STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Double-Blind, Multicenter, Randomized Study to Evaluate the Efficacy and Safety of Subcutaneous Twice Yearly Long-Acting Lenacapavir for HIV Pre-Exposure Prophylaxis in Cisgender Men, Transgender Women, Transgender Men, and Gender Nonbinary People ≥ 16 Years of Age who Have Sex with Male Partners and are at Risk of HIV Infection (PURPOSE 2)
Name of Test Drug:	Lenacapavir (LEN; GS-6207)
Study Number:	GS-US-528-9023 (PURPOSE 2)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

%CV	coefficient of variation
Ab	antibody
AE	adverse event
Ag	antigen
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARV	antiretroviral therapy
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
bHIV	background HIV-1 incidence
BL	baseline
BLQ	below the limit of quantitation
BMI	body mass index
bNAb	broadly neutralizing antibody
CD4	cluster determinant 4
CDC	Centers for Disease Control
CGM	cisgender Man
CI	confidence interval
CIAS	condomless insertive anal sex
CK	creatine kinase
CL_{cr}	creatinine clearance
COVID-19	coronavirus disease 2019
CRAS	condomless receptive anal sex
CRF	case report form
CRVS	condomless receptive vaginal (frontal) sex
CSR	clinical study report
DAIDS	Division of AIDS
DBS	dried blood spots
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOB	date of birth
DOT	directly observed therapy
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate

$eGFR_{CG}$	estimated glomerular filtration rate using Cockcroft-Gault formula
ePRO	electronic participant reported outcomes
ESDD	early study drug discontinuation
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
F/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fmol/punch	femtomoles per punch
FRR	false recency rate
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
FTC-TP	emtricitabine 5′-triphosphate
GFR	glomerular filtration rate
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GNB	gender nonbinary people
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	HCV antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HLGT	high-level group term
HLT	high-level term
I/E	inclusion/exclusion
IAS	insertive anal sex
ICE	intercurrent events
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IRT	interactive response technology
ISR	injection site reaction
ITT	intention-to-treat
IWRS	interactive web response system
LDL	low-density lipoprotein
LEN	lenacapavir
LLT	lower-level term
LMPD	last menstrual period data

ln	natural logarithm
LOQ	limit of quantitation
LPLV	last patient last visit
MDRI	mean duration of recent infections
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MSM	men who have sex with men
MST	MedDRA search term
NAAT	nucleic acid amplification testing
NLP	natural language processing
OD	optical density
ODn	normalized optical density
OL	open label
OLE	open-label extension
OLOP	OL oral PrEP
PEP	post-exposure prophylaxis
PK	pharmacokinetics
popPK	population PK
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PT	preferred term
PTM	placebo-to-match
PWBP	people who would benefit from PrEP
PY	person-year
Q1	first quartile
Q3	third quartile
RAS	receptive anal sex
RAWG	Recency Assay Working Group
RBC	red blood cell
RBP	randomized blinded phase
RITA	recent infection testing algorithm
RNA	ribonucleic acid
rSE	relative standard error
RVS	receptive vaginal (frontal) sex
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	statistical analysis software
SC	subcutaneous
SD	standard deviation

SE	standard error
SMQ	Standardized MedDRA Queries
SOC	system organ class
STI	sexually transmitted infections
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir di-phosphate
TGM	transgender men
TGW	transgender women
TV	Trichomonas vaginalis
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
ULN	upper limit of normal
UP	urine protein
UPCR	urine protein to creatinine ratio
vs	versus
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the interim efficacy analysis and primary analysis for Study GS-US-528-9023 (PURPOSE 2).

The study is structured in four phases with structured transitions; starting from the Incidence Phase, the Randomized Blinded Phase (RBP), the LEN open-label extension (OLE) Phase and ending with the PK Tail Phase. Multiple interim safety and one formal interim efficacy analyses are planned to be conducted prior to the primary analysis. This SAP includes details on the proposed analyses for the interim efficacy and the primary analyses. This SAP does not cover analyses of data from the LEN OLE phase (as no participants will enter LEN OLE until after the primary analyses and end of the RBP).

This SAP is based on the study protocol GS-US-528-9023 Amendment 3 dated 25 October 2023 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the formal interim efficacy analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The primary objective is to evaluate the efficacy of lenacapavir (LEN) in reducing the risk of HIV-1 infection relative to the counterfactual background HIV-1 incidence (bHIV) in the participant population included in the study. LEN is being evaluated for efficacy in preventing rectal acquisition of HIV-1 which includes cisgender men, transgender women, transgender men, and gender nonbinary (CGM, TGW, TGM, and GNB respectively) participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth.

1.2. Incidence Phase Objectives

The primary objective for the Incidence Phase of the study is to estimate the bHIV.

1.3. Randomized Blinded Phase Objectives

The primary objective for the RBP is as follows:

- To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP)

The secondary objectives for the RBP of this study are as follows:

- To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV-1 PrEP
- To evaluate the efficacy of LEN for HIV-1 PrEP in participants adherent to LEN

- To evaluate the safety and tolerability of LEN and F/TDF
- To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥ 16 to < 18 years of age

The exploratory objectives for the RBP are as follows:

- 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 di-phosphate (TFV-DP) levels in dried blood spots (DBS)
- To evaluate the acceptability of a once every 6 months (Q6M) 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

1.4. Study Design

The study design is structured in multiple phases with structured transitions: the Incidence Phase, the RBP, the LEN OLE Phase, and the PK Tail Phase. Participants who complete each phase will be offered to transfer to the next phase (sequentially as listed). This interim efficacy analysis/primary analysis SAP will mainly focus on data captured from the Incidence Phase, the RBP and open-label oral PrEP administered via the PK Tail Phase in participants who permanently discontinued RBP study drug, as no participants will enter the LEN OLE Phase until after primary analysis and end of the RBP.

The bHIV, computed based on the recency assay results collected from participants diagnosed with HIV-1 in the Incidence Phase using a Recent Infection Testing Algorithm (RITA), will serve as the primary comparator for evaluating the efficacy of the experimental study drug included in the RBP. Following the RBP, there are two standard design elements: the LEN OLE Phase allows for further long-term efficacy and safety follow-up and the PK Tail Phase, which is standard for long-acting HIV prevention drugs, provides known efficacious open-label oral PrEP to provide HIV prevention for participants during the time when LEN concentrations may have declined to sub-protective levels following SC LEN administration during the RBP or LEN OLE Phase.

Design Configuration and Participant Population

GS-US-528-9023 is a double-blinded, multicenter, randomized study to evaluate the efficacy and safety of Q6M SC LEN and oral daily F/TDF 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 Drug Groups

Approximately 3000 participants who meet all eligibility criteria will be randomized in a 2:1 ratio into one of the following study drug groups:

- LEN study drug group: LEN + PTM F/TDF (N = 2000)
  - SC LEN + PTM oral F/TDF; loading dose on Day 1/Injection 1 and Day 2 of Randomized Blinded Phase only: oral LEN 600 mg (2 × 300 mg tablets)
- F/TDF study drug group: F/TDF + placebo LEN (N = 1000)
  - Oral F/TDF + placebo SC LEN; loading dose on Day 1/Injection 1 and Day 2 of Randomized Blinded Phase only: PTM oral LEN (2 tablets)
  - Loading dose on first day of SC LEN injection in LEN OLE Phase and following day: oral LEN 600 mg (2 × 300 mg tablets)

Key Eligibility Criteria

Incidence Phase Key Criteria:

- CGM, TGW, TGM and GNB who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection
- Age ≥ 16 years at screening. Enrollment of adolescents (participants aged 16 and 17 years) will commence following the first data monitoring committee (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 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

- Prior use of HIV PrEP (including F/TDF or F/TAF) or HIV PEP (postexposure prophylaxis) in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir) is not allowed

- 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 (eg, placebo recipients)

RBP Key Criteria:

- 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 nucleic acid amplification testing (NAAT)

- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min at screening according to the Cockcroft Gault formula for creatinine clearance (CL_{cr})

- Body weight ≥ 35 kg

- Participants with severe hepatic impairment are not allowed

- 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

Participation in any other clinical trial (including observational and COVID-19 vaccine trials) without prior approval from the sponsor is prohibited while participating in this trial. An exception is made for participation in the sponsor-approved ancillary qualitative participant interview study (GS-US-528-6364), which is allowed and does not require medical monitor approval.

Study Periods / Phases

This study includes a cross-sectional Incidence Phase, an RBP, a LEN OLE Phase for those who complete the RBP, and a PK Tail Phase.

The Incidence Phase will include initial assessments, standard HIV 1/2 testing, followed by HIV-1 recency assay testing as indicated based on HIV test results; those results will be included in the RITA to estimate the bHIV.

In the RBP, all eligible participants will receive study drug and attend visits for a minimum of 52 weeks. Participants who prematurely discontinue blinded study drug during the RBP will transition to the PK Tail Phase. If a participant chooses not to enter the PK Tail Phase (after discussion of benefits/risk with the investigator), the participant will complete an early study drug discontinuation (ESDD) visit and a 30-day follow-up visit.

Following the completion of the primary analysis, all participants will return to the study site upon notification by Gilead. All participants who still remain on randomized blinded study drug at the time of the End of RBP visit will have the option to transition to the LEN OLE Phase at this visit (ie, End of RBP visit will coincide with LEN OLE Day 1 visit). Participants randomized to LEN who decline to participate in the LEN OLE Phase will transition to the PK Tail Phase. If a participant chooses not to enter the PK Tail Phase (after discussion of benefits/risk with the investigator), the participant will complete an ESDD visit and a 30-day follow-up visit.

Participants randomized to F/TDF who decline to participate in the LEN OLE Phase will complete the ESDD visit at this visit, be transitioned to local HIV prevention services, and be required to return for a 30-day follow-up visit.

Participants will receive OL oral F/TDF or F/TAF at US sites once daily for up to 78 weeks to cover the PK Tail Phase and complete study visits every 13 weeks (± 7 days).

Schedule of Assessments

After providing written informed consent (or assent and/or parental/guardian consent as appropriate) for the Incidence Phase procedures, participants will be screened to determine eligibility for participation in the study, including the following assessments:

- Blood collection for local rapid fourth generation HIV-1/2 Ab/Ag test, confirmatory central HIV-1/2 testing, HIV-1 RNA quantitative NAAT, HIV-1 recency assay (run as indicated based on HIV test results), cluster determinant (CD) 4 cell count (run only if local rapid HIV-1/2 test is positive), DBS storage sample, and plasma storage samples for virology, safety, and/or PK testing

- Serious adverse events (SAEs), adverse events (AEs), and any concomitant medications including prior receipt of a long-acting PrEP medication or HIV vaccine

- Urine pregnancy test for participants assigned female at birth who are of childbearing potential

- HIV risk reduction counseling including provision of condoms and lubricant

In the RBP, participants will have study visits on Day 1, Weeks 4, 8, 13, and every 13 weeks thereafter until all enrolled participants have completed at least 52 weeks of follow-up in the study and the primary analysis is completed. LEN OLE Day 1 will coincide with the end of the RBP. In LEN OLE Phase, participants randomized to LEN in the RBP will have study visits every 13 weeks, and participants randomized to F/TDF in the RBP will have study visits at Weeks 4, 8, 13, and every 13 weeks for 52 weeks. In the PK Tail Phase, participants will have study visits every 13 weeks. The following assessments will be performed at each visit:

- Urine collected for: urinalysis, urine proteins, urine chemistry, urine storage sample (End of RBP visit/LEN OLE Day 1 only), urine pregnancy test

- Blood sample collection for: chemistry and hematology profile, eGFR calculation, local rapid fourth generation HIV1/2 Ab/Ag test, central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, HIV-1 RNA quantitative NAAT storage sample, DBS storage sample, plasma storage sample for virology, safety, and/or PK testing, serum storage sample, serum pregnancy test (in the event of a positive urine pregnancy test)

- Targeted physical exam, vital signs, height, weight and waist circumference

- AEs including screening for any signs and symptoms of acute HIV-1 infection or STIs and concomitant medications

In addition, questionnaires are collected electronically at key visits. Participants can respond to all electronic participant reported outcomes (ePRO) questionnaires via a website or an app on their own personal electronic devices (mobile phone or tablet). Participants must sign into personal accounts to answer questionnaires sent to them by the investigator sites. Responses are submitted privately and are not viewable to investigator sites, with the exception of participants whom may require assistance to complete questionnaires. Questionnaires include:

- PrEP Impacts and Administration Preference Questionnaire

- Administration and Dosing Questionnaire for PrEP Medication

- Numeric Pain Rating Scale – Injection Pain Questionnaire

- Adherence to Oral Study Product Questionnaire

- Experienced Preference for PrEP Medication Questionnaire (LEN OLE only)

- Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire

More details for study procedures could be found in APPENDIX 1.

Randomization

Participants eligible for the RBP will be randomized in a 2:1 ratio to receive LEN or F/TDF, respectively.

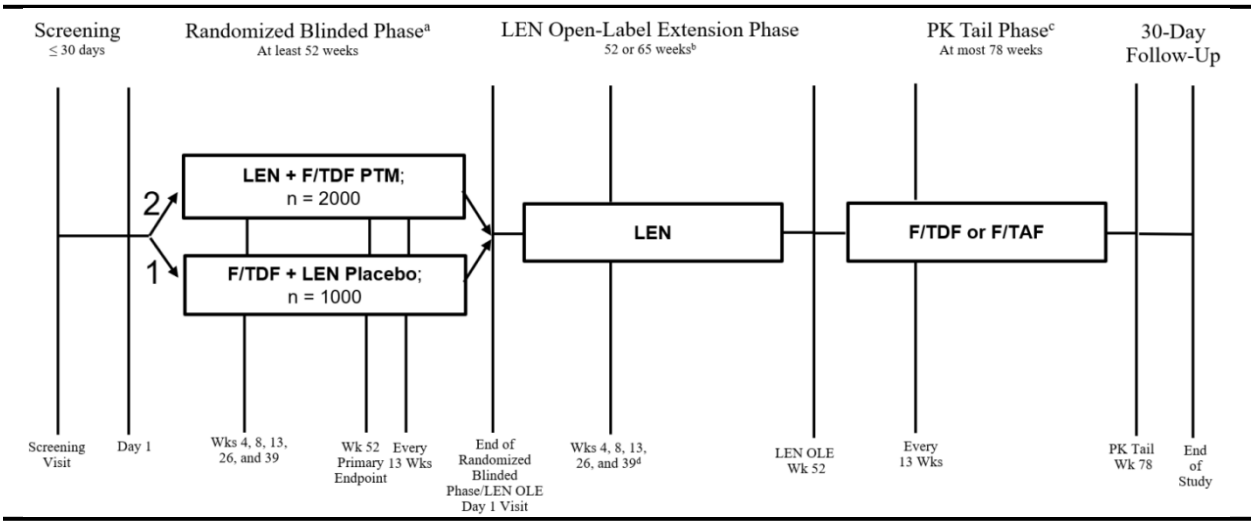
Site and/or Stratum Enrollment Limits

Approximately 100 sites in United States (US), Brazil, Peru, South Africa, Argentina, Mexico, Thailand, and Vietnam.

Study Duration

RBP is at least 52 weeks, LEN OLE Phase is up to 65 weeks, and PK Tail Phase is up to 78 weeks.

Study Schema



F/TAF = emtricitabine/tenofovir alafenamide; F/TDF = emtricitabine/tenofovir disoproxil fumarate; LEN = lenacapavir; OLE = open-label extension; PK = pharmacokinetic; PTM = placebo to match; SC = subcutaneous; Wk = week

a Participants will continue in the Randomized Blinded Phase until all enrolled participants have completed at least 52 weeks of follow-up in the study and Gilead completes the primary analysis.

b The duration will be dependent on timing of the OL LEN injection.

c Participants who prematurely discontinue study drug during the Randomized Blinded Phase or LEN OLE Phase, or those randomized to LEN in the Randomized Blinded Phase who decline to participate in the LEN OLE Phase upon unblinding, will transition to the PK Tail Phase. Participants will receive either F/TDF and/or F/TAF (available only to US sites).

d Week 4 and 8 visits are only required for participants who were randomized to oral F/TDF in the Randomized Blinded Phase.

1.4.1. Clinical Hold on the Use of Injectable Lenacapavir

On 20 December 2021, the FDA placed a clinical hold on the use of LEN injections from borosilicate vials due to a vial compatibility issue. During the clinical hold, screening and enrollment of study participants and the dosing of injectable lenacapavir were not permitted across all lenacapavir studies. Other study activities, including the monitoring of participants, continued according to the relevant study protocol. Participants were given the option to receive OL F/TDF or OL F/TAF (US sites only) prior to the approval of Protocol Amendment 2 or blinded oral LEN/PTM bridging after the approval of Protocol Amendment 2.

On 16 May 2022, the FDA removed the clinical hold following the Agency's review of Gilead's comprehensive plan and corresponding data on the storage and compatibility of LEN injection with an alternative vial made from aluminosilicate glass. Starting as early as 7 June 2022, participants were given the option to switch back (in a double-blinded fashion) to receiving their original randomized study drug treatment assignments (SC LEN or placebo, or F/TDF or PTM) at their next visit that SC injectable LEN was available or to discontinue the RBP early and receive OL oral PrEP (OL F/TDF or OL F/TAF) administered via the PK Tail Phase.

1.4.2. Sampling for LEN Plasma PK, Dried Blood Spot (F/TDF) and Hormone PK

1.4.2.1. LEN Plasma PK Sampling

1.4.2.1.1. 10% Random Sampling

An approximate 10% random sampling will provide sufficient representative data to assess the PK of LEN and adherence to oral daily PrEP.

On 30 July 2021, a random sampling of 10% of the randomizing participant numbers was selected for these analyses. During the study randomization treatment assignments conducted by interactive response technology (IRT), participants receive 5-digit participant identification numbers sequentially assigned by the randomization order, ranging from 50001 to 59999 (including extra participant identification numbers for possible over enrollment). The 10% sampling were randomly selected using these pre-specified participant identification numbers with allocation ratio of 1:9 (for LEN Plasma PK/DBS Cohort analyses vs. no LEN plasma PK/no DBS Cohort analyses) in block sizes of 10, and 1000 blocks. Only participants randomized to the LEN study drug treatment will have their LEN plasma PK samples analyzed and only participants randomized to F/TDF study drug treatment will have their DBS samples analyzed.

To serve the LEN PK objectives, adequate numbers of LEN PK samples from populations of special interest are needed. These include adolescents, participants who received oral LEN bridging during the clinical hold, transgender men (participants who identify as male but were assigned female at birth), transgender women (participants who identify as female but were assigned male sex at birth and are using feminizing hormone therapy that started before first dose of LEN and continued for ≥ 26 weeks), and participants diagnosed with HIV-1 infection during the study. Thus, additional plasma samples from the populations of special interest who were randomized to receive LEN will be analyzed in addition to the 10% prespecified general sampling.

LEN plasma PK samples will be analyzed for all LEN participants diagnosed with HIV-1 infection at least through their HIV diagnosis date (and beyond, as appropriate).

1.4.2.2. Hormone PK Sampling

Participants who were selected for the LEN plasma PK sampling (see Section 1.4.2.1), took gender affirming hormones and were randomized to receive LEN, were selected for hormone PK sampling.

The criteria to identify feminizing and masculinizing hormones for gender affirming hormone PK sampling analysis are defined below:

- Transgender men were identified as participants who were assigned as female sex at birth and taking a medication with Category for Medication = “Masculinizing hormone therapy”. Participants were included the analysis if they took testosterone, which was identified using the Standard Medication Name (WHOGEN) as specified in APPENDIX 8

— Transgender women were identified as participants who were assigned as male sex at birth and taking a medication with Category for Medication = "Feminizing hormone therapy". Participants were included in this analysis if they started estradiol prior to first SC injection and took it for at least 182 days and completed Week 26 visit. Estradiol was identified as Standard Medication Name (WHOGEN) as specified in APPENDIX 8.

1.4.2.3. Dried Blood Spot Sampling

TFV-DP concentration in the DBS samples from the prespecified 10% random sample of participants receiving F/TDF will be used to objectively assess the adherence to the oral daily PrEP.

DBS samples will also be analyzed for all F/TDF participants diagnosed with HIV-1 infection as described in APPENDIX 6.

1.5. Sample Size and Power

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

More than 95% power is 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 Table 3-1). In this sample size analysis, the following assumptions are 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 1.5 years in the study
- 2:1 allocation for LEN: F/TDF
- Alpha level of 0.025 (1-sided)

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

The MDRI and FRR are based on the Sedia limiting antigen avidity enzyme immunoassay (Lag-EIA) {Kassanjee 2016}, assuming T = 2 years and virologic cutoff of 75 copies/mL. Here T is the cutoff for the time period defined in Section 6.1.2.1. Under the assumption of T = 1 year, the power remains at > 95%. The power calculation is based on the formula in {Gao 2021} using the test statistics for rate ratio {Gao 2021}.

The statistical power to compare the randomized study drug groups is not assessed. The ratio of incidence rates (LEN over F/TDF) and the corresponding CI will be estimated to characterize the comparative evaluation.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

An external independent multidisciplinary DMC will review the progress of the study and perform interim reviews of the data (both interim efficacy and periodic safety) in order to protect participant welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will make recommendations to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

2.1.1.1. Interim Analyses of Safety Data

The first meeting of the DMC will be when the first 300 participants have completed their Week 8 visit to evaluate the safety of LEN. While enrollment will not be paused during this safety review, enrollment will not exceed 600 participants before the safety review is conducted and, if determined by the DMC, the study will be allowed to continue. Enrollment of adolescents (participants aged 16 and 17 years) will commence following the first DMC review of the safety data and recommendation to continue the study. Additional DMC review meetings of safety data will occur approximately annually thereafter during the RBP of the study.

2.1.1.2. Interim Analyses of Efficacy Data

The DMC will formally evaluate 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 may recommend stopping the study early if the prespecified efficacy or futility evaluation criteria are met. If the RBP is stopped early due to an efficacy outcome, the interim analysis will serve as the primary analysis. The criteria for interim decisions and DMC recommendations as well as alpha-spending procedures are outlined in Section 3.5.2 and in the Interim Analysis Plan (Version 3.0, 19 December 2023). The interim analyses results may be discussed with regulatory agencies to seek guidance for the overall clinical development program.

The DMC's role and responsibilities and the scope of analysis to be provided to the DMC are provided in a mutually agreed upon charter, which defines the DMC membership, meeting logistics, and meeting frequency.

2.2. Primary Analysis

If the interim analysis of efficacy data leads to stopping the RBP of the study, either for efficacy or futility, then it will serve as the primary analysis. Otherwise, the unblinded primary analysis will be conducted when all participants have a minimum of 52 weeks (1 year) of follow-up in the RBP of the study or permanent discontinuation of study (whichever occurs first) after randomization. Alpha-spending procedures are outlined in Section 3.5.2 and in the Interim Analysis Plan (Version 3.0, 19 December 2023). Analysis of the primary endpoint at this primary analysis will serve as the last alpha spending analysis to evaluate the HIV-1 incidences for the LEN study drug group compared to the bHIV and F/TDF HIV-1 incidence.

2.3. Final Analysis

The final unblinded analysis will be performed after all participants have completed the Randomized Blinded, LEN OLE, and PK Tail Phases of the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Participants who prematurely discontinue blinded randomized study drug during the RBP without HIV-1 diagnosis, regardless of reason, are offered to transition directly to the PK Tail Phase (a random transition, for the primary and interim efficacy analyses such direct transitions from RBP to PK Tail Phase, due to premature discontinuation, are considered as random intercurrent events). Participants who complete both the Randomized Blinded and the LEN OLE phases will transition to the PK Tail Phase (a structured transition). This document will refer to "OL oral PrEP" (OLOP) instead of "PK Tail" Phase to distinguish between the random and structured transitions. Consistent with the intention-to-treat (ITT) principles, all follow up data, including random transitions, prior to interim efficacy and primary analyses will be included in the interim efficacy and primary analyses.

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests of the HIV-1 incidence will be 1-sided and performed at the alpha levels specified in Section 3.5.2 and in the Interim Analysis Plan (Version 3.0, 19 December 2023). All other statistical tests will be 2-sided and performed at the 5% significance level, unless otherwise specified.

By-participant listings will be presented for all participants in the All Randomized Analysis Set and sorted by participant ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the participant. The study drug group to which participants were randomized [initially assigned] will be used in the listings. Age, sex assigned at birth, gender identity, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets, defining the participants included in each of the prespecified analyses, are listed in this section. Participants included in each analysis set will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion, as well as the number and percentage of participants who were excluded and the reasons for their exclusion, will be summarized by study drug group.

A listing of reasons for exclusion (if available) from analysis sets may be provided by participant.

3.1.1. All Screened Set

All Screened Set includes all participants who were screened for HIV-1 in the Incidence Phase and had non-missing HIV-1 diagnosis based on HIV test (defined as at least one non-missing central laboratory HIV test including the HIV-1/2 Ag/Ab screening, HIV-1/2 differentiation Ab, HIV-1/2 RNA qualitative or HIV-1 RNA quantitative test) at Incidence Screening. Any additional participants who took at least 1 dose of any study drug (but missing central laboratory HIV tests at Incidence Screening) will be included in the All Screened Set and considered as HIV-1 negative. This is the primary analysis set for estimating the bHIV.

