: 6/11/2025 3:32 PM EDT** **GUID: 2025611193225**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Hudson Roth OPQAI DPQAIII	Sections: 9 - Product Quality	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Hudson Roth			**Digitally signed by Hudson Roth** **Date: 6/11/2025 3:34 PM EDT** **GUID: 202561119340**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Tertiary Reviewer	Maureen Dillon Parker ORO DROID	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Maureen Dillon Parker			**Digitally signed by Maureen Dillon Parker** **Date: 6/11/2025 4:03 PM EDT** **GUID: 202561120332**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Timothy Jancel OID DAV	Sections: 1, 2, 3, 4, 7.7, 17	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Timothy Jancel			**Digitally signed by Timothy Jancel** **Date: 6/11/2025 4:04 PM EDT** **GUID: 202561120423**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Virology Discipline Primary Reviewer	Damon Deming OID DAV	Sections: 18, 16, 7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Damon Deming			**Digitally signed by Damon Deming** **Date: 6/11/2025 5:11 PM EDT** **GUID: 2025611211153**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Stephanie Troy OID DAV	Sections: Sections I, 1, 2, 3, 4, 6, 7, 8.3, 8.4, 10, 11, 15, 16, 17, 21, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Stephanie Troy			**Digitally signed by Stephanie Troy** **Date: 6/12/2025 8:37 AM EDT** **GUID: 2025612123754**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
PBPK Reviewer Discipline Primary Reviewer	Yuching Yang OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuching Yang			**Digitally signed by Yuching Yang** **Date: 6/12/2025 9:41 AM EDT** **GUID: 2025612134115**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Justin Earp OCP DPM	Sections: 5.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Justin Earp			**Digitally signed by Justin Earp** **Date: 6/12/2025 10:11 AM EDT** **GUID: 2025612141125**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Timothy Jancel OID DAV	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Timothy Jancel			**Digitally signed by Timothy Jancel** **Sign on behalf of as proxy for Stacey Min** **Date: 6/12/2025 12:08 PM EDT** **GUID: 202561216849**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Timothy Jancel OID DAV	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Timothy Jancel			**Digitally signed by Timothy Jancel Sign on behalf of as proxy for Stacey Min Date: 6/12/2025 12:09 PM EDT GUID: 202561216929**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Laine Myers OID DPTID	Sections: 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Laine Myers			**Digitally signed by Laine Myers Date: 6/12/2025 1:18 PM EDT GUID: 2025612171842**	

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/

STEPHANIE B TROY
06/12/2025 02:54:30 PM

WENDY W CARTER
06/16/2025 09:02:25 AM