3.1.2. All Randomized Analysis Set

All Randomized Analysis Set includes all participants who were randomized in the study.

3.1.3. Full Analysis Set (FAS)

The ideal evaluation of efficacy would follow ITT principles and based on an ITT analysis set. However, following ICH-E9 guidance, the term Full Analysis Set (FAS) is used to describe the analysis set which is as complete as possible and as close as possible to the ITT ideal that is suitable for a proper interpretation of efficacy data from a PrEP clinical trial.

The FAS includes all randomized participants who took at least 1 dose of any study drug and have not been diagnosed with HIV-1 on or prior to 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 is the primary analysis set for efficacy analyses for participants who entered the RBP of the study. Participants who have a negative rapid test at Day 1 are permitted to be dosed prior to receipt of the Day 1 central lab test results; however, participants who were diagnosed with HIV-1 based on central lab tests on or prior to first dose date will be excluded from the FAS.

3.1.4. Modified Full Analysis Set (mFAS)

The mFAS Analysis Set includes all participants in the FAS who received their first dose of study drug after the clinical hold was lifted (16 May 2022).

3.1.5. Randomized Blinded Phase Safety Analysis Set

The RBP Safety Analysis Set includes all participants who took at least 1 dose of any study drug. This is the primary analysis set for RBP safety analyses.

3.1.6. Open Label Oral PrEP (OLOP) Safety Analysis Set

The OLOP Safety Analysis Set includes all participants who receive at least 1 dose of study OL oral PrEP. Participants included in OLOP Safety Analysis Set will include those who permanently transition to the PK Tail Phase. This will include data after premature discontinuation of randomized study drug in the RBP for any reason including conversion of temporary interruptions to permanent discontinuation (eg, after clinical hold if participant did not reinitiate randomized study drug).

This is the primary analysis set for OLOP safety analyses.

3.1.7. LEN PK Analysis Set

The LEN Pharmacokinetic (PK) Analysis Set will include all randomized participants who took at least 1 dose of study drug, are selected in the random sampling of approximately 10% of the enrolled participants or in select populations of special interest as described in Section 1.4.2 and have at least 1 non-missing plasma LEN concentration value reported by the PK laboratory.

3.1.8. Hormone PK Analysis Set

The Hormone PK Analysis Set will include participants who are in the LEN PK Analysis Set, are selected in the hormone PK sampling as described in Section 1.4.2 and have at least 1 non-missing concentration value reported by the PK laboratory for any evaluated hormone (and associated metabolite(s), as appropriate).

3.1.9. DBS Cohort Analysis Set

The DBS Cohort Analysis Set will include all randomized participants who took at least 1 dose of study drug, are selected in the random sampling of approximately 10% of the enrolled participants as described in Section 1.4.2 and have at least 1 nonmissing DBS concentration value reported by the DBS laboratory. The DBS Cohort Analysis Set will be used for general DBS analyses for the cohort substudy.

3.2. Participant Grouping

All participants in the All Screened Set (from the Incidence Phase) will be considered as one group.

For analyses based on the All Randomized Analysis Set, FAS, or modified FAS participants will be grouped according to the treatment to which they were randomized. For other analyses, including those based on the Safety Analysis Set (RBP or OLOP safety analysis), participants will be grouped according to the actual treatment received. The actual treatment received in the RBP will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the LEN PK Analysis Set, Hormone PK Analysis, and DBS Cohort Analysis Set, participants will be grouped according to the actual study drug they received.

Participants will also be grouped as follows for table summaries of demographics and baseline characteristics for the Incidence Phase:

- All Screened Set
  - Diagnosed with HIV-1 at Incidence Screening
  - Diagnosed with no HIV-1 at Incidence Screening

Participants in the All Screened Set diagnosed with no HIV-1 at Incidence Screening will also be categorized by:

- Randomized
- Not Randomized

Participants will be grouped as follows for table summaries of demographics and baseline characteristics for the RBP:

- SC LEN
- F/TDF
- Total (combining all study drug groups above)

Participants will be grouped as follows for table summaries of efficacy and the RBP safety analysis (including injection site reactions):

- SC LEN
- F/TDF

Participants will be grouped as follows for table summaries of the OLOP safety analysis:

- SC LEN to OL F/TDF
- SC LEN to OL F/TAF
- F/TDF to OL F/TDF
- F/TDF to OL F/TAF

In US sites, participants are permitted to switch between OL F/TDF and OL F/TAF OL oral PrEP administered via the PK Tail Phase. The OLOP study drug groups will be based on the first OLOP study drug received.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling participants.

3.4. Examination of Participant Subgroups

If an imbalance between study drug groups is observed for other non-prespecified baseline characteristics and considered as potentially prognostic, then subgroupings based on these characteristics may also be explored for analysis of efficacy and safety endpoints.

3.4.1. Subgroups for Efficacy

The primary efficacy analysis of HIV-1 incidence per 100 PY will be examined using the following subgroups:

- Age (years): (a) 16 to ≤ 25, (b) > 25 to < 35 and (c) ≥ 35
- Race: (a) Black (includes mixed races with any black ancestry) and (b) nonblack
- Gender Identity: (a) CGM, (b) TGW, (c) TGM and (d) GNB
- Ethnicity: (a) Hispanic and (b) Non-Hispanic
- Country: (a) US (including Puerto Rico), (b) Brazil, (c) Peru, (d) Mexico, (e) Argentina, (f) South Africa, (g) Thailand
- Body Mass Index (kg/m^2): (a) < 25 and (b) ≥ 25
- Highest level of education: (a) < Some College or University Degree (ie. Did not attend Primary School, Some Primary School Education, Primary School Complete, Some Secondary School Education, Secondary School Degree Complete) and (b) Some College or University Degree
- Any history of rectal gonorrhea, rectal chlamydia, or syphilis STI in the past 24 weeks from Inclusions/Exclusion Criteria (Randomized) eCRF: (a) Yes and (b) No
- Condomless receptive anal sex (CRAS) acts in the past 3 months prior to Baseline: CRAS (a) ≤ 3 CRAS acts and (b) > 3 CRAS acts
- Taken drugs before or during sex in last 3 months prior to baseline: (a) Yes and (b) No (includes participants that never have used a needle to inject drugs)
- RBP Screening HIV risk characteristics from ePRO Integrated Sexual Behaviors and Alcohol and Substance Use questionnaire
  - Used a needle to inject drugs in past 12 weeks (injection drug users): (a) Yes, (b) No
  - Six or more drinks on one occasion: (a) Never, (b) Yes (includes Less than monthly, Monthly, Weekly, Daily or almost daily)
  - Alcohol before or during sex since last visit (or past 12 weeks): (a) Yes, (b) No

3.4.2. Subgroups for Safety

Selected renal safety endpoints in the RBP (proteinuria by urinalysis and eGFR, Sections 7.2.5.1 and 7.2.7.1) will be examined using the following subgroups:

- Age (years): (a) 16 to ≤ 25, (b) > 25 to < 35 and (c) ≥ 35
- Body Mass Index (kg/m^2): (a) < 25 and (b) ≥ 25

3.5. Multiple Comparisons

Procedures to control the overall Type I error due to multiple efficacy analyses, one due to multiple hypotheses and the other due to one planned interim efficacy analysis, are described in this section.

3.5.1. Multiple Alpha-Controlled Hypotheses

There are 4 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed below.

For simplicity, LEN and TVD are used to denote the HIV-1 incidences for the LEN arm and F/TDF arm, respectively.

Table 3-1. Testing Sequence of Null Hypotheses

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 – TVD ≥ 0.8/100PY	HIV-1 incidence in LEN is not substantially greater than F/TDF (LEN efficacy is comparable to F/TDF)
	H_{04}: LEN / TVD ≥ 1	HIV-1 incidence in LEN is significantly lower than F/TDF

The overall Type I error will be controlled at one-sided $\alpha = 0.025$ by following a fixed sequence approach (in the sequential order listed in Table 3-1).

3.5.2. Alpha Spending for Multiple Analyses (Interim and Primary Analyses)

At the interim analysis, the same sequential approach will be utilized at $\alpha_1 = 0.0026$ (one-sided). The FDA interim stopping criteria are 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 $\alpha_1 = 0.0026$. The interim analysis will serve as the primary analysis if the trial meets the stated criteria and stops early.

For the detailed testing procedure and interim stopping criteria, please see the flowcharts in the Interim Analysis Plan (Version 3.0, 19 December 2023).

If the RBP continues to the primary analysis, the null hypotheses H_{01}, H_{02}, H_{03} and H_{04} will be tested sequentially, with boundaries derived based on the Bonferroni method; at level $\alpha_2 = 0.025 - \alpha_1 = 0.025 - 0.0026 = 0.0224$. The FDA success criteria for the primary analysis are to demonstrate superiority of LEN versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$, and comparability of LEN to F/TDF, designated H_{03}, at $\alpha_2 = 0.0224$.

If adequate safety and efficacy of LEN is demonstrated, participants will be given the option to transition to the LEN open-label extension phase of the trial once the RBP is stopped.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 3.8.2.1. The handling of missing or incomplete dates for AE onset (including for start/stop dates of ISRs and last study date) is described in Section 7.1.5.2. The handling of missing prior and disease-specific prior and concomitant medications is described in Section 7.4. Imputation rules for missing DBS concentration at the time of HIV-1 diagnosis are as described in APPENDIX 6.

3.6.2. Outliers

Outliers of non-PK data will be identified during the data management and data analysis process. No supportive analyses are planned. All data will be included in the data analysis.

Outliers of PK data may be identified during review of data and maybe excluded, if necessary.

3.7. Data Handling Conventions and Transformations

Only year of birth is collected in this study.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on year of birth and the Day 1 visit date will be used instead. If a randomized participant was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For participants not randomized, the date the first Incidence Phase Screening informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance) from the central laboratory will be based on age derived from the year of birth imputing 01 July as the day and month of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The lower or upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the lower or upper LOQ, respectively).

For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios.

Natural logarithm transformation will be used for analyzing non-BLQ concentrations and PK parameters. Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing. Values that are BLQ will be treated as 0 at predose and postdose time points for summary purposes.

At predose, if all concentration values are BLQ, then the mean, and order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as 0 and the rest of the summary statistics (ie, SD and CV) will be missing. If any values are non-BLQ, then the number of samples, order statistics, and all summary statistics will be displayed.

At any given postdose time point, if more than one-third of the participants have a concentration value of BLQ, then only the number of samples and order statistics will be displayed; otherwise, order statistics and summary statistics will be displayed.

The following conventions will be used for the presentation of summary and order statistics for PK concentrations:

- If at least 1 participant has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.8. Analysis Study Day and Visit Windows

3.8.1. Definition of Screening, Baseline and Study Day

Screening Value is defined as the first nonmissing value obtained prior to Study Day 1.

Baseline Value is defined as the last nonmissing value obtained on or prior to Study Day 1 for either the RBP analysis or OL Oral PrEP analysis, as appropriate.

Study days will be calculated from the first dosing date of study drug for the RBP analysis and the OL Oral PrEP analysis, as appropriate, and derived as follows for either analysis:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first randomized study dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

3.8.2. Definition of Study Dates

Injections are counted as received if any injection dose is administered, including partial or incomplete injections. Injections are only counted as missing if none of the injection was received.

3.8.2.1. First Dose Dates

Study Day 1, First Dose Date for the RBP or First Dose Date is defined as the day when the first dose of randomized study drug is taken, as recorded on the Study Drug Administration eCRF forms. This is utilized for all analyses (including efficacy, safety analyses, the determination of baseline definition), except for injection site reactions (ISRs) to study SC injection (Sections 7.1.7.1-7.1.7.2).

First SC Dose Date for the RBP is defined as the day when the first dose of SC study drug was taken, as recorded on the Study Drug Administration eCRF forms. The earliest of the first dose dates of any SC component (ie, SC LEN or placebo) is considered as the first dose date of the SC study drug. This is utilized for analyses of injection site reactions (ISRs) to study SC injection (Sections 7.1.7.1-7.1.7.2).

Study Day 1 or First Dose Date for OL Oral PrEP administered via the PK Tail Phase is defined as the day when the first dose of OL oral PrEP (OL F/TDF or OL F/TAF) study drug was administered via the PK Tail Phase due to permanent discontinuation from the randomized study drug, as recorded on the Study Drug Administration eCRF form.

3.8.2.2. Last Dose, Last Study or Last Exposure Dates

The following dates are utilized for analyses related to safety, extent of study drug exposure or on-treatment analyses.

Last dose dates for each study phase and last study date contribute to defining the last exposure dates utilized in treatment-emergent general safety analyses.

Last Dose Date for the RBP is defined as follows for participants who prematurely and permanently discontinued study drug according to the Study Drug Completion eCRF for the RBP:

- For participants randomized to SC LEN injection, the last dose date is defined as the latest nonmissing end date of randomized active SC LEN or oral LEN study drug in the RBP.
- For participants not randomized to SC LEN injection, the last dose date is defined as the latest of the randomized active oral F/TDF study drug end dates in the RBP.
    - If the date of last dose for the RBP is missing (eg, due to lost to follow-up), the latest of the nonmissing randomized active study drug start dates and end dates, clinic visit dates and laboratory visit dates prior to the first dose date of OL oral PrEP (OL F/TDF or OL F/TAF) administered via the PK Tail Phase due to permanent discontinuation from the randomized study drug (if applicable), excluding the dates of any follow-up visits will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications (APPENDIX 9) for imputation rule details.

Last Dose Date for OL Oral PrEP administered via the PK Tail Phase is defined as the latest of the OL F/TDF or OL F/TAF study drug end dates for participants who prematurely discontinued study drug according to Study Drug Completion eCRF.

If the date of last dose of OL Oral PrEP is missing (eg, due to lost to follow-up), the latest of the nonmissing OL F/TDF or OL F/TAF study drug start dates and end dates, clinic visit dates and laboratory visit dates in the PK Tail Phase, excluding the dates of any follow-up visits will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications (APPENDIX 9) for imputation rule details.

Last Dose Date for the First OL Oral PrEP (OLOP) administered via the PK Tail Phase is based only on the first OL study drug received and defined as the latest of the OL F/TDF or OL F/TAF study drug end dates for participants who prematurely discontinued study drug according to the Study Drug Completion eCRF. If participants switch OLOP study drug multiple times (eg, from OL F/TDF to OL F/TAF and back to OL F/TDF), the interruption in the OLOP study drug will be ignored if it is less than 7 days (For example, if the OL F/TAF interruption is less than 7 days, this will be the last dose of OL F/TDF in OLOP; however, if the OL F/TAF interruption is 7 or more days, this will be the last dose of OL F/TDF prior to the switch to OL F/TAF).

If the date of last dose for the first OL Oral PrEP study drug in the PK Tail Phase is missing (eg, due to lost to follow-up), the latest of the nonmissing first OLOP study drug start dates and end dates, clinic visit dates and laboratory visit dates in the PK Tail Phase prior to the first switch of OLOP study drug, excluding the dates of any follow-up visits will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications for imputation rule details.

Last Study Date in Study is the latest nonmissing study drug (active or placebo) start dates and end dates, clinic visit dates, laboratory visit dates, and/or latest AE onset date and end date, including any follow-up visit and post-injection follow-up visit dates, for participants who prematurely discontinued study according to the Study Completion eCRF. Last study date in study is utilized for summaries of ISRs to study SC injection (Sections 7.1.7.1-7.1.7.2).

Last exposure dates are utilized for the treatment-emergent general safety analyses.

Last Exposure Date for the RBP is defined as follows for participants who prematurely discontinued study drug according to Study Drug Completion eCRF. This date is defined considering the prolonged exposure of LEN after the last dose date of LEN.

- For participants who are randomized to receive active LEN SC injection, the last exposure date is defined as the:
  - date of the Study Day 1 for OL Oral PrEP administered via the PK Tail Phase minus 1 day if participant received OL Oral PrEP administered via the PK Tail Phase due to permanent discontinuation from randomized study drug
  - last study date if participant did not receive OL Oral PrEP administered via the PK Tail Phase due to permanent discontinuation from randomized study drug
- For participants who are randomized to receive active F/TDF, the last exposure date is defined as the minimum of the last dose date in the RBP plus 30 days, the last study date and Study Day 1 for OL Oral PrEP administered via the PK Tail Phase due to permanent discontinuation from randomized study drug minus 1 day (if applicable).

Last Exposure Date for OL Oral PrEP administered via the PK Tail Phase is defined as the minimum of the last dose date of OL oral PrEP study drug in the PK Tail Phase plus 30 days and the last study date for participants who prematurely discontinued study drug in the PK Tail Phase according to the Study Drug Completion eCRF. Last exposure date for the OL oral PrEP is utilized for summaries of extent of study drug exposure and adherence.

Last Exposure Date for the First OL Oral PrEP administered via the PK Tail Phase is defined as the minimum of the last dose date of the first OL oral PrEP study drug in the PK Tail Phase plus 30 days, the date of first switch of OL Oral PrEP administered via the PK Tail Phase minus 1 day (if applicable) and the last study date for participants who prematurely discontinued study drug in the PK Tail Phase according to the Study Drug Completion eCRF. For determining the date of first switch of OL oral PrEP administered via the PK Tail Phase, if participants switch

OL oral PrEP study drug multiple times (i.e. from OL F/TDF to OL F/TAF and back to OL F/TDF), the interruption in the OL oral PrEP will be ignored if it is less than 7 days. As PURPOSE 2 US sites allow switching between OL F/TDF and OL F/TAF study drug, last exposure date for the first OL oral PrEP is utilized for summaries of extent of study drug exposure and general safety.

The following last SC dose and last oral dose dates in RBP are utilized for supportive analyses of efficacy (Section 3.8.2.3 and 6.4.2.2).

Last SC Dose Date in the RBP is defined as follows for participants who prematurely discontinued study drug according to the Study Drug Completion eCRF for the RBP: the latest nonmissing end date of SC LEN or placebo study drug in the RBP.

Last Oral Dose Date in the RBP is defined as the latest of the active oral LEN or oral F/TDF study drug end dates in the RBP.

If the date of last dose for the RBP is missing (eg, due to lost to follow-up), the latest nonmissing randomized study drug start dates and end dates, clinic visit dates and laboratory visit dates prior to the first dose date of OL F/TDF or OL F/TAF in the PK Tail Phase (if applicable), excluding the dates of follow-up visits will be used to impute the last dose date. For other partial missing last dose date, please see the programming specifications (APPENDIX 9) for imputation rule details.

3.8.2.3. Last At-Risk of HIV-1 Infection Dates

The following dates define the end of follow-up time in analyses of efficacy:

Last At-Risk of HIV-1 Infection Date in Study including both the RBP and follow-up of participants that discontinued the RBP early and may receive OL oral PrEP administered via the PK Tail Phase and/or continue in the study while off study drug is (1) the date of HIV-1 diagnosis as defined in Section 6.1.1 for participants who have been diagnosed with HIV-1 or (2) the date of the last post-baseline HIV laboratory test (either rapid, central or other local HIV laboratory tests, including the follow-up visits) for participants who have not been diagnosed with HIV-1. This is defined as the end of the follow-up time for the primary analysis of efficacy as well as analyses of STIs and sexual behaviors (Section 9).

Last At-Risk of HIV-1 Infection Date for the RBP (occurring on or prior to Study Day 1 for OL Oral PrEP administered via the PK Tail Phase, if applicable) is (1) the date of HIV-1 diagnosis for participants who have been diagnosed with HIV-1 during RBP, (2) the date of the last post-baseline HIV laboratory test (either rapid, central or other local HIV laboratory tests, including the follow-up visits) for participants who have not been diagnosed with HIV-1 during RBP.

Last At-Risk of HIV-1 Infection Date for On Randomized Study Drug

- For participants who permanently discontinued the RBP study drug: is (1) the date of HIV-1 diagnosis for participants who have been diagnosed with HIV-1 while "On Randomized Study Drug", (2) the date of the last post-baseline HIV laboratory test (either rapid, central or other local HIV laboratory tests, including the follow-up visits) for participants who have not been diagnosed with HIV-1 while "On Randomized Study Drug".

Here "On Randomized Study Drug" is defined as the first dose date up to the earliest of the following:

  - last active F/TDF dose date + 10 days for participants on active F/TDF,
  - later of last active oral LEN dose date + 60 days or last active SC LEN dose date + 28 weeks for participants on active SC LEN,
  - start of any non-randomized PrEP drug after permanent discontinuation of the randomized study drug (including transitioning to the PK Tail Phase, or any commercial PrEP such as Truvada, generic Truvada, cabotegravir for PrEP or other PrEP regimen), if applicable.

- For participants who are ongoing on RBP study drug: is the same as the Last At-Risk of HIV-1 Infection Date in Study (defined as above).

This is defined as the end of the follow-up time for supportive analysis of efficacy while participants are on randomized study drug (Section 6.4.2.2).

Last At-Risk of HIV-1 Infection Date for On OLOP

- For participants who permanently discontinued the OLOP study drug: is (1) the date of HIV-1 diagnosis for participants who have been diagnosed with HIV-1 while "On OLOP", (2) the date of the last post-baseline HIV laboratory test (either rapid, central or other local HIV laboratory tests, including the follow-up visits) for participants who have not been diagnosed with HIV-1 while "On OLOP".

Here "On OLOP" is defined as the first OLOP dose date up to the earliest of the following:

  - last F/TDF dose date + 10 days for participants on F/TDF,
  - last F/TAF dose date + 16 days for participants on F/TAF, if applicable,
  - start of any commercial PrEP drug after permanent discontinuation of the OLOP study drug (such as Truvada, generic Truvada, cabotegravir for PrEP or other PrEP regimen), if applicable.

- For participants who are ongoing on OLOP study drug: is the same as the Last At-Risk of HIV-1 Infection Date in Study (defined as above).

3.8.2.4. Clinical Hold Dates

The following dates are defined to assess the impact of clinical hold on study drug (Section 1.4.1):

First Dose Date of Oral Drug Due to Clinical Hold is defined as the day when the first dose of OL F/TDF, OL F/TAF or blinded oral weekly LEN/PTM bridging study drug was taken due to the temporary interruption of SC LEN/placebo injection study drug due to the clinical hold, as recorded on the Study Drug Administration eCRF form, occurring in the clinical hold period of 20 December 2021 through availability of LEN injectable study drug (starting as early as 7 June 2022) after the clinical hold was lifted.

End Date of Clinical Hold Impact is defined as the

- first dose date of blinded Week 26/2nd injection (LEN injection or placebo) following the availability of SC LEN/placebo injections after clinical hold was lifted (16 May 2022) for participants who resumed RBP study drug
- first dose date of OL oral PrEP administered following the availability of SC LEN injections after clinical hold was lifted for participants that did not resume but permanently discontinued RBP study drug to receive OLOP administered via the PK Tail Phase (captured in the Study Drug Administration eCRF as 'PK Tail (2)')
- last dose date for participants that did not resume RBP study drug and discontinued the study
  - last dose date for the RBP for participants on blinded oral LEN/PTM bridging during the clinical hold
  - last dose date for OL oral PrEP for participants on OLOP during the clinical hold

This will be used for summaries of duration of clinical hold impact in the RBP (Section 4.2.2)

3.8.3. Analysis Visit Windows

Participant visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows from RBP Day 1 (or OLOP Day 1) for hematology, chemistry (including glucose), urinalysis, urine protein, urine chemistry, eGFR, urine pregnancy and CD4 laboratory tests, vital signs, weight, waist circumference, questionnaire on adherence to oral study product and DBS as well as from RBP Day 1 only for HIV laboratory and HIV RAPID tests are provided in Table 3-2 and are calculated from the first dosing date of study drug for the RBP (or the first dosing date of OL oral PrEP administered via the PK Tail).

Table 3-2. Analysis Visit Windows for Hematology, Chemistry (including Glucose), Urinalysis, Urine Protein, Urine Chemistry, eGFR, Urine Pregnancy, CD4, Vital Signs, Weight, Waist Circumference, Adherence to Oral Study Product Questionnaire[a], DBS (from RBP or OLOP Day 1) as well as HIV Laboratory and HIV RAPID Tests (from RBP Day 1)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none) [a]	1 [a]
Week 4	28	2 (NA[b])	42 (NA[b])
Week 8	56	43 (NA[b])	73 (NA[b])
Week 13	91	74	136
Week 26	182	137	227
Week 39	273	228	318
Week 52	364	319	409
Week 65	455	410	500
Week 78	546	501	591
Week 91	637	592	682
Week 104	728	683	773
Week 117	819	774	864
Week 130	910	865	955
Week K (K is every 13 weeks after previous visit)	K*7	(K-6.5)*7+0.5	(K+6.5)*7-0.5

a For Adherence to Oral Study Product Questionnaire, baseline is not applicable (NA).
b For OL oral PrEP administered via the PK Tail Phase, Weeks 4 and 8 are not applicable (NA) and the study day range for Week 13 is (2, 136). Analysis windows are compared to first dosing date of OL F/TDF or OL F/TAF study drug administered via the PK Tail Phase.

The analysis windows for STI testing for GC, CT, TV, and syphilis/syphilis diagnosis and questionnaires on integrated sexual behaviors and alcohol and substance use are provided in Table 3-3 as calculated from the first dosing date of study drug for the RBP.

Table 3-3. Analysis Visit Windows for STI Testing (for GC, CT, TV, and syphilis/syphilis diagnosis) and Questionnaires on Integrated Sexual Behaviors and Alcohol and Substance Use (from RBP Day 1)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 13	91	2	136
Week 26	182	137	227
Week 39	273	228	318
Week 52	364	319	409
Week 65	455	410	500
Week 78	546	501	591
Week 91	637	592	682
Week 104	728	683	773
Week 117	819	774	864
Week 130	910	865	955
Week K (K is every 13 weeks after previous visit)	K*7	(K-6.5)*7+0.5	(K+6.5)*7-0.5

The analysis windows for fasting glucose and lipids, hepatitis B, hepatitis C, and PrEP impacts and administration preference questionnaires are provided in Table 3-4 and are calculated from the first dosing date of study drug for the RBP. The analysis windows for fasting glucose and lipids from the first dosing date of OL Oral PrEP are also provided in Table 3-4.

Table 3-4. Analysis Visit Windows for Fasting Glucose and Lipid Panel (from RBP or OLOP Day 1), Hepatitis B, Hepatitis C, and PrEP Impacts and Administration Preference Questionnaire (from RBP Day 1)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 26	182	2	273
Week 52	364	274	455
Week 78	546	456	637
Week 104	728	638	819
Week 130	910	820	1001
Week K (K is every 26 weeks after previous visit)	K*7	(K-13)*7+1	(K+13)*7

Lipid panel includes total cholesterol, triglycerides, LDL, HDL, and total cholesterol to HDL ratio.
PrEP Impacts and Administration Preference Questionnaire (Day 1) will be used for baseline analysis and the post-baseline questionnaires will be used for pose-baseline analysis.

The analysis windows for the Numeric Pain Rating Scale Questionnaire are provided in Table 3-5 and are calculated from the last SC injection date prior to administration of the questionnaire.

Table 3-5. Numeric Pain Rating Scale Questionnaire (from last SC injection date prior to administration of the questionnaire) and ISRs to Study SC Injection

Target Visit	Target Study Date	Visit Window Study Date	
		Lower Limit	Upper Limit
Day 1/Injection 1	Day 1/Injection 1date	Day 1/Injection 1 date	Week 26/Injection 2 date – 1 day
Week 26/Injection 2	Week 26/Injection 2 date	Week 26/Injection 2 date	Week 52/Injection 3 date – 1 day
Week 52/Injection 3	Week 52/Injection 3 date	Week 52/Injection 3 date	Week 78/Injection 4 date – 1 day
Week 78/Injection 4	Week 78/Injection 4 date	Week 78/Injection 4 date	Week 104/Injection 5 date – 1 day
Week 104/Injection 5	Week 104/Injection 5 date	Week 104/Injection 5 date	Week 130/Injection 6 date – 1 day
Week 130/Injection 6	Week 130/Injection 6 date	Week 130/Injection 6 date	Week 156/Injection 7 date – 1 day
Week K/Injection [(K/26)+1] (K is every 26 weeks after previous visit)	Week K/Injection [(K/26)+1] date	Week K/Injection [(K/26)+1] date	Week (K+26)/Injection [(K/26)+2] date – 1 day

The analysis windows for the Administration and Dosing Questionnaire are provided in Table 3-6 and are calculated from the last SC injection date prior to administration of the questionnaire.

Table 3-6. Analysis Visit Windows for Administration and Dosing Questionnaire for PrEP medication (from last SC injection date prior to administration of the questionnaire)

Target Visit	Target Study Date	Visit Window Study Date	
		Lower Limit	Upper Limit
Week 13/13 weeks after Injection 1	Week 13/Injection 1 date + 91 days	Day 1/ Injection 1 date	Week 26/Injection 2 date – 1 day
Week 39/13 weeks after Injection 2	Week 39/ Injection 2 date + 91 days	Week 26/Injection 2 date	Week 52/Injection 3 date – 1 day
Week 65/13 weeks after Injection 3	Week 65/ Injection 3 date + 91 days	Week 52/Injection 3 date	Week 78/Injection 4 date – 1 day
Week 91/13 weeks after Injection 4	Week 91/ Injection 4 date + 91 days	Week 78/Injection 4 date	Week 104/Injection 5 date – 1 day
Week K/13 weeks after Injection [(K/26)+0.5] (K is every 13 weeks after each injection visit)	Week K/Injection [(K/26)+0.5] date + 91 days	Week (K-13)/ Injection [(K/26)+0.5] date	Week (K+13)/Injection [(K/26)+1.5] date – 1 day

The analysis windows for height are provided in Table 3-7 as calculated from the first dosing date of study drug for the RBP and from the first dosing date of OL Oral PrEP.

Table 3-7. Analysis Visit Windows for Height (from RBP or OLOP Day 1)

Nominal Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 52	364	2	546
Week 104	728	547	910
Week K (K is every 52 weeks after previous visit)	K*7	(K-26)*7+1	(K+26)*7

Height collected at screening and Day 1 of RBP only for all participants. For participants < 20 years old, height is also to be measured annually until they reach 20 years of age.

3.8.4. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For chlamydia or gonorrhea infection at each anatomic location [rectal, pharyngeal, or urethral] and trichomonas vaginalis infection, both central and local laboratory results (including central lab affiliated local laboratory tests) will be combined for summaries.

- For safety laboratory data (including chemistry, hematology, and urine [urinalysis, urine protein, urine chemistry, urine pregnancy]), only central laboratory results (excluding both local laboratory tests and central lab affiliated local laboratory tests) will be summarized.

- For screening values (Sections 5.1 to 5.2) and baseline values, the first (for screening) and last (for baseline) nonmissing value on or prior to the first dosing date (dosing time will not be incorporated even where collected) of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the screening and baseline values will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal) for categorical data except for STIs where the worst severity value / newest disease stage will be selected (ie, abnormal will be selected over normal) and except for questionnaires. For all questionnaires, all responses from the first (for baseline) complete set of responses (with the same date/time) on or prior to the first dosing date will be selected (data query is needed if multiple questionnaires are recorded at the same day/time).

- For postbaseline values:
  - Excluding STIs and questionnaires:
    - The record closest to the nominal day / target date for that visit will be selected.
    - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
    - If there is more than 1 record on the selected day, the average will be taken for continuous data, the worse severity will be taken for categorical data.
  - For STIs, the worst severity value within the window will be selected (ie, abnormal will be selected over normal).
  - For all questionnaires including Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire, Adherence to Oral Study Product Questionnaire, PrEP Impacts and Administration Preference Questionnaire, Numeric Pain Rating Scale-Injection Pain, Administration and Dosing Questionnaire for PrEP Medication, the first complete set of responses (with the same date/time) will be selected.

3.9. Transition Dates Between Study Phases

Depending on the type of endpoint, some analyses will be conducted combining both study phases (while in study), while other analyses will be conducted by study phase separately.

Analyses conducted in study include the primary analysis of the primary efficacy endpoint (Section 6.1), ISRs to study SC injection (Section 7.1.7.1), sexual behaviors (from lab STIs or questionnaires, Section 9) and PrEP impacts and administration preferences questionnaires, Section 10). Analyses conducted by each study phase separately include AEs, safety labs, adherence to oral study drug (from pill counts or questionnaires).

For analyses conducted by each study phase separately, the records on the date of first dose of OLOP (defined in Section 3.8.2) that occurs after permanent discontinuation of RBP study drug will be included as noted below. In general, RBP analyses will disregard temporary interruptions in the RBP study drug administration, unless indicated otherwise. Temporary interruption to RBP study drug includes the clinical hold period during which participants may receive temporary oral study drug [open label F/TDF or open-label F/TAF or blinded weekly oral LEN/PTM bridging] as well as blinded weekly oral LEN/PTM bridging following late SC injections outside of clinical hold.

RBP analyses

Adverse events (AE), concomitant medication, pregnancy, and death data collected up to last exposure date of the RBP study drug and **prior to** the first dose date of OLOP study drug (if applicable) will be included in the safety summaries, unless specified otherwise. An exception is for treatment-emergent ISRs to study SC injections which will only be counted in the RBP even if the onset date is on or after OLOP first dose date.

All other available safety data including laboratory data (eg, hematology, chemistry, and urine analysis) and vital signs data collected up to last exposure date of the RBP study drug and **on or prior** to the first dose date of OLOP study drug (if applicable) will be included in the safety summaries, unless specified otherwise.

For PK, questionnaires, and HIV-1 diagnosis dates for supportive analyses while on randomized study drug (Section 6.4.2.2), those collected **on or prior to** the first dose date of OLOP study drug will be included with the RBP analyses.

OLOP analyses

The OLOP analyses will include (1) all available AE, concomitant medication, pregnancy, and death data with start date **on or after** the first dose date of OLOP study drug and (2) all available other data, such as laboratory, vital sign and questionnaire data, collected **after** the first dose date of OLOP study drug. An exception is that the data collected **on or prior** to the first dose date of OLOP study drug will be used to derive the baseline value for the OLOP safety analyses.

In addition, PURPOSE 2 US participants are permitted to switch between OL F/TDF and OL F/TAF for the OLOP administered via the PK Tail Phase.

For adherence to oral daily study drug analyses (from pill counts or questionnaires), any switches in OLOP will be ignored and all data included.

All other OLOP analyses will be limited to the duration while participants were on the first OLOP study drug received. (ie, Participants who switch from OL F/TDF to OL F/TAF will be summarized with the OL F/TDF group and include data while on OL F/TDF and up to the first dose of OL F/TAF.) Short period switches (defined as less than 7 days) will be ignored for participants with multiple switches (eg, switching from OL F/TDF to OL F/TAF for less than 7 days and returning to OL F/TDF).

OLOP AE, concomitant medication, pregnancy, and death data collected **prior to** the first dose date of the first switch of OLOP study drug (if applicable) will be included in the safety summaries, unless specified otherwise. All other available OLOP data including laboratory, vital sign, PK and questionnaire data (except adherence questionnaires) collected **on or prior** to the first dose date of first switch OLOP study drug will be included in the safety summaries.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Key study dates (i.e., first participant screened, first participant randomized, last participant randomized, last participant last visit for the primary endpoint (last at-risk of HIV-1 infection date in study), and last participant last visit for the clinical study report) will be provided.

A summary of participant screening in the Incidence Phase and randomization in the RBP will be provided for each country and investigator within a country). The summary will present the number and percentage of participants in the All Screened Set and in the RBP Safety Analysis Set by study drug group and overall). For each column, the denominator for the percentage calculation will be the total number of participants analyzed for that column.

The randomization schedule used for the study will be provided as an appendix to the CSR.

An overall summary of participant disposition as well as two separate summaries for i) those who received the first dose of study drug on or prior to the clinical hold (21 December 2021) and ii) those who received the first dose of study drug after the lift of clinical hold (16 May 2022) will be provided by study drug group and study phase for the number of participants in the below categories.

The number and percentage of participants for the following categories will be provided:

- Status of HIV-1 diagnosis in the Incidence Phase (All Screened Set as the denominator)
- Status of study drug (and study) completion and reasons for premature discontinuation by study phase (Safety Analysis Set by study phase as the denominator)
- Receipt of oral study drug for clinical hold (RBP Safety Analysis Set as the denominator)

In addition, a flowchart will be provided to depict the disposition in the study phases.

<u>Incidence Screening Phase Disposition</u>

- Screened in Incidence Phase
  - Screen Failed Incidence Screening Phase Eligibility Criteria
    - Any HIV Test Result at Incidence Screening (defined as having any non-missing rapid or central laboratory HIV test)
    - Any Central HIV Test Result at Incidence Screening (defined as having any non-missing central laboratory HIV test including the HIV-1/HIV-2 Ag/Ab screening, HIV-1/HIV-2 differentiation Ab, HIV-1 RNA qualitative or HIV-1 RNA quantitative test)

- Met all Incidence Screening Phase Eligibility Criteria
  - Any HIV Test Result at Incidence Screening
  - No HIV Result at Incidence Screening (with Reasons Did Not Receive Any HIV Test, from RAPID HIV-1/2 Result-Screening (Incidence Phase) eCRF Reason Not Performed)
  - Any Central HIV Test Result at Incidence Screening
  - No Central HIV Result at Incidence Screening
- Central HIV Test Performed after Initial Screening Visit, Prior to Randomization and were Randomized and Dosed in RBP

- Any Central HIV Test Result or Dosed (All Screened Set)
  - Diagnosis of HIV-1 at Incidence Screening, defined in Section 6.1.1.1.
    - Recent HIV-1 (defined in Table 6-2)
    - Not Recent HIV-1 (defined in Table 6-2)
    - Undeterminable HIV-1 (defined in Table 6-2)
  - Diagnosis of No HIV-1 at Incidence Screening

RBP Disposition

- Met all Incidence Screening Phase Eligibility Criteria, but not Screened in RBP (including Reasons Not Screened, from Enrollment eCRF)
- Did not meet all Incidence Screening Phase Eligibility Criteria, but Screened in RBP
- Screened in RBP
  - Screen Failed RBP Eligibility Criteria
    - Randomized
    - Not Randomized
  - Met all RBP Eligibility Criteria
    - Randomized
    - Not Randomized (with Reasons Not Randomized, from Enrollment eCRF)

- Diagnosis of HIV-1 after Incidence Screening and Never Dosed in RBP (met HIV diagnosis definition defined in Section 6.1.1.1 after Incidence Screening)
- Randomized
- Randomized and Never Dosed
- Randomized and Dosed (RBP Safety Analysis Set)
- Randomized and Dosed with Diagnosis of HIV-1 On or Prior to First Dose (excluding Screening HIV-1 diagnosis)
- Randomized and Dosed with Diagnosis of no HIV-1 On or Prior to Day 1 (Full Analysis Set)
- Continuing study drug in RBP
- Did not complete study drug in RBP with reasons for premature discontinuation of study drug in RBP
- Continuing study in RBP
- Did not complete study in RBP with reasons for premature discontinuation of study in RBP

OLOP Phase Disposition

- Entered OLOP Phase
- Dosed with OLOP
- Continuing study drug in OLOP Phase
- Completed study drug in OLOP Phase
- Did not complete study drug in OLOP Phase with reasons for premature discontinuation of study drug in OLOP Phase
- Continuing study in OLOP Phase
- Completed study in OLOP Phase
- Did not complete study in OLOP Phase with reasons for premature discontinuation of study in OLOP Phase

Clinical Hold Disposition

- Screening (Incidence Phase or RBP), Randomization or First Dose Interrupted by Clinical Hold, which includes the following:
  - Rescreened participants, defined as participants who were screened but not dosed on or prior to 21 December 2021 and rescreened after the clinical hold
    - Diagnosis of HIV-1 during Rescreening, diagnosis of HIV-1 defined in Section 6.1.1.1 occurring at rescreening after the clinical hold was lifted on 16 May 2022
    - Diagnosis of No HIV-1 during Rescreening
  - Not Rescreened participants. Not rescreened participants are defined as participants who met all the following conditions (1) not dosed on or prior to 21 December 2021, (2) either Incidence Phase Screening or RBP Screening visit on or between 20 November 2021 and 21 December 2021, (3) had no other visits after FDA removed the clinical hold on 16 May 2022 and (4) reason for not enrolling includes "Clinical Hold" on the Enrollment eCRF
- RBP Potentially Impacted by Clinical Hold. This includes participants whose first dose date was on or prior to 21 December 2021 and who either (1) received oral study drug during the clinical hold (between the first and last dose dates of oral drug due to clinical hold defined in Section 3.8.2.4) or (2) permanently discontinued RBP study drug due to the clinical hold (study drug discontinuation reason of "clinical hold"). Note this excludes participants who permanently discontinued RBP study drug prior to 21 December 2021 as well as any participants who discontinued during the clinical hold but for other reasons (AE, participant decision, etc.)
  - Diagnosis of HIV-1 during Clinical Hold (defined as (1) between the first dose date of oral drug due to clinical hold and end date defined in Section 3.8.2.4) for those that received oral study drug due to clinical hold or (2) through the Last At-Risk of HIV-1 Infection Date in Study (defined in Section 3.8.2.3) for participants that permanently discontinued RBP study drug due to the clinical hold).
- Received Oral Study Drug for Clinical Hold
  - Resumed RBP study drug
  - Did not resume RBP study drug
- Received Open-Label Oral F/TDF
  - Resumed RBP study drug
  - Did not resume RBP study drug

- Received Open-Label Oral F/TAF
  - Resumed RBP study drug
  - Did not resume RBP study drug
- Received Open-Label Oral F/TDF and Open-Label Oral F/TAF
  - Resumed RBP study drug
  - Did not resume RBP study drug
- Received Blinded Oral Weekly LEN/PTM Bridging
  - Resumed RBP study drug injections
  - Did not resume RBP study drug injections

The following by-participant listings will be provided by participant identification (ID) number in ascending order to support the above summary tables by study phase if applicable:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Lot number and kit number

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug, defined as duration of exposure, and the level of adherence relative to the prescribed study drug regimen specified in the protocol will be summarized. Study drug administration and study drug dispensing information will be collected in the Study Drug Administration and Study Drug Accountability eCRFs. All data including lot number and kit ID (if applicable) will be listed.

4.2.1. Duration of Exposure to Study Drug

Due to the long-acting nature of LEN, duration of follow-up to study drug will consider the prolonged exposure of LEN after the last dose date of LEN. Duration of exposure will be summarized in the study (including both the RBP and follow-up of participants that discontinued the RBP early and may receive OL oral PrEP administered via the PK Tail Phase separately) by study phase. Duration will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). For PURPOSE 2, the OL oral PrEP exposure will be summarized separately for the first OL oral PrEP administered and overall for any OLOP including switches in OLOP study drug.

Within each study phase, duration of exposure to study drug will be defined as the last exposure date of the study phase – the first dose date of the study phase + 1, regardless of any temporary interruptions in study drug administration. Last exposure date for each study phase is defined in Section 3.8.2 for participants who prematurely discontinued study drug. For PURPOSE 2, the overall duration of exposure will be summarized separately for the first OL oral PrEP administered and overall for any OLOP including switches in OLOP study drug.

The total duration of follow-up in study will be defined as (the last study date – the first dose date + 1), regardless of any temporary interruptions in study drug administration.

For participants who are still on study drug at the data cutoff date, the last exposure dates for each study phase and last study date will be imputed for the calculation of the duration of study drug exposure or duration of follow-up in study using the same definitions in Section 3.8.2 with:

- Last dose date imputed with the latest of active randomized study drug (for RBP) or of OLOP (for OLOP) start dates and end dates, the clinic visit or laboratory visit dates excluding the follow-up visits (within each study phase, respectively).
- Last study date imputed with the latest of the study drug (active or placebo for RBP or OLOP for OLOP) start dates and end dates, the clinic visit dates, the laboratory visit dates, the AE onset date and end dates, including any follow-up visits.

For PURPOSE 2, the imputation for last exposure date for the first OLOP study drug is the minimum of the above and the date of first switch of OLOP study drug.

The total duration of exposure to study drug and total duration of follow-up in study will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and the total person-years) and using the number (ie, cumulative counts) and percentage of participants exposed and remained through the following time periods: ie, ≥ 4 weeks (28 days) and ≥ 8 weeks (56 days) for the RBP only as well as ≥ 13 weeks (91 days), ≥ 26 weeks (182 days), ≥ 39 weeks (273 days), ≥ 52 weeks (364 days), ≥ 65 weeks (455 days), ≥ 78 weeks (546 days), ≥ 91 weeks (637 days), ≥ 104 weeks (728 days), ≥ 117 weeks (819 days), ≥ 130 weeks (910 days), etc. Summaries will be provided for total duration of exposure to study drug by study drug group for the Safety Analysis Set by study phase. No formal statistical testing is planned.

4.2.2. Duration of Clinical Hold Impact in the RBP

The duration of clinical hold impact (defined as the duration from the first dose date of study drug due to clinical hold to the end date of clinical hold impact defined in Section 3.8.2.4) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum and the total person-years) and as the number and percentage of participants receiving oral study drugs during clinical hold for specified periods, ie, ≥ 4 weeks (28 days) and ≥ 8 weeks (56 days), ≥ 13 weeks (91 days), ≥ 26 weeks (182 days), ≥ 39 weeks (273 days), etc. Both separate and combined overall summaries will be provided for the durations of OLOP (for OL F/TDF, OL F/TAF and either OLOP, separately) and blinded oral weekly LEN/PTM bridging during clinical hold.

In addition, the number of blinded oral LEN/PTM bridging doses during clinical hold will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of participants receiving specified doses, ie, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, >=14.

4.2.3. Duration of Exposure to Bridging with Blinded Oral LEN/PTM During the RBP (Outside of Clinical Hold)

The protocol allows for bridging with blinded oral weekly LEN/PTM, outside of clinical hold upon medical monitor approval, if participants are unable to return to the clinic to receive on-time blinded LEN/placebo injections during the RBP. The number of blinded oral LEN/PTM bridging doses outside of clinical hold during the RBP will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and the total person-years) and as the number and percentage of participants receiving specified doses, i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, >=14, etc. in total and by injection visit.

4.2.4. Adherence to Study Drug

Four measures of study drug regimen adherence will be estimated based on data collected at the site or reported directly by study participants:

1) On-time SC Injection (in-RBP study phase) assessed by adherence to the prescribed SC injection schedule (last injection date + 26 weeks) on the Study Drug Administration Injection (SC LEN) eCRF,

2) On-Time Day 2 LEN or PTM Oral Study Drug (in-RBP study phase) assessed by adherence to the prescribed oral SC LEN schedule expected on Day 2 on the Study Drug Administration eCRF,

3) Prescribed pill counts for once daily dosing of oral study drug based on pill dispensations and returns on the Study Drug Accountability eCRF,

4) Self-reported Adherence to Oral Study Product from electronic patient reported outcome (ePRO) questionnaire

Using a randomly selected cohort of study participants, TFV-DP and FTC-TP levels in red blood cells (RBCs) from DBS analyses (APPENDIX 6) are planned in order to provide objective data for estimating drug adherence for F/TDF. TFV-DP and FTC-TP levels in RBCs from DBS while participants are in RBP (excluding OLOP) will be included.

4.2.4.1. On-Time SC Injection via Adherence to Prescribed SC Injection Schedule in RBP

The adherence to SC injection will be assessed by adherence to the prescribed injection interval, which is 26 weeks (182 days) after the last injection visit for the RBP. On-time LEN/placebo SC injection will include SC injections that occur ≤196 days (≤14 days beyond 26 weeks) after the last injection visit (the protocol recommends oral re-loading with LEN or PTM for SC injections

that occur later than 28 weeks after the last injection). Injections are considered received if any injection dose is administered, including partial or incomplete injections. Each injection visit consists of 2 SC injections and the first injection date will be used for that visit if injections were split over different dates.

A summary of on-time injection will be provided for all participants with at least one SC injection as well as those who randomized and first dosed after the clinical hold was lifted (16 May 2022).

The number of days from the projected injection visit date will be calculated for each injection visit (excluding the 1st injection visit) as the injection visit date – the previous injection visit date minus 182 days. The number of days from the projected injection visit date will also be classified into the following categories:

- On-time SC injection (LEN/placebo) that occurs within ≤ 14 days beyond 26 weeks after the last injection visit
  - < - 14 days
  - -14 to -8 days
  - ± 7 days
  - 8 to 14 days
- Late SC Injection that occurs > 14 days beyond 26 weeks after the last injection visit
  - Received Open-Label Oral F/TDF, Open-Label Oral F/TAF or Oral Weekly LEN/PTM during Clinical Hold
  - Did Not Receive Open-Label Oral F/TDF, Open-Label Oral F/TAF nor Oral Weekly LEN/PTM during Clinical Hold or Started RBP Study Drug After Clinical Hold Lift (06 May 2022, for Week 26 / SC Injection 2 only)
- Did Not Receive SC Injection
  - Started RBP Study Drug On or Prior to Start of Clinical Hold (21 December 2021)
    - Permanently Discontinued RBP Study Drug Prior to Start of Clinical Hold (21 December 2021, for Week 26 / SC Injection 2 only)
    - Permanently Discontinued RBP Study Drug On or Following Start of Clinical Hold (for Week 26 / SC Injection 2 only)
  - Started RBP Study Drug After Clinical Hold Lift (06 May 2022, for Week 26 / SC Injection 2 only)

- RBP Study Drug Discontinuation Prior to the Upper Limit of the Clinical Injection Visit Window, but Remained in RBP Study Phase (based on last SC injection date + 189 days (i.e. 26 weeks + 7 days)
- Remained in RBP Study Phase but Missed SC Injection

The number and percentage of participants in each category will be summarized for each post-baseline injection visit. The denominator for calculation of percentage is the number of participants who were expected to receive an SC injection, who had the potential to be followed up on or beyond the upper limit of the clinical injection visit window (based on last SC injection date + 189 days (i.e. 26 weeks + 7 days) and have not prematurely discontinued the RBP study phase prior to the upper limit of the clinical injection visit window).

In addition, participants who had a SC injection at the visit (including partial injections) will also be counted as expected participants at the visit.

The summary for the Week 26/2nd injection visit will include categories for participants impacted by the clinical hold.

4.2.4.2. On-Time Day 2 LEN or PTM Oral Study Drug

The adherence to Day 2 LEN or PTM oral study drug will be assessed by on-time Day 2 study drug administration in the RBP Safety Analysis Set. The day that the Day 2 LEN or PTM oral study drug was taken will be classified into the following categories:

- Participants Missing Day 1 SC Injections
- Participants with Incomplete Day 1 SC Injections (Not Administered 2 SC Injections Per Protocol)
- Participants with Complete Day 1 SC Injections (Administered 2 SC injections, Per Protocol)
  - Day 1 (may occur from dosing error)
  - Day 2
  - Day 3 to 8
  - > Day 8 up to the earlier of (Week 26/2nd injection or date discontinued RBP study drug)
  - Day Unknown (includes any partial LEN dose dates)
  - Missed Dose

Day 2 LEN or PTM oral loading dose is defined as the second oral LEN administration of 2 tablets up until the earlier of (Week 26/2nd injection, date discontinued RBP study drug, or last study date). The number and percentage of participants in each day of second oral LEN or PTM category will be summarized using the RBP Safety Analysis Set among participants who had complete Day 1 injections (both injections at Day 1 administered, excluding partial doses).

4.2.4.3. Adherence to Once Daily Oral Study Drug Regimen via Pill Counts

The adherence to the prescribed oral study drug regimen will be computed based on pill counts by study phase.

For RBP, the F/TDF study drug group regimen includes active F/TDF as well as OL F/TDF or OL F/TAF administered during clinical hold.

For RBP, the SC LEN study drug group regimen includes F/TDF or PTM as well as OL F/TDF or OL F/TAF administered during clinical hold.

For OLOP, OLOP participant groupings will be based on the first OL oral drug received (OL F/TDF or OL F/TAF per Section 3.2), however, both study groups will include OL F/TDF and OL F/TAF as adherence will be calculated over the entire OLOP phase regardless of switches in study drug regimens among PURPOSE 2 US sites.

The numbers of pills of study drug dispensed and returned are captured on the Study Drug Accountability eCRF.

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the expected total amount of study drug (1 pill per day for the duration of study participation based on the protocol) and will be calculated from first dose date to the to the end date by study phase. The end date is defined as the latest of any oral or SC injection study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the 30-day follow-up visit date for each study phase. For participants in RBP that received OLOP due to permanent discontinuation from randomized study drug (transitioned to the PK Tail Phase), the end date for the RBP study phase is defined as date of the Study Day 1 for OLOP administered via the PK Tail Phase minus 1 day. If the participant has been diagnosed with HIV-1, the later date of either the 1) HIV-1 diagnosis date or 2) last dose date of any oral or SC injection study drug in the study phase will be used as the end date. Per study design, participants that have been diagnosed with HIV-1 must immediately discontinue study drug but may remain in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

$$\textit{Prescribed Adherence (\%)} = \frac{\textit{Total Amount of Study Drug Administered}}{\textit{Total Amount of Study Drug Expected While Participating in Study Phase}} \times 100$$

[1] Total amount of study drug administered is the number of pills dispensed minus the number of pills returned.
[2] Total amount of study drug expected while participating in the study phase is calculated as the daily number of pills prescribed for the study drug multiplied by the duration of study participation defined as from first oral daily dose date to the end date defined as the latest of the any oral or SC injection study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the follow-up visit dates for each study phase. For participants in RBP that received OLOP due to permanent discontinuation from randomized study drug (transitioned to the PK Tail Phase), the end date for the RBP study phase is defined as date of the Study Day 1 for OLOP Oral PrEP administered via the PK Tail Phase minus 1 day. If the participant has been diagnosed with HIV-1, the later date of either the 1) HIV-1 diagnosis date or 2) last dose date of any oral or SC injection study drug will be used as the end date.

If any study drug bottle was not returned, the bottle return status is considered unknown or the number of pills returned is missing, then it is assumed the number of pills returned is zero. The number of pills taken after the last bottle dispensation visit will be the minimum of 1) the number of pills dispensed minus the number of pills returned (if some bottles were returned) or 2) the number of days between the last bottle dispensation date to the end date as defined in this section. Each participant's adherence rate will be capped at 100%.

Descriptive statistics for overall prescribed adherence (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (ie, < 30%, ≥ 30% to < 60%, ≥ 60% to < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) will be provided by study drug group for participants in the Safety Analysis Set by study phase.

No formal statistical testing is planned.

A by-participant listing of study drug administration and drug accountability will be provided separately by participant ID number (in ascending order) and visit (in chronological order).

4.2.4.4. Adherence to Oral Study Product ePRO Questionnaire by Study Phase While On-Treatment

Participants' self-reported adherence to the once daily oral study drug will be collected from the Adherence to Oral Study Product ePRO questionnaire and summarized by visit and a listing will be provided:

- Took study pills yesterday: (a) Yes, (b) No, (c) Prefer not to answer
- Ability to take your study pills every day in the past month: (a) Very poor, (b) Poor, (c) Fair, (d) Good, (e) Very Good, (f) Excellent, (g) Prefer not to answer
- Took study drug pills every day as recommended over the past month: (a) None of the time, (b) Some of the time, (c) Half of the time, (d) Most of the time, (e) All of the time, (f) Prefer not to answer
- Shared pills with someone else in the past month: (a) Yes, (b) No, (c) Prefer not to answer
- Frequency of finding it inconvenient or difficult to take oral study medication: 0 (None of the time), 1, 2, 3 (Half of the time), 4, 5, 6 (All of the time), Prefer not to answer

The number and percentage of participants with each response category while on-treatment will be provided by study drug group for participants in the Safety Analysis Set for each study phase. On-treatment data includes visits occurring through the upper limit of the analysis window corresponding to the date of permanent discontinuation of study drug for participants that permanently discontinued study drug or all available postbaseline data for participants who were still on study drug for each study phase.

4.3. Protocol Deviations

Participants who did not meet the eligibility criteria for study entry but enrolled or randomized in the study will be summarized by study phase. The summary will present the number and

percentage of participants who did not meet at least 1 eligibility criterion and the number of participants who did not meet specific criteria for the Incidence Phase based on the All Screened Set and for the RBP by study drug group and overall based on the RBP Safety Analysis Set. A by-participant listing will be provided for those participants who did not meet at least 1 eligibility (inclusion or exclusion) criterion.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations and the total number of important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized by study drug group for the RBP Safety Analysis Set. A by-participant listing will be provided for those participants with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-participant listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable.

4.4.2. Protocol Deviations Due to COVID-19

A by-participant listing will be provided for participants with important protocol deviations related to COVID-19. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19.

4.4.3. Missed and Virtual Visits due to COVID-19

A by-participant listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in APPENDIX 10.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ narrow search. A by-participant listing of AEs of COVID-19 will be provided if applicable.

4.4.5. Overall Assessment of COVID-19 Pandemic Impact

For participants affected by COVID-19 infection and/or pandemic while participating in the study, a listing of the following individual COVID-19 related outcome categories will be provided:

- Death due to COVID-19
- Adverse event of COVID-19, as determined by COVID-19 Standardized MedDRA Queries (SMQ) narrow search (see APPENDIX 7)
- Specific COVID-19 adverse event directly associated with the pathogen causing COVID-19, as determined by "COVID-19_DIAGNOSIS-FOCUSED" MST
- Hospitalization (using data from AE eCRF) due to adverse event of COVID-19 as defined above
- Study drug discontinuation due to COVID-19
- Study discontinuation due to COVID-19
- Missed visits due to COVID-19
- Missed key assessments due to COVID-19: Missing all central HIV testing at Week 4, 8, 13 and every 13 weeks

In addition, composite broad COVID-19 impact indicator will be derived based on the following individual categories defined above: death, adverse event, hospitalization, study drug discontinuation, study discontinuation, missed visits, and missed key assessments. Composite specific COVID-19 impact indicator will be derived based on death and specific adverse event.

5. BASELINE CHARACTERISTICS

All participant demographics, baseline characteristics and medical history will be summarized by study drug group (and total) for the RBP Safety Analysis Set in the RBP. When applicable, an additional table will be included for the Incidence Phase (for the All Screened Set by Incidence Screening HIV-1 diagnosis status as well as by randomization status for the All Screened Set diagnosed with no HIV-1 at Incidence Screening) or DBS Cohort Analysis Set (by study drug group and total).

5.1. Demographics and Screening or Baseline Characteristics

Participant demographic variables (ie, age, sex assigned at birth, gender identity, sexual orientation, race, and ethnicity) and screening or baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], waist circumference [in cm]) will be summarized by study drug group and overall for the RBP using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic data will also be provided for the Incidence Phase and the DBS Cohort Analysis Set and will include:

- Age (years)
- Age categories (years): (a) 16 to < 18, (b) 18 to ≤ 25, (c) > 25 to < 35, (d) 35 to < 50, (e) ≥ 50
- Sex assigned at birth
- Gender identity: (a) Cisgender Man (CGM), (b) Transgender Man (TGM), (c) Transgender Woman (TGW), (d) Non-binary (i. assigned male at birth, ii. assigned female at birth), (e) Other (i. assigned male at birth, ii. assigned female at birth)
- Sexual orientation (a) Straight/Heterosexual, (b) Gay, (c) Lesbian, (d) Bisexual, (e) Other, (f) Prefer not to disclose
- Race: (a) American Indian or Alaska Native, (b) Asian, (c) Black, (d) Native Hawaiian or Pacific Islander, (e) White, (f) Multiracial – Black/White, (e) Multiracial – Black/Asian, (f) Multiracial – Black/American Indian or Alaska Native, (g) Multiracial – Black/Native Hawaiian or Pacific Islander, (h) Multiracial – Asian/White, (i) Multiracial – Asian/American Indian or Alaska Native, (j) Multiracial – Asian/Native Hawaiian or Pacific Islander, (k) Multiracial – White/American Indian or Alaska Native, (l) Multiracial – White /Native Hawaiian or Pacific Islander, (m) Multiracial – American Indian or Alaska Native/Native Hawaiian or Pacific Islander, (n) Multiracial – Other, (o) Not Multiracial – Other , (p) Not Permitted
- Ethnicity: (a) LatinX/Hispanic, (b) Non-LatinX/Non-Hispanic, (c) Not Permitted
- Race and Ethnicity categories above will also be summarized by country

The summary of demographic data also includes screening information from the Demographics – Additional Participant Information eCRF:

- Highest Education Level: (a) Did not attend Primary School, (b) Some Primary School Education, (c) Primary School Complete, (d) Some Secondary School Education, (e) Secondary School Degree Complete, (f) Some College or University Degree
- Needs help with completion of electronic questionnaires (a) Yes, (b) No

The summary of screening and baseline characteristics data will also be provided for the Incidence Phase and DBS Cohort Analysis Set, respectively and will include:

- Body weight (kg)
- Height (cm)
- Body mass index [BMI] (kg/m^2)
- Waist circumference (cm)

A by-participant demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline medical characteristics to be summarized will include:

- HBV infection status (Yes/No/Missing)

Participants with HBV infection at baseline are defined as participants meet any of the following two criteria:

  — Positive HBsAg on or prior to the first dose date, or

  — Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.

- HCV infection status (Yes/No/Missing)

  — Participants with HCV infection at baseline are defined as participants with positive HCVAb or quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL) on or prior to the first dose date.

- $eGFR_{CG}$ (mL/min)
- Serum creatinine (mg/dL)
- Proteinuria toxicity grade by urinalysis (dipstick)

Other screening HIV risk characteristics data will also be provided for the Incidence Phase and will include:

- Prior HIV test (prior to the Screening Visit of the Incidence Phase): (a) Yes (negative result), (b) Yes (positive result), (c) Yes (result not available), (d) No
- Time since last HIV test performed prior to the Screening Visit of the Incidence Phase (months)
- Any prior long-acting PrEP medication (at Incidence Phase Screening)
- Prior HIV vaccine (at Incidence Phase Screening)
- Baseline PrEP medication (at Incidence Phase Screening): (a) Yes (F/TDF), (b) Yes (F/TAF), (c) Yes (Other), (d) No (defined in Section 7.4.2)
- Any prior PrEP medication (at Incidence Phase Screening) : (a) Yes (F/TDF), (b) Yes (F/TAF), (c) Yes (Other), (d) None (defined in Section 7.4.1)
- Time since latest prior PrEP medication (months) among participants not on baseline PrEP medications at Incidence Phase Screening (defined in Section 7.4.1)
- History of syphilis, rectal gonorrhea or rectal chlamydia in the past 24 weeks (from Inclusion/Exclusion Criteria (Incidence) eCRF)
- Condomless receptive anal sex with ≥ 2 partners in the last 12 weeks (from Inclusion/Exclusion Criteria (Incidence) eCRF)
- Self-reported use of stimulants with sex in the last 12 weeks (from Inclusion/Exclusion Criteria (Incidence) eCRF)

Other baseline HIV risk characteristics to be summarized will include:

- Chlamydia (from laboratory test)
  - Urine
  - Rectal
  - Pharyngeal
- Gonorrhea (from laboratory test)
  - Urine
  - Rectal
  - Pharyngeal

- Trichomonas vaginalis [TV] (urine, from laboratory test), limited to participants for whom TV was tested

- Syphilis Diagnosis (Yes/No/Missing) from investigator report

  — (a) Primary, (b) early latent, (c) secondary, (d) tertiary, (e) late latent, (f) other

- Selected Baseline ePRO questionnaire responses to the number of sexual partners (or sexual acts) and categories of participants (or sexual acts) with responses of 0, 1-2, 3, 4-5, 6-10, ≥11 partners (or sexual acts) or prefer not to answer in the past 3 months for PURPOSE 2 include:

  — Sex partners

  — Sex partners living with HIV

  — Sex partners living with HIV and on HIV medication and undetectable

  — Receptive anal sex (RAS) acts

  — CRAS acts

  — Insertive anal sex (IAS) acts

  — Condomless insertive anal sex (CIAS) acts

  — Receptive vaginal (frontal) sex (RVS) acts

  — Condomless receptive vaginal (frontal) sex (CRVS) acts

  — Taken drugs before or during sex (chemsex acts)

  — Sex for money, food, clothes, place to sleep, cell phone other support (commercial or transactional sex)

- Baseline AUDIT questionnaire responses to be included are:

  — Frequency of alcohol use: (a) Never, (b) Monthly or less, (c) 2 to 4 times a month, (d) 2 to 3 times a week, (e) 4 or more times a week, (f) Prefer not to answer

  — Six or more drinks on one occasion: (a) Never, (b) Less than monthly, (c) Monthly, (d) Weekly, (e) Daily or almost daily, (f) Prefer not to answer

- Alcohol before or during sex since last visit (or past 12 weeks): (a) Yes, (b) No, (c) Prefer not to answer

- Use drugs before or during sex since the last visit or past 12 weeks: (a) Yes, (b) No, (c) Prefer not to answer.

- Baseline substance use questionnaire responses to be included are:

  — Any substance (Cannabis, Cocaine, Amphetamine-type stimulants, Inhalants, Sedatives or sleeping pills, Hallucinogens, Opioids, Prescription drugs for non-prescription purposes) use in past 12 weeks: (a) Yes (less than monthly, monthly, weekly (at least once a week), daily or almost daily), (b) No, (c) Prefer not to answer (summarized separately for each recreational drug type)

  — Smoked cigarettes, in past 3 months: (a) Yes, (i) less than 10 cigarettes per day, (ii) between 10 and 20 cigarettes per day, (iii) more than 20 cigarettes per day, (iv) prefer not to answer, (e) No, (f) Prefer not to answer, from electronic questionnaires

A by-participant listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for study relevant and general conditions (i.e., conditions not specific to the disease being studied).

Study relevant medical history (including history of gender affirming surgery and organ inventory from the Gender Affirming Surgery and Organ Inventory eCRFs, respectively, in PURPOSE 2) will be summarized by study drug group and overall by the number and percentage of participants with each prepopulated condition for the RBP Safety Analysis Set. No formal statistical testing is planned.

General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and will be listed only.

6. EFFICACY ANALYSES

The primary efficacy endpoint is the diagnosis of HIV-1 infection for the randomized phase and diagnosis of recent HIV-1 infection for the incidence phase of the study. The recent HIV-1 infection will be used to estimate the bHIV reported per 100 PY computed based on the RITA.

A high-level description of efficacy objectives and analyses is presented in Table 6-1 to frame the efficacy analysis plan detailed in later sections.

Table 6-1. Summary for Key (Alpha-Controlled) Efficacy Evaluations

Objectives	Analysis Set	Population-Level Summary	Analysis Period & Intercurrent Events (ICE)
Primary: To evaluate the efficacy of LEN in reducing the risk of HIV-1 infection	Incidence Phase: All Screened Set[1] Randomized groups: Full Analysis Set (FAS)[2]	Rate Ratio: LEN/bHIV	bHIV: In the Incidence Phase prior to the first dose date & No applicable ICE LEN: In study[3] regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy
Secondary: To evaluate the comparability of LEN to TVD	FAS	Rate Difference: LEN-TVD	LEN and TVD: In study regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy
Secondary: To evaluate the superiority of LEN to TVD	FAS	Rate Ratio: LEN/TVD	LEN and TVD: In study regardless of ICEs (the clinical hold and early discontinuation of study drug); a treatment policy strategy)

1. All Screened Set: defined in Section 3.1.1.
2. FAS: defined in Section 3.1.3.
3. At risk of HIV-1 infection in study (see Section 6.1.2.2 and 3.8.2.3).

6.1. Analysis of the Primary Efficacy Endpoint

6.1.1. Definition of HIV-1 Infection

6.1.1.1. Incidence Phase HIV-1 Infection

Identification of prevalent HIV-1 cases in the Incidence Phase necessitates a case definition that allows for the identification and inclusion of acute HIV-1 cases (which may have not yet seroconverted) while minimizing the risk of including participants with false positive HIV-1 testing. To this end, considering the cross-sectional characteristics of this phase, we define HIV-1 cases in the Incidence Phase as those having at least one of the following lab results at the Incidence Phase screening visit:

a. Positive HIV-1/2 differentiation Ab, OR

b. Positive HIV-1 RNA qualitative test, OR

c. HIV-1 RNA quantitative test ≥200 copies/mL.

Notably, HIV-1/2 differentiation and HIV-1 RNA qualitative tests are confirmatory tests per the study protocol's HIV testing procedures and are therefore only performed when central laboratory HIV-1/2 Ab/Ag testing is positive. The use of HIV-1 RNA quantitative test to assess for acute HIV-1 infection is CDC guideline recommended, and HIV-1 RNA quantitative test results of ≥200 copies/mL are unlikely to be a false positive result {Centers for Disease Control (CDC) 2021}.

6.1.1.2. HIV-1 Infection for Randomized Participants

This study engages an HIV adjudication committee who will review potential HIV-1 infection events in the randomized participants. The committee will, in a blinded, consistent, and unbiased manner, adjudicate and confirm both the diagnosis of each HIV-1 infection (identifying false positive HIV-1 cases) and the date of each diagnosis and when necessary, pinpoint the earliest diagnosis date by back-testing archived samples. This process could identify cases with confirmed HIV-1 diagnosis that occur on or prior to Day 1 (ie, cases where HIV was present at baseline). The roles and responsibilities of the committee are detailed in the HIV Adjudication Committee Charter.

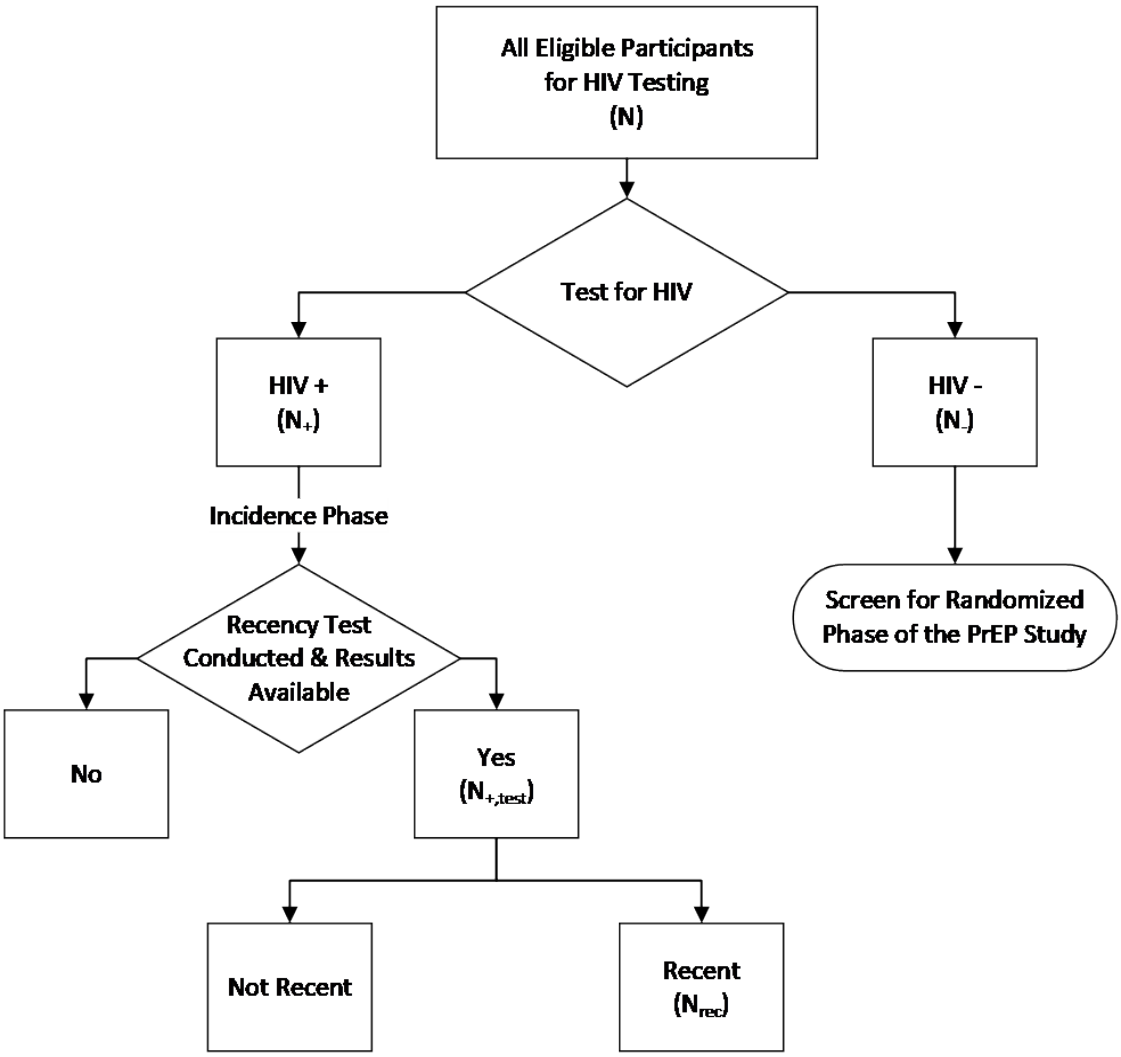
The adjudicated HIV-1 diagnosis and date will be used for all planned reports including the formal interim efficacy analysis (DMC reports), and clinical study reports (primary or any post-primary).

6.1.2. Estimation of HIV-1 Incidence

6.1.2.1. Incidence Phase

For the Incidence Phase of this study, the bHIV will be reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to {Kassanjee 2012}, adjusting for participants with HIV-1 who may not have recency results (See Figure 6-1).

Figure 6-1. A High-Level 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

The bHIV will be estimated by the formula:

$$\hat{\lambda}_0 = \frac{N_{rec}/(N_{+,test}/N_+) - \beta N_+}{N_-(\Omega - \beta T)}$$

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, as provided by {Gao 2021} (see below), considering the variance of Ω, β, and the observed counts of N_-, $N_{+,test}$, N_{rec}:

$$\hat{\sigma}^2_{\log(\hat{\lambda}_0)} = \frac{N_{rec}(N_{+,test} - N_{rec})}{N_{+,test}(N_{rec} - N_{+,test}\beta)^2} + \frac{N}{N_+ N_-} + \sigma^2_\beta \frac{N_{+,test}(N - N_{+,test})}{N(N_{rec} - N_{+,test}\beta)^2}$$

$$= + \frac{\sigma^2_\Omega}{(\Omega - \beta T)^2} + \sigma^2_\beta \left[\frac{N_{+,test}\Omega - N_{rec}T}{N_{rec} - N_{+,test}\beta)(\Omega - \beta\ \ )} \right]^2$$

The $(1-\alpha) \times 100\%$ confidence interval (CI) for $\log(\lambda_0)$ will be constructed as $\log(\hat{\lambda}_0) \mp z_{\alpha/2}\hat{\sigma}_{\log(\hat{\lambda}_0)}$, and the $(1-\alpha) \times 100\%$ CI for λ_0 will be $\hat{\lambda}_0 \exp\left(\mp z_{\alpha/2}\hat{\sigma}_{\log(\hat{\lambda}_0)}\right)$. Here $z_{\alpha/2}$ is the $(\alpha/2)$-th upper quantile of the standard normal distribution.

6.1.2.1.1. Choice of Recency Assay, Assay Parameters and Algorithm Parameters

The Sedia LAg-EIA will be the primary recency assay as it is the most widely used and has been field validated. The number of recent infections N_{rec} will be classified based on the RITA {Kassanjee 2016}. A participant, diagnosed with HIV-1, will be counted as a recent infection if the normalized optical density (ODn) is below the 1.5 threshold, provided that the HIV-1 RNA viral load is above the cutoff of 75 copies/mL. Table 6-2 presents the recency outcome from the RITA.

The ODn threshold of 1.5 has been recommended by the Forum for Collaborative Research Recency Assay Working Group (RAWG) in their closing publication {Parkin 2022}, by {Duong 2015} the CDC and the Sedia LAg-EIA package insert.

Although the study's eligibility criteria do not allow people who know that they have acquired HIV-1 to be screened, the RITA includes a viral load cutoff of 75 copies/mL to help prevent the overestimation of bHIV by reducing the number of false recent samples from people living with HIV who are virologically suppressed on antiretroviral therapy. When virologically suppressed people with HIV-1 are inadvertently screened, the avidity of their antibodies can be reduced due to the limited exposure of the immune system to actively replicating HIV-1 which can then lead to an inaccurate recent infection result in the Sedia LAg-EIA. The viral load cutoff used in the RITA must be above the limit of detection of the immunoassay used for determination of the HIV-1 infection, which is 20 copies/mL. Recency assay parameters (MDRI, FRR, etc.) were calculated for a range of viral load cutoffs by {Kassanjee 2016} and the lowest cutoff above 20 copies/mL, that is, 75 copies/mL was chosen for use in the RITA for this study. If a screened participant with HIV-1 has a viral load lower than or equal to the cutoff, the participant will be considered as not recently infected, and will be counted in $N_{+,test}$, regardless of the Sedia Lag-EIA test result, or whether the Sedia LAg-EIA result is available. If an HIV-1 positive participant's viral load is above the cutoff but the ODn is missing, the participant will be considered as having undeterminable recency outcome, hence excluded from $N_{+,test}$ and N_{rec} but will be included in N_+. If a participant's viral load is missing, the participant will be excluded from $N_{+,test}$ and N_{rec}, but included in N_+. See Table 6-2 for details.

Table 6-2. 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_{+}.

For participants who may have multiple HIV test visits, only tests done at the first HIV test date at Incidence Screening will be used for determining the recency outcome.

For the primary analysis, the assay parameters given by {Kassanjee 2016} will be used for bHIV estimation. Table 6-3 gives the assay parameters and their rSEs for $T = 2$ years (based on the RITA cutoffs in Table 6-2). The sample size calculation in the protocol was also based on {Kassanjee 2016} with $T = 2$ years for pooled samples.

Table 6-3. MDRI and FRR (Kassanjee et al, 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 2016}; parameters for subtype AE are not available in {Kassanjee 2016}, and are estimated using R package "inctools" (https://cran.r-project.org/web/packages/inctools/inctools.pdf) based on data from {Klock 2020} (see APPENDIX 2 for details).

a Based on the Sedia LAg-EIA and RITA cutoffs in Table 6-2 (ie, 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.

Since subtype data will not be available for analysis, we will use country, as a correlate, to estimate the percentage of each subtype instead. Based on a literature review for the geographical distribution of our study sites, we assume 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. For detailed literature and rationale on the subtype assumptions please refer to APPENDIX 3.

The MDRI used in estimating the bHIV for this study will be calculated as the weighted average of the MDRI for the subtypes included in the study. More specifically, 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:

5) Subtype B: $w_2+w_3+w_4+0.12w_5+w_6+0.92w_7$

6) Subtype C: $w_1+0.08w_7$

7) Subtype AE: $0.88w_5$

Let Ω_B, Ω_C, Ω_{AE} be the MDRI for the subtypes B/C/AE, and $\sigma_{\Omega,B}$, $\sigma_{\Omega,C}$, $\sigma_{\Omega,AE}$ be the corresponding standard errors, which will be computed as the product of MDRI and the rSE of the MDRI in Table 6-3. The overall MDRI will be estimated by

$$\Omega = (w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\Omega_B + (w_1 + 0.08w_7)\Omega_C + 0.88w_5\Omega_{AE}.$$

And the standard error of the overall MDRI will be estimated by

$$\sigma_\Omega = \sqrt{(w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)^2\sigma^2_{\Omega,B} + (w_1 + 0.08w_7)^2\sigma^2_{\Omega,C} + (0.88w_5)^2\sigma^2_{\Omega,AE}}.$$

The rSE of the overall MDRI will be calculated as σ_Ω/Ω, reported as a percentage (%).

The overall FRR will be estimated by the weighted average of the FRR for the subtypes. Let β_B, β_C, and β_{AE} be the FRR for the subtypes B/C/AE, and $\sigma_{\beta,B}$, $\sigma_{\beta,C}$, and $\sigma_{\beta,AE}$ be the corresponding standard errors, which will be computed as the product of the FRR and the rSE of the FRR in Table 6-3. The overall FRR will be estimated by

$$\beta = (w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)\beta_B + (w_1 + 0.08w_7)\beta_C + 0.88w_5\beta_{AE}.$$

And the standard error of the overall FRR will be estimated by

$$\sigma_\beta = \sqrt{(w_2 + w_3 + w_4 + 0.12w_5 + w_6 + 0.92w_7)^2\sigma^2_{\beta,B} + (w_1 + 0.08w_7)^2\sigma^2_{\beta,C} + (0.88w_5)^2\sigma^2_{\beta,AE}}.$$

The rSE of the overall FRR will be calculated as σ_β/β, reported as a percentage (%).

It should be noted that the FRR has been shown to be zero {Kassanjee 2016, Parkin 2022} for antiretroviral therapy (ARV)-treated HIV-1-positive participants but this is a PrEP trial and the ARV-treated participants and those on PrEP at screening should be excluded by the eligibility criteria. Hence, Table 6-3 only lists FRRs for untreated participants. However, the possibility that a few, ARV-treated participants may be screened, cannot be ruled out. For the primary efficacy analysis using $T = 2$ years, we will conservatively use the untreated FRR for all participants in calculating the bHIV.

6.1.2.2. While Participants are At-Risk of HIV-1 Infection in Study

The HIV-1 incidence will be reported per 100 PY in LEN and F/TDF study drug groups while at-risk of HIV-1 infection in study.

The HIV-1 incidence in LEN and F/TDF study drug groups will be estimated using a method appropriate for a single Poisson rate based on the FAS. The HIV-1 incidence λ_1 will be estimated by the number of HIV-1 infections in study divided by the total follow-up time in study for each arm. Here "in study" includes 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 stopped taking any PrEP during the study].

The exact $(1-\alpha)\times 100\%$ CI for λ_1 will be constructed as follows {Ulm 1990}:

$$(L_l, L_u) = \left(\frac{\chi^2_{2Y,\frac{\alpha}{2}}}{2D}, \frac{\chi^2_{2(Y+1),1-\frac{\alpha}{2}}}{2D}\right).$$

Here (L_l, L_u) is the lower and upper bound of the exact CI. Y is the observed number of infections, D is the total follow-up time, and $\chi^2_{\nu,\alpha}$ is 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 will be set to 0.

The standard error of the incidence estimate $\hat{\lambda}_1$ in the log scale $\hat{\sigma}_{\log(\hat{\lambda}_1)}$ will be estimated by $1/\sqrt{Y}$, based on the Poisson assumption {Gao 2021}.

6.1.2.2.1. Definition of Duration of At-Risk of HIV-1 Infection in Study

Duration of at-risk of HIV-1 infection in study is defined as the time after Day 1 (first dose date) through the last at-risk of HIV-1 infection date in study defined in Section 3.8.2 (last at-risk of HIV-1 infection date in study – Day 1 date +1).

Duration of time at-risk of HIV-1 infection in the study will be summarized, in weeks, using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum and total person-years) and as the number and percentage of participants at risk of HIV-1 infection in study for specified periods, ie, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 13 weeks (91 days), ≥ 26 weeks (182 days), ≥ 39 weeks (273 days), ≥ 52 weeks (364 days), ≥ 65 weeks (455 days), ≥ 78 weeks (546 days), ≥ 91 weeks (637 days), ≥ 104 weeks (728 days), ≥ 117 weeks (819 days), ≥ 130 weeks (910 days), etc.

6.1.2.2.2. 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) according to their original randomized study drug assignment after Protocol Amendment 2.

This clinical hold and early discontinuation of study drug will be considered intercurrent events during the RBP. However, consistent with the ITT approach, these intercurrent events will be handled with a treatment policy strategy for the primary efficacy evaluations, meaning that participant outcomes will be included in the analysis whether or not the intercurrent event occurred.

6.1.3. General Considerations of Analyses of the Primary Efficacy Endpoint

A formal interim efficacy analysis will be performed after 50% of participants enrolled have completed at least 52 weeks of follow-up in the study or have prematurely discontinued from the study (50th percentile randomized participant has reached Week 52 or prematurely discontinued from the study). The details of the interim analysis are described in Section 6.3 and the Interim Analysis Plan (Version 3.0, 19 December 2023).

Procedures to control the overall Type I error due to multiple efficacy analyses and the planned interim efficacy analysis, are detailed in Section 3.5, and in the Interim Analysis Plan (Version 3.0, 19 December 2023).

6.2. Efficacy Evaluations for Key (Alpha-Controlled) Statistical Hypotheses

Four alpha-controlled statistical hypotheses tests are planned for this study and the null hypothesis for each one is listed in Section 3.5. The testing procedures and methods to control the alpha is also presented in Section 3.5.

6.2.1. Primary Efficacy Evaluations (Comparison with bHIV)

The primary efficacy evaluation is a comparison of the observed HIV-1 incidence in the LEN arm during the RBP to the bHIV. The statistical hypotheses are:

Null hypothesis: H_{01}:LEN/bHIV ≥ 1.0

Alternative hypothesis: $\text{LEN/bHIV} < 1.0$

It will be concluded that HIV-1 incidence in the LEN group is significantly lower compared to the bHIV if the null hypothesis is 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 for the US FDA regulatory review is 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 ≤ 0.5 and comparability to F/TDF formulated as the key alpha-controlled H_{03}.

6.2.1.1. Methods for the Primary Efficacy Evaluations

The methods for estimating the HIV-1 incidence and the associated CI in the LEN group and bHIV are discussed in Section 6.1.2.1 and 6.1.2.2, respectively. The incidence rate ratio of the LEN group ($\hat{\lambda}_1$) over the bHIV ($\hat{\lambda}_0$) will be calculated, and the associated CI will be estimated using the delta method as provided by {Gao 2021} (see below):

Let R denote the incidence rate ratio λ_1/λ_0. In log scale, $\log R$ (ie, $\log(\lambda_1) - \log(\lambda_0)$) can be estimated by $\log \hat{R} = \log\left(\hat{\lambda}_1\right) - \log\left(\hat{\lambda}_0\right)$. $\log \hat{R}$ has an asymptotic normal distribution {Gao 2021}:

$$\log \hat{R} \sim N\left(\log R, \hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}\right).$$

The $(1-\alpha) \times 100\%$ CI for $\log R$ can then be constructed as $\log\left(\hat{\lambda}_1\right) - \log\left(\hat{\lambda}_0\right) \mp z_{\alpha/2} \sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}$, and the $(1-\alpha) \times 100\%$ CI for the incidence rate ratio R will be $\frac{\hat{\lambda}_1}{\hat{\lambda}_0} \exp\left(\mp z_{\alpha/2} \sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}\right)$. Here $z_{\alpha/2}$ is the $(\alpha/2)$-th upper quantile of the standard normal distribution.

The test statistic $Z = \frac{\log \hat{R} - \log R_0}{\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}}$ will be used for hypothesis testing, where R_0 will be set to 1 for testing H_{01} and set to 0.8 for testing H_{02}. The 1-sided p-value will be calculated based on the asymptotic normal distribution of Z.

If the number of HIV-1 infections diagnosed in the LEN group is zero, a plausible scenario especially for the interim analysis or the subgroup analysis, the estimated HIV-1 incidence $\hat{\lambda}_1$ will be zero, and the methods specified above would fail. In this case, the CI and the 1-sided p-value will be estimated using a likelihood-based method proposed by {Shao 2024}.

6.2.2. Secondary Efficacy Evaluations (Comparison with F/TDF)

6.2.2.1. Analysis Methods for Difference in HIV-1 Incidence Rates

Difference in HIV-1 incidence rates will evaluate comparability of LEN relativeto F/TDF, that is, null hypothesis H_{03}. Rejection of this hypothesis will support a conclusion that the HIV-1 incidence in the LEN arm is comparable to F/TDF. In order to test this hypothesis, a CI will be

constructed using a hybrid approach recommended by {Li 2011} with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI recommended {Li 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}:

$$(l_i,u_i) = \left(\frac{\chi^2_{2Y_i,\alpha/2}}{2D_i}, \frac{\chi^2_{2(Y_i+1),1-\alpha/2}}{2D_i}\right), i = 1,2$$

where Y_i's are the observed numbers of infections and D_i's are the total follow-up times for each of the study drug groups, respectively, and $\chi^2_{\nu,\alpha}$ is 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 will be set to 0.

Then, the hybrid $(1-\alpha)\times 100\%$ CI for the incidence rate difference $\lambda_1 - \lambda_2$ is given by Equations (4) and (5) in {Li 2011} as follows:

$$L = \hat{\lambda}_1 - \hat{\lambda}_2 - \sqrt{\left(\hat{\lambda}_1 - l_1\right)^2 + \left(u_2 - \hat{\lambda}_2\right)^2},$$

$$U = \hat{\lambda}_1 - \hat{\lambda}_2 + \sqrt{\left(u_1 - \hat{\lambda}_1\right)^2 + \left(\hat{\lambda}_2 - l_2\right)^2}.$$

It will be concluded that LEN is comparable to F/TDF if U, the upper bound of the CI of the incidence rate difference (LEN – F/TDF), is less than 0.8 per 100 PY.

After we get the CI, we can use the duality of hypothesis testing and CI {Rohatgi 1984} (pp 224-225) to get the corresponding p-value. For any specified α, we can compute the upper bound of the $(1-\alpha)\times 100\%$ CI, U. Therefore, we can view U as a decreasing function of α, ie, view it as $U(\alpha)$. Solve the equation $U(\alpha) = 0.8/100\text{PY}$ for α, then $\alpha/2$ will be the 1-sided p-value.

6.2.2.2. Analysis Methods for Ratio of HIV-1 Incidence Rates

Ratio of HIV-1 incidence rates will evaluate the relative statistical difference between LEN and F/TDF. The rate ratios of HIV-1 incidence between LEN and F/TDF will be calculated, and the associated CI will be 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 is zero in any of the experimental groups (LEN or F/TDF), the Poisson model would fail. Therefore, an exact conditional Poisson regression model will be used as the prespecified alternate to the generalized Poisson model specified above.

As specified earlier, H_{04} will be tested sequentially after H_{03} has been rejected.

A supportive analysis for the rate ratios may also be performed using time-to-event analysis methods including Kaplan-Meier estimates and/or the proportional hazards model. Participants

without HIV-1 diagnosis will be censored at the last at-risk of HIV-1 infection date in study defined in Section 3.8.2.3.

6.3. Interim Analysis

6.3.1. Timing

A formal interim efficacy analysis will be performed when 50% of participants have completed Week 52 or have prematurely discontinued from the study (50th percentile randomized participant has reached Week 52 or prematurely discontinued from the study).

If the interim analysis of efficacy data leads to stopping the RBP of the study, either for efficacy or futility, then it will serve as the primary analysis. Otherwise, the unblinded primary analysis will be conducted when all participants have a minimum of 52 weeks (1 year) of follow-up in the RBP of the study or permanent discontinuation of study (whichever occurs first) after randomization.

6.3.2. Efficacy Boundary

At the interim analysis, an alpha of 0.0026 (1-sided) will be spent, based on the Bonferroni's method, and the remaining alpha at the primary analysis will be 0.025-0.0026=0.0224.

At the interim analysis, given the FDA interim stopping criteria, the RBP of the trial will 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 $\alpha_1 = 0.0026$ are demonstrated. The interim analysis will serve as the primary analysis if the trial meets the stated criteria and stops early.

The testing procedures and the alpha-spending scheme details are presented in Section 3.5 and the Interim Analysis Plan (Version 3.0, 19 December 2023).

6.3.3. Futility Boundary

The study will be stopped if F/TDF is found to be superior to LEN at $\alpha_1 = 0.0026$.

6.3.4. RITA Malperformance

The use of the recency assay and RITA to estimate the bHIV in PrEP studies is a novel approach. The estimate of the bHIV is subject to assay and operational issues. Specifically for the interim analysis, if the point estimate of the RITA based counterfactual bHIV is less than 1.5/100 PY, the estimate of bHIV by the recency assay-based methodology will be deemed as not performing as expected. Gilead expects the bHIV (point estimate) in screened participants in both studies to be at least 3.5/100 PY or higher due to the selection of sites in geographies with high bHIV in eligible people who would benefit from PrEP (PWBP). There exists the possibility of unforeseen factors with operationalizing the RITA methodology in the clinical trial context which may result in RITA estimates that are much lower than expected based on the available estimates of the bHIV in these locations, which we refer to here as RITA malperformance. In the case of RITA

malperformance, hypotheses H_{01} and H_{02} will be skipped (no gating or alpha adjustment) at the interim efficacy analysis for testing hypotheses H_{03} and H_{04}. If both hypotheses for testing comparability and superiority to F/TDF are rejected at $\alpha_1 = 0.0026$, the RBP of the study will be stopped, and the study will move to the LEN open-label extension phase in order to provide participants randomized to F/TDF the option for the superior HIV prevention option. Otherwise, the RBP will continue to the primary analysis. This provision serves an important ethical purpose in the study, ensuring that a study arm with inferior efficacy is not continued longer than necessary due to malperformance of the RITA.

For the detailed testing procedure and interim stopping criteria, please see the flowchart in the Interim Analysis Plan (Version 3.0, 19 December 2023).

6.4. Supportive Efficacy Analyses

Multiple supportive efficacy comparisons may be considered, as the primary comparator is not a randomized arm. Therefore, a few HIV-1 incidence estimates are proposed to evaluate the impact of recency assay parameters, analysis set and analysis period on interpretation of efficacy results in the study. The same statistical methods in Section 6.1.2 will be used for all supportive efficacy analyses. Table 6-4 and Table 6-5 present a high-level approach for these evaluations which are detailed in the following sections.

Table 6-4. Estimation of the bHIV in the Incidence Phase

bHIV Estimate	Analysis Set	Recency Parameters
Primary	All Screened Set	Kassanjee et al, 2016 ($T = 2$)
Supportive 1	All Screened Set	Kassanjee et al, 2016 ($T = 1$)
Supportive 2	All Screened Set	RAWG (Parkin et al, 2022) ($T = 2$)
Supportive 3	All Screened Set, excluding participants who do not meet Incidence Phase inclusion/exclusion (I/E) Criteria	Kassanjee et al, 2016 ($T = 2$)
Supportive 4	All Screened Set, excluding participants who do not meet Incidence Phase I/E Criteria	Kassanjee et al, 2016 ($T = 1$)
Supportive 5	All Screened Set, excluding participants who do not meet Incidence Phase I/E Criteria	RAWG (Parkin et al, 2022) ($T = 2$)

Table 6-5. Estimation of HIV-1 Incidence for Randomized Groups (LEN and TVD)

HIV-1 Incidence Estimate	Analysis Set	Analysis Period
Primary	FAS	In study[1]
Supportive 1	FAS	While on randomized study drug[2]
Supportive 2	FAS, excluding participants who do not meet Incidence Phase I/E Criteria	In study

HIV-1 Incidence Estimate	Analysis Set	Analysis Period
Supportive 3	FAS, excluding participants who do not meet Incidence Phase I/E Criteria	While on randomized study drug
Supportive 4	mFAS[3]	In study
Supportive 5	mFAS	While on randomized study drug
Supportive 6	mFAS, excluding participants who do not meet Incidence Phase I/E Criteria	In study
Supportive 7	mFAS, excluding participants who do not meet Incidence Phase I/E Criteria	While on randomized study drug

1. At risk of HIV-1 infection in study (see Section 6.1.2.2 and 3.8.2.3).
2. At risk of HIV-1 infection while on randomized study drug (see Section 3.8.2.3).
3. mFAS: defined in Section 3.1.4 and includes all participants in the FAS who received their first dose after the clinical hold was lifted.

6.4.1. Analyses Evaluating Impact of Alternative Recency Assay Parameters

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 2022}.

6.4.1.1. Assay Parameters Based on $T = 1$ Year

As noted earlier, the assay parameters MDRI and FRR, used in estimating the incidence of recent infections, depend on the choice of the cutoff time, T. $T = 2$ years is generally considered preferable over a shorter cutoff (eg, $T = 1$ year) because it provides a more precise estimate of the bHIV with a longer MDRI and a smaller FRR. The choice of $T = 2$ years, is the default proposed in {Parkin 2022} and is the specified T for the primary efficacy analysis of this study (also used in sample size calculations). Estimation of bHIV using $T = 1$ year will be explored as a supportive analysis. Relevant assay parameters are presented in Table 6-6.

Table 6-6. MDRI and FRR (Kassanjee et al, 2016, $T = 1$ Year)[a]

Subtype	MDRI		FRR[b]	
	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
AE	172.6	9.96	0.0	NA[c]

Source: Assay parameters for subtypes A, B, C and D are from {Kassanjee 2016}; parameters for subtype AE are not available in {Kassanjee 2016}, and are estimated using R package "inctools" (https://cran.r-project.org/web/packages/inctools/inctools.pdf) based on data from {Klock 2020} (see APPENDIX 2 for details). .

a Based on the Sedia LAg-EIA and RITA cutoffs in Table 6-2 (ie, 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.

The eligibility criteria of this PrEP protocol require no HIV testing in at least the last 3 months prior to screening. However, HIV testing in the preceding 3-12 months may still impact the bHIV estimation. People who undergo HIV testing relatively recently, before screening for the trial, artificially skew the screened set towards known HIV-negative (as those recently diagnosed with HIV will be excluded from the screening process), leading to an underestimation of the bHIV. Both choices of $T = 2$ years and $T = 1$ year would underestimate the bHIV.

Similar to the primary efficacy analysis using $T = 2$ years, we will conservatively use the untreated FRR in Table 6-6 in calculating the bHIV. However, the possibility that a few, ARV-treated participants may be screened, cannot be ruled out. If at the time of analysis, > 25% of all screened participants are known to be ARV-treated at screening, then a weighted approach, similar to the approach used above for subtypes, will be used to estimate the bHIV to adjust for the proportion of ARV treated participants (ie, using FRR=0 and a standard error of zero for the proportion of ARV-treated participants in the calculation). An HIV-1 positive participant at Incidence Phase screening will be assumed to be ARV-treated if the viral load is ≤75 copies/mL, which is a rather conservative assumption for incidence estimating purposes.

6.4.1.2. Assay Parameters from the Recency Assay Working Group

The RAWG published a set of recommendations {Parkin 2022} on the use of recency assay for PrEP development which included assay parameters by subtype. The recommended assay parameters are given in Table 6-7, which will be used for supportive bHIV estimation.

Table 6-7. MDRI and FRR (Parkin et al, 2022, $T = 2$ 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	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 RAWG {Parkin 2022}(except that the FRR parameters for subtype D is not available, and we will use the 0.0% reported in {Kassanjee 2016} and a standard error of zero [see Table 6-3]); parameters for subtype AE are not available in {Parkin 2022}, and are estimated using R package "inctools" (https://cran.r-project.org/web/packages/inctools/inctools.pdf) based on data from {Klock 2020} (see APPENDIX 2 for details).

a Based on the Sedia LAg-EIA and RITA cutoffs in Table 6-2 (ie, 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.

6.4.2. Analyses Evaluating Impact of Analysis Set and Analysis Period

Alternative approaches for estimating the bHIV and HIV-1 incidence in the randomized groups are considered to evaluate the impact of not meeting the Incidence Phase I/E Criteria, transition to the PK Tail Phase for those who had premature discontinuation of randomized study drug, and the clinical hold.

6.4.2.1. Participants Who Did Not Meet Incidence Phase Inclusion/Exclusion Criteria

Participants who did not meet the Incidence Phase I/E criteria may be included in the primary efficacy analysis HIV-1 incidence estimation for both the bHIV and the randomized groups. Supportive estimates excluding such participants from the HIV-1 incidence estimation for both the bHIV and the randomized groups will be calculated.

6.4.2.2. While Participants are On Randomized Study Drug

During the study, participants may permanently discontinue their randomized study drug and start non-randomized drug (including transitioning to the PK Tail Phase, or any commercial PrEP such as Truvada, generic Truvada, cabotegravir for PrEP or other PrEP regimen). Supportive estimates of the primary efficacy endpoint will be calculated by including the events and follow-up time while participants are on randomized study drug (while including the clinical hold period), up to the last at-risk of HIV-1 infection date for on randomized study drug as defined in Section 3.8.2.3.

6.4.2.3. Participants Who Received First Dose After the Clinical Hold Was Lifted

As discussed in Section 6.1.2.2.2, the clinical hold will be ignored (ie, a treatment policy strategy) for the primary efficacy evaluations consistent with the ITT approach. Clinical hold occurred relatively early in the study and it may have had direct or indirect impact (eg, lead to more early discontinuation of participants in the blinded setting). To evaluate the impact of clinical hold on the efficacy results, supportive HIV-1 incidences will be estimated for participants who received their first dose after the clinical hold was lifted (ie, the mFAS as defined in Section 3.1.4).

6.5. Adherence-Efficacy Relationship

On-time directly observed dosing of SC LEN injections serves as both a measure of adherence for the LEN group (as discussed in Section 4.2.4) and a measure of compliance to study protocol visits in general.

The association of adherence to efficacy (HIV-1 incidence) in the LEN study group will be explored in the FAS by estimating the HIV-1 incidence per 100 PY while at-risk of HIV in RBP for participants who had:

a) all on-time SC LEN injections (with SC injections ≤28 weeks of the previous injection) up to (for those without HIV-1 in RBP) or prior to (for those diagnosed with HIV-1 in RBP) last at-risk of HIV-1 infection date for the RBP.

b) at least one late or missing SC injection where i) a late SC injection is defined as >28 weeks from the previous injection and ii) a missing SC injection is defined as >28 weeks between the end of the at-risk period and the last SC injection.

For this analysis, i) as each administration of LEN requires two SC injections, any incomplete (<2 SC injections) will be considered as a missed SC injection and ii) the follow up duration will be calculated based on "Last At-Risk of HIV-1 Infection Date for the RBP" as defined in Section 3.8.2.3.

6.6. Subgroup Analysis of the Primary Efficacy Endpoint

The primary endpoint of HIV-1 infection may be evaluated within each subgroup specified in Section 3.4 based on the FAS for randomized groups and the All Screened Set for bHIV.

For each level of the subgroup factors, the incidence within each study drug group as well as the bHIV, and 95% CIs, will be computed.

6.7. Exploratory Analysis of the Primary Efficacy Endpoint

Other bHIV estimates will also be explored.

6.7.1. Predicted HIV-1 Incidence Based on Rectal Gonorrhea Incidence

A supportive measure of predicted HIV-1 incidence will be calculated based on regression modeling of HIV-1 and rectal gonorrhea incidence from historical studies {Mullick 2019}(APPENDIX 4).

6.7.2. Estimate bHIV Using F/TDF Adherence-Efficacy Relationship

The adherence, based on DBS, and efficacy relationship for F/TDF is well characterized. The available DBS and HIV-1 diagnosis data from the F/TDF arm of the study may be used to back-calculate a contemporaneous counterfactual estimate of the bHIV during the study {Glidden 2021} (APPENDIX 5).

6.7.3. External Controls

Available estimates of historic or recent surveillance HIV-1 incidence may serve as external controls to better contextualize and interpret the observed bHIV. These may include US CDC HIV-1 surveillance data and clinical trials data (eg, ImPrEP).

6.8. Changes From Protocol-Specified Efficacy Analyses

6.8.1. Change from Protocol-Specified Methods for Rate Ratio

For the primary comparison of LEN to the bHIV, the method specified in the protocol (ie, the delta method proposed by {Gao 2021}) would fail if the number of HIV-1 infections diagnosed in the LEN group is zero, which is a plausible scenario especially for the interim analysis or the subgroup analysis. This SAP prespecifies a likelihood-based method proposed by {Shao 2024} in Section 6.2.1.1, which can be applied in such a scenario.

For the secondary comparison of LEN to the F/TDF group, the method specified in the protocol (ie, the Poisson model) would fail if the number of infections is zero in any of the experimental groups (LEN or F/TDF). This SAP prespecifies in Section 6.2.2.2 that an exact conditional Poisson regression model will be used in such a scenario.

6.8.2. Changes from Protocol-Specified Interim Stopping Criteria

This SAP reflects changes to the interim stopping criteria after discussions with the FDA on 28 Nov 2023 (Type C meeting). The original interim stopping criteria specified in the study protocol required only the superiority of LEN versus bHIV, designated H_{02} with the point estimate of $LEN/bHIV \leq 0.5$. The updated interim stopping criteria for the study require not only superiority of LEN versus bHIV but also superiority of LEN versus F/TDF, designated H_{04}.

7. SAFETY ANALYSES

Safety data will be summarized separately for the RBP Safety Analysis Set for the RBP and the OLOP Safety Analyses Set for OLOP, using the transitions between study phases as defined in Section 3.9. All safety data from both phases of the study will be included in data listings. For RBP safety analyses, the terms "study drug start date (ie, the first dose date)", "last exposure date", and "baseline" in the text below refer to the first dose date, the last exposure date, and baseline defined for the RBP; the term "study drug" in the text below refers to the randomized study drugs. The RBP safety analyses will include any safety data during the temporary interruptions in the study drug administration in summaries and with the randomized study drug group (eg. safety data collected while any SC LEN randomized participants received open label F/TDF or open label F/TAF due to the clinical hold are summarized with the SC LEN study drug group). Temporary interruption to RBP study drug includes the clinical hold period during which participants may receive temporary oral study drug [open label F/TDF or open-label F/TAF or blinded weekly oral LEN/PTM bridging] as well as blinded weekly oral LEN/PTM bridging following late SC injections outside of clinical hold.

For OLOP safety analyses, the terms "study drug start date (ie, the first dose date)", "last exposure date", and "baseline" in the text below refer to the first dose date, the last exposure date, and baseline defined for the OLOP; the term "study drug" in the text below refers to OL F/TDF or OL F/TAF (PURPOSE 2 US sites). In PURPOSE 2 US sites, participants are permitted to switch between OL F/TDF and OL F/TAF OL oral PrEP administered via the PK Tail Phase. The OLOP study drug groups and safety analyses will be based on the first OLOP study drug received. In case the OLOP study drug is switched, the summary tables will be limited to the duration of the first OLOP study drug. (eg, Participants who switch from OL F/TDF to OL F/TAF will be summarized with OL F/TDF up to the first dose of OL F/TAF.)

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Grade 1 and Grade 2 study drug injection site pain or tenderness will be interpreted as referring to any study drug injection site rather than referring just to "limb" as stated in the grading scale. Injection site nodule and injection site induration measured at < 2.5 cm should be recorded as Grade 1 despite the DAIDS "induration and swelling" cutoff of 2.5 cm as the lower limit for Grade 1.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs leading to premature discontinuation of study drug, or
- Any AEs with an onset date on or after the study drug start date and no later than the last exposure date after permanent discontinuation of the study drug.

For the RBP analysis, the AE onset date will be compared with the first dose and last exposure dates for the RBP. For the OLOP analysis, the AE onset date will be compared with the first dose and last exposure dates for the OLOP analysis.

An exception to the treatment-emergent definition will be for injection site reactions (ISRs) to study SC injection (with HLT = injection site reactions and related to either study drug or study procedures, Sections 7.1.7.1-7.1.7.2) where TE ISRs to study SC injection are 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.

In addition, TEAEs for blinded oral LEN/PTM bridging during clinical hold are defined as any AEs with an onset date on or after first dose date of blinded oral LEN/PTM bridging due to clinical hold and up to:

- the first dose date of resumed SC injection for participants who resumed SC LEN/PTM (excluding the day of resumed SC injection) or
- the first dose date of OL F/TDF or OL F/TAF for participants who transition to the PK Tail Phase (excluding the start day of OL F/TDF or OL F/TAF) or
- 60 days after last dose date of blinded oral LEN/PTM bridging for participants who prematurely discontinued study drug from blinded oral bridging of LEN/PTM and do not resume SC LEN/PTM or transition to PK Tail Phase

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dose date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent as follows:

- The AE onset date is the same as or after the month and year (or year) of the first dose date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the last exposure date

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dose date of study drug will be considered treatment emergent.

When calculating the duration of event or time to onset for ISRs to study SC injection (Section 7.1.7) or for partial AE dates in their contribution to last study date (Section 3.8.2), the following imputation rule will be used:

- Missing start month/day: Jan 1/first day of the month will be used
  - unless this is before the start date of study drug; in this case the study drug start date will be used or
  - unless this is a missing AE start day with the AE start month and year on the same month and year as a study SC injection date; in this case the study SC injection date will be used. An additional condition for nodules/indurations is that the imputed missing start month/day must start on or after the injection date associated with the event from the Injection Site Reaction eCRF.
- Missing stop month/day: Dec 31/last day of the month will be used, unless this is after the last study date; in this case the last study date will be used.
- Completely missing start or end dates will remain missing, with no imputation applied. An exception to this is for calculating the duration of an ISR to study SC injection with ongoing stop date, where the stop date will be imputed as last study date.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized by study phase based on the RBP Safety Analysis Set and OLOP Safety Analysis Set and will include injection site reactions (ISRs) to study SC injection in the RBP (Sections 7.1.7.1-7.1.7.2) which will also be summarized separately.

A brief, high-level summary of the number and percentage of participants who experienced at least 1 TEAE will be provided by study drug group for the RBP Safety Analysis Set (both including and excluding ISRs to study drug SC injection) and OLOP Safety Analysis Set. All deaths observed in the study will also be included in this summary.

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT (if applicable), PT, and study drug group:

- TEAEs

For the AE categories described below, summaries will be provided by SOC, PT, and study drug group:

- TEAEs with Grade 3 or higher (by severity)
- TEAEs with Grade 2 or higher
- TE study drug related AEs
- TE study drug related AEs with Grade 3 or higher (by severity)
- TE study drug related AEs with Grade 2 or higher
- TE SAEs
- TE study drug related SAEs
- TEAEs leading to premature discontinuation of [any] study drug
- TEAEs leading to premature discontinuation of study
- Death (i.e., outcome of death)

Multiple events will be counted only once per participant in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE study drug related AEs, and TE study drug related SAEs and TEAEs for blinded oral LEN/PTM bridging during clinical hold will be summarized by PT only, in descending order of total frequency. Summaries by age < 18 and ≥18 years will not be included due to few participants in the study with age < 18 years.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All AEs with severity of Grade 3 or higher
- All AEs leading to premature discontinuation of [any] study drug
- All AEs leading to premature discontinuation of study

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Treatment-Emergent Injection Site Reactions to Study SC Injection

Additional analysis will be performed for injection site reaction AEs to study SC injection sites, which is defined as any AE reported with the MedDRA HLT of "Injection Site Reactions" and logged as related to study drug or study procedure on the AE eCRF, while in study (including all phases). The following summaries will be provided for each SC injection visit (eg, Day 1, Week 26/Injection 2, Week 52, Week 78, Week 104, Week 130, as defined in Table 3-5) and overall visits by study drug group.

<u>Participant-level</u>

- Number of participants that received SC injection
- Number and percentage of participants with
  - ISRs to study SC injection
    - by grade
    - by PT
  - serious ISRs to study SC injection (overall visits only)
  - ISRs to study SC injection leading to premature discontinuation of study drug (overall visits only)
  - ISRs to study SC injection leading to premature discontinuation of study (overall visits only)

For the participant-level summaries above, the denominator for the percentage calculation for the by visit summary and the overall summary will be based on the total number of participants who receive at least 1 SC injection at the visit of interest and the total number of participants who receive at least 1 SC injection at any injection visit, respectively.

Event-level

- Number and percentage of injections with
  - ISRs to study SC injection
    - by grade
    - by PT

For the event-level summaries above, the denominator for the percentage calculation for the by visit summary and the overall summary will be based on the total number of SC injections.

Duration of the ISRs to study SC injection in study will also be calculated and summarized. Duration for a given ISR event is defined as the ISR stop date minus the ISR onset date plus 1 day. For the purposes of calculating duration of ISRs, incomplete ISR start and end dates will be imputed per Section 7.1.5.2. For an ISR with ongoing stop date, the stop date will be imputed as last study date or data cutoff date, whichever occurs earlier. Duration of ISR events in days will be summarized using descriptive statistics. A by-participant listing for ISRs to study SC injection and the corresponding duration will be provided.

7.1.7.2. Treatment-Emergent Injection Site Nodules and Induration to Study SC Injection

Additional details for each event of ISRs to study SC injection of nodules and indurations are collected on the Injection Site Reaction eCRF prospectively following the clinical hold for nodules or indurations observed by the study site. Nodules and indurations to study SC injection are defined as any AE reported with the MedDRA PT of “Injection Site Nodule” or “Injection Site Induration” and logged as related to study drug or study procedure on the AE eCRF, while in study (including all phases). A participant may have multiple nodules or indurations associated with multiple injection visits or 2 injection sites at the same visit (as each injection visit consists of SC injections at 2 locations (in abdomen or thighs [pregnant participants only]).

Nodules and indurations will be summarized separately and with both participant-level and event-level summaries. The texts below describe the summaries for nodules but similar summaries will be produced for induration.

Participant-level

Participant-level summaries will include the total number of visits when SC injections were administered and the number and percentage of participants both by SC injection visit and overall across all SC injection visits with:

- 1, 2, 3, 4 (etc.) nodules (unique nodules events based on unique participant, AE preferred term and AE onset date, with bilateral events recorded as separate AE records)
- Any ongoing nodules
- All nodules resolved

For the participant-level summary, the denominator for the percentage calculation will be the number participants at each SC injection visit or overall, respectively.

The longest nodule diameter for each participant (overall across all SC injection visits) will be summarized by descriptive statistics.

Event-level

Event-level summaries will be based on the total number of SC injections (2 x the number of injection visits, except when only partial injections were administered) and the number and percentage of nodule (or induration) events both by SC injection visit and overall across all SC injection visits that are:

- Nodule size, n (%) for size (of longest diameter) >2.5 cm
- Nodule duration, n (%) for duration > 182 days (26 weeks)
- Associated skin findings due to nodule (including bruising, discoloration, erythema, pruritus, swelling, tenderness, warmth, other)

For the event-level summary, the denominator for the percentage calculation will be the total number of SC injections (2 x the number of injection visits, except when only partial injections were administered).

The duration of ongoing and resolved injection site nodules as well as the longest nodule diameter for each nodule event, will be summarized by descriptive statistics, both by SC injection visit and overall.

Treatment-emergent injection site indurations to study SC injection will be summarized in the same manner as defined for treatment-emergent injection site nodules to study SC injection. A by-participant listing for treatment-emergent injection site nodules and indurations to study SC injection and the corresponding durations, associated skin findings and nodule sizes will be provided.

7.1.7.3. Proximal Renal Tubulopathy

Treatment-emergent proximal renal tubulopathy (PRT) events (determined by Proximal Renal Tubulopathy MedDRA Search Term [MST]; see APPENDIX 7) will be summarized by study drug group for the RBP Safety Analysis Set and the OLOP Safety Analysis Set, separately.

The number and percentage of participants who experienced PRT events will be summarized by study drug group and PT and compared between the LEN study drug group with the F/TDF study drug group using Fisher's exact test in the RBP Safety Analysis Set.

7.1.7.4. Grade 3 or Higher Renal Insufficiency

Treatment-emergent Grade 3 or higher renal insufficiency events (determined by Renal Failure Events MST; see APPENDIX 7) will be summarized by study drug group for the RBP Safety Analysis Set and the OLOP Safety Analysis Set, separately.

7.1.7.5. Hypersensitivity

Treatment-emergent hypersensitivity events (determined by Hypersensitivity SMQ – narrow; see APPENDIX 7) will be summarized by study drug group for the RBP Safety Analysis Set and the OLOP Safety Analysis Set, separately.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided by study phase for the RBP Safety Analysis Set and the OLOP Safety Analysis Set. Data collected from baseline up through the last exposure dates by study phase (defined in Section 3.8.2) for participants who have permanently discontinued study drug, or all available data at the time of the database snapshot for participants who were ongoing at the time of the analysis will be included. The analysis will be based on values reported in conventional units. When values are reported as below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL))

Toxicity grading for calcium will be applied based on the corrected values.

Estimated Glomerular Filtration Rate

The following formulae will be used to calculate the estimated glomerular filtration rate using Cockcroft-Gault formula ($eGFR_{CG}$):

$eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms and SCr is serum creatinine.

A by-participant listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 will be flagged in the data listings, as appropriate.

In general, no formal statistical testing is planned unless otherwise specified.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by study drug group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of study drug for each study phase (RBP and OLOP), respectively. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) and mean ± 95% CI of the change from baseline values for serum creatinine and median (Q1, Q3) of the change from baseline values for $eGFR_{CG}$ will be plotted using a line plot by study drug group, visit and study phase.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase 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 treatment at the time of an analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed at any postbaseline visit will be considered treatment emergent.

Fasting glucose and nonfasting glucose for hyperglycemia (including glucose results without a known fasting status) are graded based on different grading scales in DAIDS. Treatment emergent laboratory abnormalities will be summarized for fasting glucose hyperglycemia. Maximum postbaseline grade will be summarized for nonfasting glucose for hyperglycemia (including glucose results without a known fasting status), as nonfasting glucose was not assessed at baseline for many of the participants; therefore, whether an abnormality is treatment-emergent cannot be determined for these participants. Treatment emergent laboratory abnormalities for glucose hypoglycemia (which is graded without regard to fasting status) will also be summarized.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit by study phase.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test, study drug group and study phase; participants will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or higher laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up through the last exposure date for each study phase.

A by-participant listing of all Grade 3 or higher laboratory abnormalities will be provided by participant ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The summary will include data from all postbaseline visits up through last exposure date. For individual laboratory tests, participants will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin and the composite endpoint of AST or ALT, total bilirubin, and ALP, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of participants in the Safety Analysis Set for each study phase, respectively, who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of participants who met at least 1 of the above criteria will be provided.

7.2.4. Proteinuria by Quantitative Assessment

Participants will be classified into three categories based on their urine protein (UP) and urine protein to creatinine ratio (UPCR) results: UPCR ≤ 200 mg/g (including participants with UP < 4.0 mg/dL), UPCR > 200 mg/g, and Missing, where UPCR will only be calculated when UP ≥ 4.0 mg/dL. The number and percentage of participants in each UP and UPCR category will be summarized by visit and baseline category for each study phase{KDIGO Guideline Development Staff 2013}. The distribution of the UP and UPCR categories will be compared by visit between the LEN study drug group with the F/TDF study group adjusting for baseline categories using rank analysis of covariance {LaVange 2008} in the RBP Safety Analysis Set.

7.2.5. Proteinuria by Urinalysis (Dipstick)

The distribution of treatment-emergent proteinuria toxicity grade at the highest postbaseline graded value will be summarized by study phase. Comparisons between the LEN study drug group with the F/TDF study group adjusting for baseline proteinuria toxicity grade using rank analysis of covariance will be done for the RBP Safety Analysis Set.

7.2.5.1. Subgroup Analysis for Proteinuria by Urinalysis (Dipstick)

The distribution of treatment-emergent proteinuria toxicity grade at the highest postbaseline graded value will be compared between study drug groups in the RBP within each subgroup specified in Section 3.4.2. Comparisons between the LEN study drug group with the F/TDF study group will be adjusted for baseline proteinuria toxicity grade using rank analysis of covariance in the RBP Safety Analysis Set.

7.2.6. Serum Creatinine

Baseline, postbaseline, and change from baseline in serum creatinine will be summarized by study drug group, visit and study phase using descriptive statistics. Baseline serum creatinine will be compared between the LEN study drug group with the F/TDF study group using an analysis of variance (ANOVA), which includes treatment as a fixed effect in the RBP Safety Analysis Set. Change from baseline will be compared between the LEN study drug group with the F/TDF study group using an analysis of covariance (ANCOVA) that includes treatment as a fixed effect and baseline serum creatinine as a covariate in the RBP Safety Analysis Set.

Median (Q1, Q3) and mean (95% CI) of change from baseline in serum creatinine over time will be plotted by study phase and study drug group.

7.2.7. $eGFR_{CG}$

Baseline, postbaseline, and change from baseline in $eGFR_{CG}$ will be summarized by study drug group, visit and study phase using descriptive statistics. Baseline and change from baseline will be compared between the LEN study drug group with the F/TDF study group using a 2-sided Wilcoxon rank sum test at each visit in the RBP Safety Analysis Set.

Median (Q1, Q3) of change from baseline in $eGFR_{CG}$ over time will be plotted by study phase and study drug group.

7.2.7.1. Subgroup Analysis for $eGFR_{CG}$

The analysis of baseline, postbaseline, and change from baseline in $eGFR_{CG}$ will be summarized by study drug group and visit in the RBP using descriptive statistics within each subgroup specified in Section 3.4.2. Baseline and change from baseline will be compared between the LEN study drug group with the F/TDF study group using a 2-sided Wilcoxon rank sum test at each visit in the RBP Safety Analysis Set.

7.3. Body Weight , Height, BMI, Waist Circumference and Vital Signs

Descriptive statistics will be provided by study drug group for body weight, height (until participants reach 20 years of age), BMI, waist circumference and vital signs for the RBP Safety Analysis Set and the OLOP Safety Analysis Set, as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug for each study phase. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.4.

For body weight, BMI and waist circumference, values will be excluded for pregnant participants starting on and after the date (or month and year, if only month and year available) of the last menstrual period for the first pregnancy (from the Pregnancy Report eCRF) (after first dose date). If the last menstrual period for the first pregnancy is missing or year only, exclude values for pregnant participants starting on and after the date the first pregnancy was confirmed.

For body weight, BMI and waist circumference, baseline, change from baseline and percentage change from baseline (percentage change for body weight only) will be summarized by study drug group, visit and study phase using descriptive statistics. Baseline will be compared between the LEN study drug group with the F/TDF study group using ANOVA, which includes treatment as a fixed effect in the RBP Safety Analysis Set. Change from baseline and percentage change from baseline (percentage change for body weight only) will be compared between the LEN study drug group with the F/TDF study group using ANCOVA that includes treatment as a fixed effect and baseline value as a covariate in the RBP Safety Analysis Set.

A by-participant listing of vital signs will be provided by participant ID number and visit in chronological order. Body weight, height, waist circumference, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the Gilead-modified World Health Organization (WHO) Drug dictionary.

7.4.1. Prior PrEP Medications

Prior PrEP medications are defined as any PrEP medications taken on or prior to the Incidence Phase Screening as captured on the Disease Under Study (HIV) eCRF.

The time since the latest prior PrEP medication (from the Disease Under Study (HIV) eCRF) from the Incidence Phase screening visit date will be calculated among participants not on baseline PrEP medications at Incidence Phase Screening (as defined in Section 7.4.2).

Prior oral PrEP medication includes F/TDF or F/TAF.

F/TDF will include both commercial and generic F/TDF (entered in the 'Other, Specify' free text including 'F/TDF', 'FTC/TDF', 'FTC-TDF', 'F-TDF' or other variations)

The number and percentage of participants with any prior PrEP medication by medication (F/TDF, F/TAF or other) will be summarized by study drug group and overall with other baseline HIV risk characteristics in Section 5.2.

7.4.2. Baseline PrEP Medications

Baseline PrEP medications are defined as any PrEP medications taken during the Incidence Phase Screening as captured on the Disease Under Study (HIV) eCRF. Baseline PrEP medications will also include the most recent PrEP medication with a last dose date occurring on or within 14 days prior to Incidence Phase screening as captured on the Disease Under Study (HIV) eCRF.

Baseline oral PrEP medication includes F/TDF or F/TAF.

F/TDF will include both commercial and generic F/TDF (entered in the 'Other, Specify' free text including 'F/TDF', 'FTC/TDF', 'FTC-TDF', 'F-TDF' or other variations.)

The number and percentage of participants with any baseline PrEP medication by medication (F/TDF, F/TAF or other) will be summarized by study drug group and overall with other baseline HIV risk characteristics in Section 5.2.

7.4.3. PEP Medications While At-Risk of HIV-1 Infection During the Study

Post-exposure prophylaxis is defined as treatment with any non-study drug ARV medication with an indication of 'HIV Post-Exposure Prophylaxis (PEP)' in the Non-Study ARV Medication eCRF while participants are at-risk of HIV-1 infection in the study as defined in Section 6.1.2.2.1.

The number of participants with any PEP use and the number of PEP uses per participant while at-risk of HIV-1 infection during the study will be summarized for the FAS.

The number of PEP uses per participant will be based on unique PEP medication start dates within each participant. Multiple PEP medications with overlapping start and end dates will be counted as only one PEP use. Consecutive PEP medications where the complete medication end date of one PEP medication differs from the complete medication start date of another PEP medication by one day or less will be counted as only one PEP use.

For PEP uses while at-risk of HIV-1 infection during the study, if the start or stop date of the ARV medication is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine whether the ARVs occurred during the at-risk of HIV-1 infection period or not. The medication occurred during the at-risk of HIV-1 infection period if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the date of the end of the at-risk of HIV-1 infection in study period
- The month and year of stop of the medication is on or prior to the date of the first dose of RBP study drug

If the start and stop date of ARV medications are complete, the start date is not after the date of the end of the at-risk of HIV-1 infection period and the stop date is not on or before first dose date, or the ARV medications are marked as ongoing and start date is on or prior to the date of the end of the at-risk of HIV-1 infection period, the non-ARV medications are considered as occurring during the at-risk of HIV-1 infection period. Medications with completely missing start and end dates will not be considered as occurring while at-risk of HIV-1 infection during the study.

7.4.4. Concomitant Medications

Concomitant medications are defined as medications taken while a participant took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each study drug group. A participant reporting the same medication more than once [within each ATC drug class] will be counted only once when calculating the number and percentage of participants who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date or started after the first dosing date but prior to or on the last exposure date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last exposure date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last exposure date of study drug will be excluded from the concomitant medication summary. If a partial stop date is

entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug last exposure date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the RBP Safety Analysis Set or OLOP Safety Analysis Set, separately. No formal statistical testing is planned.

Gender affirming therapy may be provided in separate listings.

Gender affirming therapies will be identified from the following:

- Prior and Concomitant Medication eCRF, category for medication of 'Feminizing hormone therapy', 'Masculinizing hormone therapy', 'Non-hormonal gender affirming therapy' or 'Other Gender-affirming medical therapy'.

- Standard Medication Name (WHOGEN) as specified in APPENDIX 8

In addition, a separate listing for hormone PK analysis purpose will be provided for the hormone PK analysis set for gender affirming therapy identified by Standard Medication Name (WHOGEN) as specified in APPENDIX 8.

All other prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-participant listing sorted by participant ID number and administration date in chronological order.

7.5. Pregnancies

A by-participant listing of participant pregnancies during the study will be provided by participant ID number.

7.6. Other Safety Measures

Physical examination data was not collected in the eCRF. Therefore, it will not be included in the analysis.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

A single PK blood sample will be collected at any time at Weeks 4, 8, 13, 26, 39, 52 and every 13 weeks during the RBP, at Day 1 and every 13 weeks while participants on OL oral PrEP during the PK Tail Phase and at the 30 day follow up, the 30 day post-HIV infection follow up and ESDD for any phase for all participants.

Relevant plasma PK samples collected until last patient last visit (LPLV) date were analyzed for a subset of participants (Section 1.4.2) and included in the primary analysis.

8.2. PK Analyses Related to PK Sampling

For following analytes with the corresponding specimen types will be included for PK analyses:

- LEN: plasma
- Estradiol: serum
- Testosterone and its metabolite dihydrotestosterone: plasma

8.2.1. PK Concentration

Individual participant concentration data will be listed and summarized using descriptive statistics. Summary statistics (number of participants, mean, SD, coefficient of variation [%CV], median, min, max, Q1, Q3 and 90% CI) will be presented. Moreover, the geometric mean, 90% CI, and the mean and SD of the natural log-transformed values will be presented. Only concentration data collected from on-time SC injection timepoints will be included in summary statistics. SC injection will be considered on time if both SC injections are completed with full dose and occur ≥ 168 days and ≤196 days (≤14 days prior to and ≤ 14 days beyond 26 weeks) after the last injection visit. Each injection visit consists of 2 SC injections and the first injection date will be used for that visit if injections were split over different dates.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and postdose time points.

The following tables will be provided for each analyte and/or populations of special interest (as appropriate) for each study phase if there are sufficient samples in the study phase:

- Individual participant concentration data for LEN (GS-6207) will be listed and summarized as appropriate using descriptive statistics by time point for the LEN PK Analysis Set,

excluding adolescents, participants who became pregnant during the study (if any), participants who received oral LEN bridging during the clinical hold, and participants diagnosed with HIV-1 infection during the study, as applicable.

- Individual participant concentration data for LEN (GS-6207) will be listed and summarized as appropriate using descriptive statistics by time point for adolescents in the LEN PK Analysis Set, excluding participants who became pregnant during the study (if any), participants who received oral LEN bridging during the clinical hold, and participants diagnosed with HIV-1 infection during the study, as applicable.

- For participants who are in the LEN PK Analysis Set and received oral LEN bridging during clinical hold, individual participant concentration at oral bridging pre-dose visit and oral bridging C_{trough} (concentration before resuming planned SC injection) may be listed and summarized using descriptive statistics.

- Individual participant concentration data for relevant hormones of interest (eg, estradiol, testosterone and its metabolite dihydrotestosterone) may be listed and summarized using descriptive statistics by time point for the Hormone PK Analysis Set.

The following figures may be provided for analyte(s) of interest and/or population(s) of interest:

- Mean (± SD) and/or mean (90% CI) concentration data versus time (on linear and semilogarithmic scales)

- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

- Box plots of concentration data versus time (on linear and semilogarithmic scales)

Data from relevant reference groups may be overlaid in the aforementioned figures (as applicable) to facilitate clinical interpretation of the findings.

Additionally, the following figure may be provided for each LEN participant diagnosed with HIV-1 infection during the study:

- Individual participant LEN concentrations at all available time points through at least the HIV-1 diagnosis date (and beyond as appropriate).

PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

8.3. Population PK Analyses Related to Sparse PK Sampling

Population PK (popPK) models for LEN were developed for the LEN HIV treatment program as part of the LEN NDA submission in 2021/2022. An updated population PK model may be developed with sparse PK data collected from this study to characterize the PK of LEN using mixed-effect modeling techniques. Additionally, impact of hormones on LEN PK may be evaluated using popPK approaches. Details of the popPK analysis of LEN may be provided in a separate popPK modeling analysis plan.

A population PK report based on data from this and possibly other studies may be prepared by the PK scientist.

9. SEXUALLY TRANSMITTED INFECTIONS AND SELF REPORTED SEXUAL BEHAVIORS

Sexual behaviors, sexual partner characteristics, and clinical outcomes of sexual behavior (sexually transmitted infections [STI]) while at-risk of HIV-1 infection during the study will be summarized for the participants in the FAS. STI data is collected through local and central labs. Sexual behaviors are collected privately from ePRO questionnaires (Section 1.4).

All sexual risk characteristics data will be included in data listings.

9.1. Sexually Transmitted Infections While At-Risk of HIV-1 Infection During the Study

STIs considered to have occurred while at-risk of HIV-1 infection are defined as those occurring after the first dose date (excluding the Day 1 first dose date) and on or prior to the last at-risk of HIV-1 infection date in study defined in Section 3.8.2.3 (last at-risk of HIV-1 infection date in study – Day 1 date +1).

9.2. Sexually Transmitted Infections

9.2.1. Definition of STI Infections from Laboratory Data While At-Risk of HIV-1 Infection During the Study

9.2.1.1. Definition of Chlamydia, Gonorrhea or Trichomonas Vaginalis Infection from Laboratory Data

For each STI (chlamydia, gonorrhea or trichomonas vaginalis infection), both central and local laboratory results will be combined for summaries.

Participants with chlamydia, gonorrhea or trichomonas vaginalis infection are defined as participants with results of either ‘detected’ from the central laboratory tests (including central lab affiliated local laboratory tests) or ‘positive’ from the Local Lab eCRFs.

For each STI (chlamydia, gonorrhea or trichomonas vaginalis infection), the number of unique infection events is defined based on unique laboratory collection dates within each participant; however, within a participant, multiple positive infection results from laboratory collection dates within a 14 day period will be counted as only one infection event on the date of the first positive result.

9.2.1.2. Definition of Syphilis Infection (Investigator Reported)

Participants with syphilis infection are defined as participants with a diagnosis of either new, re-infection or missing syphilis infection status (excluding treatment failures) from the Syphilis Diagnosis eCRF.

The number of unique syphilis infection events is defined based on unique diagnosis dates within each participant for each disease stage and disease status as captured on the Syphilis Diagnosis eCRF with a syphilis infection status of new, re-infection or missing (excluding treatment failures).

9.2.2. Summaries of Gonorrhea, Chlamydia, Trichomonas Vaginalis or Syphilis STIs While At-Risk of HIV-1 Infection During the Study

The following summaries of STIs while at-risk of HIV-1 infection will be provided by study drug group for the FAS among participants with the corresponding post-baseline STI test while at-risk of HIV-1 infection during the study:

- Gonorrhea, Chlamydia or Trichomonas vaginalis (overall or urethral/urine, based on central or local laboratory data)
- Gonorrhea or Chlamydia (based on central or local laboratory data)
  - Rectal
  - Pharyngeal
  - Urethral (Urine)
- Gonorrhea (based on central or local laboratory data)
  - Rectal
  - Pharyngeal
  - Urethral (Urine)
- Chlamydia (based on central or local laboratory data)
  - Rectal
  - Pharyngeal
  - Urethral (Urine)
- Trichomonas vaginalis (based on central or local laboratory data) limited to participants for whom trichomonas vaginalis was tested
  - Urethral (Urine)
- Syphilis (based on investigator report)
  - Disease stage (Primary, Early Latent, Secondary, Tertiary, Late Latent, Other or Missing)
  - Status (New, Re-infection or Missing)

For each STI summary above, the number and percentage of participants will be summarized by study drug group and overall on the FAS among participants with the corresponding post-baseline STI test while at-risk of HIV-1 infection during the study.

For each STI summary above, except for trichomonas vaginalis, the STI incidence per 100 person-years of follow-up will be computed as the number of unique events occurring while at-risk of HIV-1 infection in study divided by the summation of all participants' total number of years (where a year is 365.25 days) of follow-up while at-risk of HIV-1 infection in study (defined in Section 3.8.2.) The STI incidences will be summarized by study drug group and overall for the FAS among participants with the corresponding post-baseline STI test while at-risk of HIV-1 infection during the study.

9.2.3. Incidence of Gonorrhea, Chlamydia or Trichomonas vaginalis STIs Based on Laboratory Data by Visit While At-Risk of HIV-1 Infection During the Study

The incidence of new STIs based on central or local laboratory data will be summarized by visit and study drug group for the FAS for participants with

- Any Gonorrhea, Chlamydia or Trichomonas vaginalis (rectal, pharyngeal, or urethral/urine)
- Rectal Gonorrhea or Rectal Chlamydia

Incidence of these STIs by visit will be plotted by study drug group based on the FAS.

9.3. Sexual Behaviors While At-Risk of HIV-1 Infection During the Study (ePRO)

Sexual behaviors are captured from the ePRO Integrated Sexual Behaviors and Alcohol and Substance Use questionnaire. Sexual behaviors from ePRO questionnaire responses will be summarized by study drug group and visit while at-risk of HIV-1 infection during the study, using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and/or the number and percentage of participants (i.e. with 0, 1-2, 3-5, 6-9, ≥10 sex partners or acts) on the FAS. The following summaries of number of sexual partners or acts in the past 3 months will be provided:

- Sex partners
- Sex partners living with HIV
- Sex partners living with HIV and on HIV medication and undetectable
- RAS acts
- CRAS acts
- IAS acts
- CIAS acts

- RVS acts
- CRVS acts

In addition, the number and percentage of participants who did the following in the past 3 months will be summarized on the FAS.

- Sex for money, food, clothes, place to sleep, cell phone or other support (commercial or transactional sex): (a) Yes, (b) No, (c) Prefer Not to Answer
- Taken drugs before or during sex since the last visit (or past 12 weeks) (chemsex acts): (a) Yes, (b) No, (c) Prefer not to answer
- Alcohol before or during sex: (a) Yes, (b) No, (c) Prefer not to answer

While at-risk of HIV-1 infection during the study includes visits occurring through the upper limit of the analysis window corresponding to the last at-risk of HIV infection date in study as defined in Section 3.8.1.

Listings will also be provided.

10. PREP IMPACTS AND ADMINISTRATION PREFERENCE, DOSING AND PAIN RATING SCALE

Participant assessment of PrEP Impacts and Administration Preference, Administration and Dosing, and Numeric Pain Rating Scale will be collected using questionnaires. The electronically captured responses to each question will be summarized by study drug group, overall and visit for RBP Safety Analysis Set as well as in listings. Categorical responses will be summarized with the number and percentage of participants in each category. Categorical responses will be coded into numeric scales based on the coding book (APPENDIX 11). These coded numeric scales of the categorical responses as well as their changes from baseline will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum).
Mean ± 95% CI of Numeric Pain Rating Scale will be plotted using a line plot by study drug group and visit.

10.1. PrEP Administration Preference

PrEP medication preference from PrEP Impacts and Administration Preference questionnaire will be summarized and coded as: a) Injection, strong preference = 3, (b) Injection, moderate preference = 2, (c) Injection, slight preference = 1, (d) No preference = 0, (e) Pill, slight preference = -1, (f) Pill, moderate preference = -2, (g) Pill, strong preference = -3.

The number and percentage of participants with each PrEP medication preference (daily pill, no preference, injection) will be summarized by visit.

10.2. Additional Questionnaires

Additional details on questions from the PrEP Impacts and Administration Preference, Administration and Dosing, and Numeric Pain Rating Scale questionnaires are listed in APPENDIX 11 and will be summarized similarly.

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12. SOFTWARE

All analyses will be performed using SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

13. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

14. APPENDICES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Procedures for Incidence Phase and Randomized Blinded Phase

Study Procedure	Screening		Randomized Blinded Phase – Weeks (± 7 Days; ± 2 days for Week 4 and 8)[v]									ESDD[a]	30-Day Follow-up[b] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[c] (± 14 days)
	Incidence Phase	Randomized Blinded Phase	Day 1	4	8	13	26	39	52	Post Week 52 Every 13 or 26 Weeks	Oral Bridging Visit[d]				
Informed Consent (and assent for adolescents)[e]	X														
Medical History	X[e]	X[f]													
Demographics	X														
Query on sexual activity with partners assigned male at birth, including receptive anal sex	X														
Concomitant Medications		X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Complete Physical Examination		X													
Targeted Physical Examination			X[g]	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Vital Signs and Weight, Height[h], and Waist Circumference		X	X[g]	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Asymptomatic STI Testing for GC, CT, TV, and syphilis[i]		X	X			X	X	X	X	Every 13 weeks	Every 13 weeks		X	X	
Local Rapid 4th Generation HIV-1/2 Ab/Ag	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X		

Study Procedure	Screening		Randomized Blinded Phase – Weeks (± 7 Days; ± 2 days for Week 4 and 8)[v]									ESDD[a]	30-Day Follow-up[b] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[c] (± 14 days)
	Incidence Phase	Randomized Blinded Phase	Day 1	4	8	13	26	39	52	Post Week 52 Every 13 or 26 Weeks	Oral Bridging Visit[d]				
Central 4th Generation HIV-1/2 Ab/Ag	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X		
HIV-1 RNA quantitative NAAT	X		X												
Hepatitis B Testing (HBsAg/HBsAb/ HBcAb)		X					X		X	Every 26 weeks	Every 26 weeks				
Hepatitis C Testing (HCV Ab)		X					X		X	Every 26 weeks	Every 26 weeks				
Blood Sample for Chemistry/ Hematology		X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Blood storage sample for HIV-1 RNA NAAT				X	X	X	X	X	X	Every 13 weeks	X	X	X		
Blood sample for recency assay	X[j]		X[j]												
Blood Sample for DBS	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X		
Blood Sample for Metabolic Assessments[k]			X				X		X	Every 26 weeks	Every 26 weeks				
Anytime Plasma PK sample				X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Plasma Storage Sample	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Serum Storage Sample			X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Estimated GFR		X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Urinalysis, Urine Protein, Urine Chemistry		X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Urine Storage Sample			X	X	X	X	X	X	X	Every 13 weeks	X	X			

Study Procedure	Screening		Randomized Blinded Phase – Weeks (± 7 Days; ± 2 days for Week 4 and 8)[v]									ESDD[a]	30-Day Follow-up[b] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[c] (± 14 days)
	Incidence Phase	Randomized Blinded Phase	Day 1	4	8	13	26	39	52	Post Week 52 Every 13 or 26 Weeks	Oral Bridging Visit[d]				
Urine Pregnancy Test[l]	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	
Serum Pregnancy Test[l]		X													
Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire		X	X			X	X	X	X	Every 13 weeks		X			
Adherence to Oral Study Product Questionnaire				X	X	X	X	X	X	Every 13 weeks		X			
PrEP Impacts and Administration Preference Questionnaire (Day 1)			X												
PrEP Impacts and Administration Preference Questionnaire							X		X	Every 26 weeks (at injection visits)		X			
Numeric Pain Rating Scale - Injection Pain Questionnaire[-]			X				X		X	Every 26 weeks (at injection visits)					
Administration and Dosing Questionnaire for PrEP Medication						X		X		Every 26 weeks (at 13 weeks after each injection visit)					
Participants contacted 1 week (± 2 days) after each injection visit for postinjection follow-up assessment			X[m]				X		X	Every 26 weeks					
Randomization and enrollment[n] in IWRS			X												
Intimate partner violence screening, when applicable		X	X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	

Study Procedure	Screening		Randomized Blinded Phase – Weeks (± 7 Days; ± 2 days for Week 4 and 8)[v]									ESDD[a]	30-Day Follow-up[b] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[c] (± 14 days)
	Incidence Phase	Randomized Blinded Phase	Day 1	4	8	13	26	39	52	Post Week 52 Every 13 or 26 Weeks	Oral Bridging Visit[d]				
HIV Risk Reduction Counseling	X	X[o]	X	X	X	X	X	X	X	Every 13 weeks	X	X	X		
Adherence Counseling			X	X	X	X	X	X	X	Every 13 weeks	X				
F/TDF or PTM F/TDF Dispensation and Accountability[o]			X[p]	X	X	X	X	X	X	Every 13 weeks	X	X[q]			
Oral LEN or PTM LEN Dispensation and Accountability			X[r]	X[q]							X				
CD4 cell count (Screening if local rapid HIV-1/2 test is positive and for participants diagnosed with HIV after receiving study drug)	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X	X
HIV-1 RNA quantitative NAAT and HIV resistance genotype (for participants diagnosed with HIV after receiving study drug)			X	X	X	X	X	X	X	Every 13 weeks	X	X	X	X[s]	X[t]
SC LEN/Placebo for SC LEN administration[u]			X				X		X	Every 26 weeks					

Ab = antibody; Ag = antigen; CD4 = cluster determinant 4; CT= *Chlamydia trachomatis*; DBS = dried blood spot; ESDD = early study drug discontinuation; F/TDF = emtricitabine/tenofovir disoproxil fumarate; GC = *Neisseria gonorrhea*; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; IWRS = interactive web response system; LEN = lenacapavir; NAAT = nucleic acid amplification test; OLE = open-label extension; PK = pharmacokinetic; PrEP = pre-exposure prophylaxis; PTM = placebo-to-match; SC = subcutaneous; STI = sexually-transmitted infection; TV = *Trichomonas vaginalis*

a Early study drug discontinuation visit occurs once in the study when the participant permanently discontinues dosing with any assigned study drug prior to completing the study (regardless of study phase) for any reason other than acquiring HIV. The participant will be asked to return to the clinic for an ESDD visit within 72 hours of stopping study drug in the Randomized Blinded Phase.

b Participants who have received at least 1 dose of study drug will be required to complete a follow-up visit 30 days (± 14) days after discontinuation of the study drug for participants who complete an ESDD visit.
c Participants will only be requested to return to the clinic for a post-HIV-infection follow-up visit 90 (± 14) days after the HIV diagnosis visit if the required information is not available from participant's HIV physician. Participants whose HIV-1 RNA is ≥ 50 copies/mL at the 90-day Post-HIV infection follow-up visit will continue to have follow-up visits every 3 months until HIV-1 RNA < 50 copies/mL, at which point their participation will conclude. Participants will be followed up for a maximum of 1 year from the date of they were diagnosed with HIV infection.
d Only applicable to participants who require oral weekly bridging if an SC LEN injection cannot be administered for any reason within the protocol visit window.
e Main study informed consent/assent is a single ICF to obtain consent for the Incidence Phase and Randomized Blinded Phase. Participants who are willing to will also provide a separate consent to use their already collected samples and data for future research.
f Obtain the following information: date of last HIV-1 test, a prior PrEP use and HIV vaccine history, history of osteoporosis or fragility fracture and ongoing treatment for tuberculosis, in the Incidence Phase and a complete medical history at the Randomized Blinded Phase.
g To be performed if Day 1/Injection 1 visit is > 7 days after screening visit.
h Height collected at screening and Day 1/Injection 1 of Randomized Blinded Phase only for participants ≥ 20 years of age. For participants < 20 years of age, height is to be measured annually until they reach 20 years of age.
i GC and CT testing are to be performed by urine, pharyngeal, and rectal swabs by central laboratory. Swabs may be self-collected by the participant at the discretion of the investigator. Asymptomatic blood syphilis analysis per local testing protocol. For participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion.
j Run as indicated based on HIV test results.
k Lipid panel: Participants should be instructed to fast (no food or drinks, except water) at least 8 hours prior to blood collection.
l For participants assigned female at birth who are of childbearing potential only. After screening visit, positive urine pregnancy tests will be confirmed with a serum pregnancy test.
m The site staff will also confirm the participant has administered the Day 2 dose.
n Enrollment into the Randomized Blinded Phase.
o Only if Incidence Phase screening occurs on a separate day.
p Study drug dispensation only.
q Drug accountability will be performed by pill count for adherence.
r Oral LEN/PTM is to be dosed on Day 1/Injection 1 and Day 2.
s Genotype will be performed only if not already collected at time of infection.
t HIV-1 RNA quantitative NAAT only.
u LEN injections are to be given every 26 weeks (± 7 days) after the previous one.
v All study visits are to be scheduled relative to the previous injection visit date, except in instances of oral LEN/placebo bridging.

Procedures for PK Tail Phase

Study Procedure	PK Tail Phase – Weeks (± 7 days)[n]					ESDD[b]	30-Day Follow-up[c] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[d] (± 14 days)
	Randomized Blinded Phase to PK Tail Day 1	LEN OLE Phase to PK Tail Day 1[a]	13	26	Post Week 26 Every 13 or 26 Weeks to Week 78				
Concomitant Medications	X	X	X	X	Every 13 weeks	X	X	X	X
Adverse Events	X	X	X	X	Every 13 weeks	X	X	X	
Targeted Physical Examination	X	X	X	X	Every 13 weeks	X	X	X	
Vital Signs and Weight, Height[e], and Waist Circumference	X	X	X	X	Every 13 weeks	X	X	X	
Asymptomatic STI testing for GC, CT, TV, and syphilis[f]	X	X		X	Every 13 weeks		X	X	
Local Rapid 4th Generation HIV-1/2 Ab/Ag	X	X	X	X	Every 13 weeks	X	X		
Central 4th Generation HIV-1/2 Ab/Ag	X	X	X	X	Every 13 weeks	X	X		
Hepatitis B Testing (HBsAg/HBsAb/ HBcAb)	X	X		X	Every 26 weeks				
Hepatitis C Testing (HCV Ab)	X	X		X	Every 26 weeks				
Blood Sample for Chemistry/Hematology	X	X	X	X	Every 13 weeks	X	X	X	
Blood storage sample for HIV-1 RNA NAAT	X	X	X	X	Every 13 weeks	X	X		
Blood Sample for DBS	X[g]		X	X	Every 13 weeks	X	X		
Blood Sample for Metabolic Assessments[h]	X	X		X	Every 26 weeks				
Anytime Plasma PK sample	X	X	X	X	Every 13 weeks	X	X	X	
Plasma Storage Sample	X	X	X	X	Every 13 weeks	X	X	X	

Study Procedure	PK Tail Phase – Weeks (± 7 days)[n]					ESDD[b]	30-Day Follow-up[c] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[d] (± 14 days)
	Randomized Blinded Phase to PK Tail Day 1	LEN OLE Phase to PK Tail Day 1[a]	13	26	Post Week 26 Every 13 or 26 Weeks to Week 78				
Serum Storage Sample	X	X	X	X	Every 13 weeks	X	X	X	
Estimated GFR	X	X	X	X	Every 13 weeks	X	X	X	
Urinalysis, Urine Protein, Urine Chemistry	X	X	X	X	Every 13 weeks	X	X	X	
Urine Pregnancy Test[i]	X	X	X	X	Every 13 weeks	X	X	X	
Urine Storage Sample						X			
Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire	X	X	X	X	Every 13 weeks	X			
Adherence to Oral Study Product Questionnaire	X		X	X	Every 13 weeks	X			
PrEP Impacts and Administration Preference Questionnaire	X								
Administration and Dosing Questionnaire for PrEP Medication	X	X							
Experienced Preference for PrEP Medication Questionnaire		X							
Intimate partner violence screening, when applicable	X	X	X	X	Every 13 weeks	X	X	X	
HIV Risk Reduction Counseling	X	X	X	X	Every 13 weeks	X	X		
Adherence Counseling	X	X	X	X	Every 13 weeks				
F/TDF Dispensation and Accountability[j]	X	X	X	X	Every 13 weeks	X[k]			

Study Procedure	PK Tail Phase – Weeks (± 7 days)[n]					ESDD[b]	30-Day Follow-up[c] (± 14 days)	30-Day Post-HIV Infection Follow-up (± 14 days)	90-Day Post-HIV Infection Follow-up[d] (± 14 days)
	Randomized Blinded Phase to PK Tail Day 1	LEN OLE Phase to PK Tail Day 1[a]	13	26	Post Week 26 Every 13 or 26 Weeks to Week 78				
CD4 cell count, HIV-1 RNA quantitative NAAT, and HIV resistance genotype (for participants diagnosed with HIV only)	X	X	X	X	Every 13 weeks	X	X	X[l]	X[m]

Ab = antibody; Ag = antigen; CD4 = cluster determinant 4; CT = *Chlamydia trachomatis*; DBS = dried blood spot; ESDD = early study drug discontinuation; F/TDF = emtricitabine/tenofovir disoproxil fumarate; GC = *Neisseria gonorrhoeae*; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LEN = lenacapavir; NAAT = nucleic acid amplification test; OLE = open-label extension; PK = pharmacokinetic(s); SC = subcutaneous; STI = sexually transmitted infection; TV = *Trichomonas vaginalis*

a The duration of the LEN OLE Phase may be 52 or 65 weeks; the last visit of the LEN OLE Phase is 26 weeks after the last LEN injection and coincides with PK Tail Day 1.
b Early study drug discontinuation visit occurs once in the study when the participant permanently discontinues dosing with any assigned study drug prior to completing the study (regardless of study phase) for any reason other than acquiring HIV. The participant will be asked to return to the clinic for an ESDD visit within 72 hours of stopping study drug in the PK Tail Phase.
c Participants who have received at least 1 dose of study drug will be required to complete a follow-up visit 30 days (± 14 days) after discontinuation of the study drug for participants who complete an ESDD visit or completing the PK Tail Phase.
d Participants will only be requested to return to the clinic for a post-HIV-infection follow-up visit 90 (± 14) days after the HIV diagnosis visit if the required information is not available from participant's HIV physician. Participants whose HIV-1 RNA is ≥ 50 copies/mL at the 90-Day Post-HIV Follow-Up visit will continue to have follow-up visits every 3 months until HIV-1 RNA < 50 copies/mL, at which point their participation will conclude. Participants will be followed up for a maximum of 1 year from the date of they were diagnosed with HIV infection.
e For participants < 20 years of age, height is to be measured annually until they reach 20 years of age.
f GC and CT testing are to be performed by urine, pharyngeal, and rectal swabs by central laboratory. Swabs may be self-collected by the participant at the discretion of the investigator. Asymptomatic blood syphilis analysis per local testing protocol. For participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion.
g Only collect if the participant prematurely discontinues from the Randomized Blinded Phase.
h Lipid panel: Participants should be instructed to fast (no food or drinks, except water) at least 8 hours prior to blood collection.
i For participants assigned female at birth who are of childbearing potential only. Serum pregnancy test will be performed in the event of a positive urine pregnancy test.
j Drug accountability will be performed by pill count for adherence.
k No study drug will be dispensed.
l HIV resistance genotype will be performed only if not already collected at time of infection.
m CD4 cell count and HIV-1 RNA quantitative NAAT only.
n All PK tail visits should be scheduled from PK Tail Day 1.

APPENDIX 2. RECENCY ASSAY PARAMETERS FOR HIV-1 SUBTYPE AE

Recency assay parameters (eg, MDRI, FRR) for HIV-1 subtype AE are not available from literature. For this study, recency data from {Klock 2020} were used to estimate the recency assay parameters for subtype AE. Only untreated participants were included. Twenty-three of these participants (123 samples) were subtype AE, and all of them were from Thailand. R package "inctools" (https://cran.r-project.org/web/packages/inctools/inctools.pdf) was used. R functions mdrical() and frrcal() from this package were used to estimate MDRI and FRR parameters. The ODn and viral load cutoffs, as input to the functions, were set the same as those in Table 6-2 (ie, an infection classified as recent if ODn ≤ 1.5 and HIV-1 RNA viral load > 75 copies/mL).

The estimated recency assay parameters are in Appendix Table 1. Among the 35 samples that are over 1 year since infection, none of them were misclassified as recent infections, therefore, the estimated FRR was zero.

Appendix Table 1. Recency Assay Parameters for Subtype AE

T	MDRI (rSE)	FRR
2 years	172.6 (9.93%)	0.0%
1 year	172.6 (9.96%)	0.0%

Note that the rSE of MDRI was estimated by bootstrap method embedded in the R function mdrical(), which could vary slightly in each simulation (functionality of setting a seed to reproduce results is not available in mdrical()). The estimated recency assay parameters are almost the same for T of 2 years and 1 year, except for the minor differences in the rSE of MDRI (which could have been due to bootstrap randomness). The reason is that in the dataset, there were no false recency results among the samples that are >1 year since infection, and the estimated probability of recency function $P_R(t)$ function is almost zero for t of over 1 year. Therefore, the estimated MDRI and FRR are almost identical for T of 2 years and 1 year. In this case, the choice of T will only have a minimal impact on the bHIV estimate.

APPENDIX 3. HIV-1 SUBTYPE ASSUMPTION BY COUNTRY

Since HIV-1 subtyping analysis will not be available at the time of the Interim Analysis for this study, we will use country, as a correlate, to estimate the percentage of each subtype. The HIV-1 subtype assumption by country is determined by simplifying and incorporating the information from relevant literature publications. The selected publications will follow these basic rules:

- The subtype distribution came from a recent study.
- The sample size was moderate or large.
- The study population was primarily male (Cisgender Men, Transgender Women, Transgender Men, and Gender Nonbinary People who Have Sex with Male Partners and are at Risk for HIV Infection).
- The sites in the literature are similar to the sites in this study.

The literature search focused on the most recently collected subtyping data and similar site demographics to the study to provide the greatest confidence that the subtyping results in the literature will be applicable for this study. When possible, studies with larger sample sizes were used to further increase the confidence that the subtype distribution in the literature reflects the subtype distribution in the study population. Since the majority of the participants in the study are male, when possible, the publications were focused on subtype distribution found in males or serodiscordant couples. Due to the limited numbers of publications, all references that meet any two basic rules will be taken into consideration. Based on the selected literature, the HIV-1 subtype distribution by country is detailed in Appendix Table 2 to Appendix Table 8.

Appendix Table 2. HIV-1 Subtype Distribution for South Africa

Country	Subtype (%)						Sample size	Reference
	A	B	C	G	AG	Other*		
South Africa			98.4			1.6	204573	{Giovanetti 2020}
			99.5			0.5	201	{Sivay 2017}
	0.4	0.4	98.8	0.1	0.1	0.4	5907	{Hemelaar 2019}

* Other unknown or undeterminable subtypes

For South Africa, the proportion of subtype C is greater than 98% among the three selected references and other subtypes are extremely rare. Thus, 100% is assigned as the proportion of subtype C in Appendix Table 13 for South Africa.

Appendix Table 3. HIV-1 Subtype Distribution for Mexico

Country	Subtype (%)						Sample size	Reference
	B	AE	AG	BF	BG	Other*		
Mexico	99.9			0.06		0.06	1655	{Avila-Rios 2011}
	98.7	0.26	0.29	0.17	0.20	0.38	6661	{Garcia-Morales 2021}

* Other unknown or undeterminable subtypes

For Mexico, the proportion of subtype B is greater than 98% among the two selected references and other subtypes are extremely rare. Thus, 100% is assigned as the proportion of subtype B in Appendix Table 13 for Mexico.

Appendix Table 4. HIV-1 Subtype Distribution for United States

Country	Subtype (%)									Sample size	Reference
	A	B	C	D	F	G	AE	AG	Other*		
United States	0.70	93.60	1.30	0.20	0.10	0.50	0.60	0.90	2.10	121793	{Kline 2019}
		95.20							4.80	114034	{Kline 2019}

* Other unknown or undeterminable subtypes

For the United States, the proportion of subtype B is greater than 93% in the population reported by the selected reference. Although other subtypes such as A, C, D, F, G, AE, and AG also appear, each one is rare (ranging from 0.1% to 1.3%). To simplify the calculation for the overall recency assay parameters, 100% is assigned as the proportion of subtype B in Appendix Table 13 for United States.

Appendix Table 5. HIV-1 Subtype Distribution for Peru

Country	Subtype (%)								Sample size	Reference
	A	B	C	F	H	BC	BF	Other*		
Peru	0.6	96.2	0.2	0.2		0.2	2.6		470	{Trebelcock 2019}
	0.8	98	0.4		0.4			0.4	245	{Yabar 2012}

* Other unknown or undeterminable subtypes

For Peru, the proportion of subtype B is greater than 96% among the two selected references. Since recency assay parameters for subtype BF is unavailable, we allocate the proportion of subtype BF to the most prevalent subtype B. After allocation, other subtypes are extremely rare. Thus, 100% is assigned as the proportion of subtype B in Appendix Table 13 for Peru.

Appendix Table 6. HIV-1 Subtype Distribution for Thailand

Country	Subtype (%)				Sample size	Reference
	B	AE	B/AE	Other*		
Thailand	6	82.3	11.6	0.1	215	{Lam 2017}

* Other unknown or undeterminable subtypes

For Thailand, we split the proportion of subtype B/AE equally to subtype B and AE.

So, the proportion of subtype B is 6 + 11.6/2 = 11.8, the proportion of subtype AE is 82.3+ 11.6/2 = 88.1. After rounding, 12% is assigned as the proportion of subtype B, and 88% is assigned as the proportion of subtype AE in Appendix Table 13 for Thailand.

Appendix Table 7. HIV-1 Subtype Distribution for Argentina

Country	Subtype (%)					Sample size	Reference
	B	C	F	BF	Other*		
Argentina	89.5		10.5			95	{Avila 2002}
	71.5	0.6		26	1.9	312	{Cevallos 2017}

* Other unknown or undeterminable subtypes

Since recency assay parameters for subtype F and BF are unavailable, the proportion of subtype F and BF are allocated to the most prevalent subtype B. After allocation, the proportion of subtype B is greater than 97% among the two selected references, and each of other subtypes is rare for Argentina. Thus, 100% is assigned as the proportion of subtype B in Appendix Table 13 for Argentina.

Appendix Table 8. HIV-1 Subtype Distribution for Brazil

Country	Subtype (%)								Sample size	Reference	Region from reference
	B	C	D	F	AG	BC	BF	Other*			
Brazil	79.1	5.3		7.6		2.0	4.6	1.4	302	{Alcalde 2012}	southeast
	82.6					4.3	13.0	0.1	23	{Alves 2017}	southeast
	72.4	6.6		12.0			7.4	1.6	171	{Arruda 2018}	southeast
	90.7	3.1		0.9			5.3		227	{Crispim 2019}	north
	80.2	6.0		3.4			4.3	6.1	117	{Andrade 2017}	north
	87.2	2.1		4.3			6.4		47	{de Moraes Soares 2014}	north
	72.0	5.0	1.0	6.0	1.0	4.0	11.0		140	{Delatorre 2017}	northeast
	79.0			6.7			6.5	7.8	1300	{Filho 2017}	northeast
	77.0	4.2		10.6			7.4	0.8	171	{Arruda 2018}	northeast
	68.1	1.9		8.7			20.9	0.4	263	{Amaral 2017}	northeast
	31.0	54.0		3.0		8.0		4.0	153	{Arruda 2018}	south
	36.7	34.7		6.1		18.3	4.0	0.2	47	{de Moraes Soares 2014}	south

* Other unknown or undeterminable subtypes

For Brazil, the literature indicates that subtype is not homogenous across sites so to account for these differences, subtype distribution will be calculated by weighted averages across regions. With the information from Appendix Table 8, using the sample sizes from the references as weights, the averaged subtype proportions by region are calculated in Appendix Table 9. For example, the proportion of subtype B in southeast is calculated as $79.1\frac{302}{302+23+171}+82.6\frac{23}{302+23+171}+72.4\frac{171}{302+23+171}=77.0$.

Appendix Table 9. HIV-1 Subtype Distribution by Region for Brazil

Country	Region	Subtype (%)							
		B	C	D	F	AG	BC	BF	Other*
Brazil	southeast	77.0	5.5		8.8		1.4	6.0	1.4
	northeast	76.8	1.0	0.1	7.3	0.1	0.3	8.9	5.5
	north	87.1	3.8		2.1			5.1	1.8
	south	32.3	49.5		3.7		10.4	0.9	3.1

* Other unknown or undeterminable subtypes

In this study, 120 participants from Brazil were identified in the Incidence Phase as having acquired HIV-1. The site distribution for the 120 participants from Brazil is detailed in the Appendix Table 10.

Appendix Table 10. Site Distribution for the 120 HIV-1 Positive Participants from Brazil

City	Region	N
Rio de Janeiro	southeast	38
Sao Paulo	southeast	32
Nova IguaSu, Rio de Janeiro	southeast	6
Belo Horizonte - MG, CEP	southeast	2
Canela-Salvador	northeast	18
Manauas	north	18
Porto Alegre	south	6

Note: study data as of 02AUG2024 snapshot (enrollment closed prior to this snapshot).

Brazil is officially divided into five regions by geography: north, northeast, central-west, southeast, south. Based on official information, the region for each city in Appendix Table 10 is determined. Then Appendix Table 11 is obtained by combining the participants from the same region.

Appendix Table 11. Region Distribution for the 120 HIV-1 Positive Participants from Brazil

Region	N	Percent
southeast	78	65%
northeast	18	15%
north	18	15%

south	6	5%

Note: study data as of 02AUG2024 snapshot (enrollment closed prior to this snapshot).

Finally, the summary table for the subtype distribution in Brazil is obtained by weighted average across regions:

Appendix Table 12. Summarized Subtype Distribution in Brazil

	Subtype (%)							
Country	**B**	**C**	**D**	**F**	**AG**	**BC**	**BF**	**Other***
Brazil	76.2	6.8	0.0	7.3	0.0	1.5	6.0	2.2

* Other unknown or undeterminable subtypes

For example, the proportion of subtype B in Appendix Table 12 is calculated by 77.0*65%+76.8*15%+87.1*15%+32.3*5%= 76.2.

After obtaining the proportions for each subtype by weighted average in Appendix Table 12, subtype D and AG are ignored since these subtypes are rare. Since recency assay parameters for subtype F, BC and BF are unavailable, the proportions of subtype F and BF are allocated to the most prevalent subtype which is B. Then, the proportion of subtype BC is equally split to subtype B and C. Since subtype B is the predominant subtypes in Brazil, the subtype "other" (ie, other unknown or undeterminable subtypes) is allocated to subtype B.

Eventually, the subtype assumption in Appendix Table 13 for Brazil was determined. For instance, the proportion of subtype B is calculated by 76.2+7.3+1.5/2+6.0+2.2 = 92.

Appendix Table 13. HIV Subtype Assumption by Country

	Subtype (%)		
Country	**B**	**C**	**AE**
South Africa		100	
Mexico	100		
United States	100		
Peru	100		
Thailand	12		88
Argentina	100		
Brazil	92	8	

The HIV-1 subtype assumption provided by this table will be used to calculate the overall MDRI, the rSE of the overall MDRI, the overall FRR, and the rSE of the overall FRR (refer to Section 6.1.2.1.1).

APPENDIX 4. PREDICTED HIV-1 INCIDENCE BASED ON RECTAL GONORRHEA INCIDENCE

The predicted HIV-1 incidence, in the absence of PrEP, will be estimated using data from a linear regression model characterizing the expected HIV-1 incidence as a function of anal/rectal gonorrhea incidence (as an indicator of engaging in sexual behavior putting participant at risk of acquiring HIV-1). This model is constructed based on incidences for HIV-1 and rectal gonorrhea in 8 studies with men who have sex with men (MSM) not using PrEP {Mullick 2019}. The studies and incidences considered for constructing the model are listed in Appendix Table 14.

Appendix Table 14. Incidence of Rectal Gonorrhea Infection and HIV-1 Infection in HIV-uninfected MSM not using PrEP

Source Publication	Rectal Gonorrhea Incidence (per 100 PY)	HIV-1 Incidence (per 100 PY)	Study Location
Morris SR, CID 2006 (EXPLORE)	3.5	2.5	United States
Jin F, JAIDS 2010	2.3	0.9	Australia
Sanders 2014*	9.3	35.2	Kenya
Molina JM, NEJM 2015 (IPERGAY)	15.5	6.6	France, Canada
Castillo R, JAIDS 2015	10.1	3.6	Peru
Kelley CF, AIDS 2015	6.2	3.8	United States
McGowan I, PLOS One 2016	16.1	6.4	United States
McCormack S, Lancet 2016 (PROUD)	33.1	9.0	United Kingdom
Girometti N, Sex Transm Infect 2017	33.0	8.3	United Kingdom

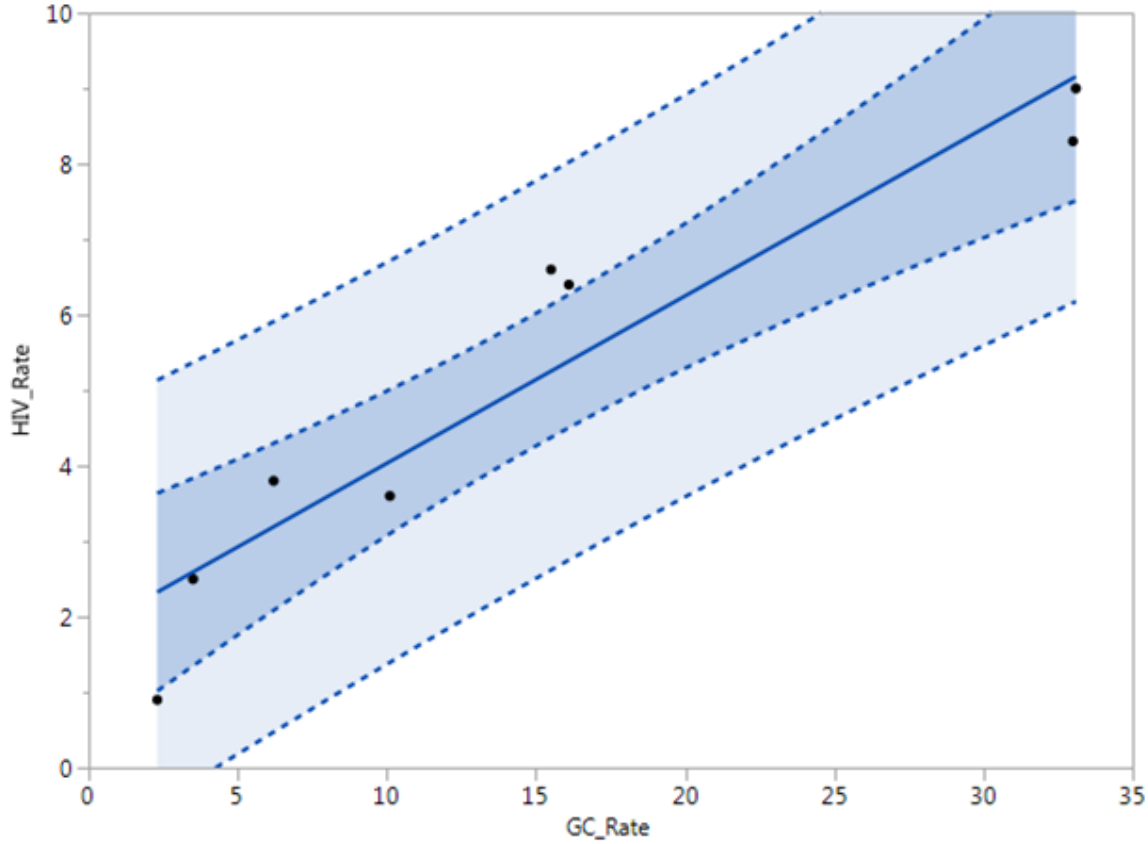
* Sanders data is considered an outlier, hence excluded from the model {Mullick 2019}.

Based on these data (excluding the outlier Sanders 2014 data) the constructed regression model is characterized by

$$\hat{y} = 1.8168 + 0.2218 \times x,$$

where $\hat{y}$ is the predicted HIV-1 incidence (events/100PY) in the absence of HIV prophylaxis and x is the rectal gonorrhea incidence (events/100PY).

Appendix Figure 1. Graphical Presentation of the Regression Analysis from Data Points in 8 Studies



To assess if treatment with LEN is superior to the historical placebo with respect to the HIV-1 incidence, the following steps will be done:

1) Construct a 95% prediction band around the regression line for the predicted HIV-1 incidence in the absence of HIV prophylaxis given the observed rectal gonorrhea incidence for study participants receiving LEN. The rectal gonorrhea incidence will be computed based on laboratory data as specified in Section 9.1-9.2. This 95% prediction interval is characterized below:

$$\hat{y} \pm t_{n-2} \times S_y \sqrt{1 + \frac{1}{n} + \frac{(x-\bar{x})^2}{(n-1)S_x^2}},$$

where n is the total number of studies in the meta-analysis, S_y is the standard deviation of the regression model residuals, S_x is the standard deviation of the anal/rectal gonorrhea incidences, $\bar{x}$ is the average anal/rectal gonorrhea incidence, and t_{n-2} is the 2.5%-th upper quantile of the t distribution with $n-2$ degrees of freedom.

2) Construct a 95% CI for the observed HIV-1 incidence for study participants receiving LEN. This 95% exact CI (L_l, L_u) for the incidence is calculated using the formula in Section 6.1.2.2.

3) If $L_u \leq \hat{y} - t_{n-2} \times S_y \sqrt{1 + \frac{1}{n} + \frac{(x-\bar{x})^2}{(n-1)S_x^2}}$, then declare LEN superior to the historical placebo HIV-1 incidence.

Appendix Table 15. Predicted HIV-1 Incidence[a] Using Rectal Gonorrhea Incidence as the Determinant

Rectal Gonorrhea incidence (per 100 PY)	Predicted HIV-1 Incidence and 95% Prediction Interval (per 100 PY)
15	5.1 (2.51, 7.78)
20	6.3 (3.59, 8.91)
21	6.5 (3.80, 9.15)
22	6.7 (4.01, 9.38)
23	6.9 (4.21, 9.62)
24	7.1 (4.41, 9.86)
25	7.4 (4.62, 10.10)
30	8.5 (5.59, 11.34)
35	9.6 (6.53, 12.63)

a Predictive model based on HIV-1 and rectal gonorrhea regression analysis from 8 studies.

APPENDIX 5. PREDICTED HIV-1 INCIDENCE BASED ON F/TDF ADHERENCE-EFFICACY RELATIONSHIP

bHIV 1.1 Background

The adherence, based on DBS, and efficacy relationship for F/TDF is well characterized. The available DBS and HIV-1 diagnosis data from the F/TDF arm of the study may be used to back-calculate a contemporaneous counterfactual estimate of the bHIV during the study using the methodology developed by {Glidden 2021}. In this appendix, we provide details on how study data will be summarized for the modeling. Please refer to {Glidden 2021} for methodology details.

bHIV 1.2 Summary Data from the Study

bHIV 1.2.1 Baseline Infection and Follow-Up Time

Participants in the All Screened Set who are confirmed HIV-1 negative at Incidence Screening are eligible for RBP screening and may be randomized to receive LEN or F/TDF for HIV PrEP for a minimum follow-up of 52 weeks.

Among the participants randomized in RBP, assume that n_0 participants are not on any PrEP at Incidence Screening. The total PY t_0 for the n_0 participants during their "without PrEP" period in study will be calculated as the period between Incidence Screening and RBP Baseline/Day 1 (if a participant is never dosed, the PY will be the period between Incidence Screening and the HIV-1 positive diagnosis date or, if not diagnosed as HIV-1 positive, the last HIV test date). Assume that Δ_0 HIV-1 positive cases are identified prior to first dose (ie, baseline infections) among the n_0 participants during the "without PrEP" period (see Appendix Table 17).

bHIV 1.2.2 Follow-Up Time for Participants in the DBS Cohort Analysis Set by TFV-DP Level of F/TDF

The follow-up time will be calculated for each participant who received F/TDF in the DBS Cohort Analysis Set based on low, medium, and high adherence levels based on the TFV-DP concentration from the DBS data. Low adherence is defined by TFV-DP concentration lower than 350 fmol/punches, medium adherence is defined by TFV-DP concentration lower than 700 fmol/punches and greater than or equal to 350 fmol/punches, and high adherence is defined by TFV-DP concentration greater than or equal to 700 fmol/punches.

Per protocol, after RBP Baseline/Day 1, DBS samples are collected at Week 4, Week 8, Week 13 and every 13 weeks afterwards. If sample collection date is missing, the nominal visit date will be used to calculate the follow-up time. If the first visit with non-missing adherence level is after Week 4, then impute the adherence level for all previous visits using this adherence level; otherwise, a missing adherence level will be imputed by that of the previous visit. The follow-up time calculation for each participant is illustrated by an example in Appendix Table 16.

Appendix Table 16. Example for Calculating Follow-Up Time for a Participant in the DBS Cohort Analysis Set Followed for 52 Weeks

Analysis Visit	Study Day	Adherence Level	Imputed Adherence Level	Follow-Up Time
Week 4	Day d1	Low	Low	d1
Week 8	Day d2	Missing	Low	d2 - d1
Week 13	Day d3	High	High	d3 - d2
Week 26	Day d4	High	High	d4 - d3
Week 39	Day d5	Low	Low	d5 - d4
Last at-risk of HIV-1 infection date for on randomized study drug*	Day d6	Missing	Low	d6 - d5

* defined in Section 3.8.2.3

In the above example, the follow-up time categorized as low adherence (denoted t_{20}) is d1+(d2-d1)+(d5-d4)+(d6-d5); the follow-up time categorized as high adherence (denoted t_{22}) is (d3-d2)+(d4-d3), see Appendix Table 17.

For each HIV-1 infection among participants in the DBS Cohort Analysis Set while on randomized study drug, the adherence level at the diagnosis visit will be used for analysis. The total number of HIV-1 infections and total PY for each adherence level will be calculated (denoted Δ_{20}, Δ_{21} and Δ_{22} in Appendix Table 17).

bHIV 1.2.3 Follow-Up Time for Participants on F/TDF but Not in the DBS Cohort Analysis Set

For the participants on F/TDF but not selected for DBS sampling (hence with unknown adherence levels), the total number of HIV-1 infections Δ_2 and total PY t_2 will be summarized.

Appendix Table 17 provides the notations used for summary data from the study as input for the modeling approach by {Glidden 2021}.

Appendix Table 17. Notations for Summary Data from the Study

Drug Group	Adherence Level	HIV-1 Infection	Total Person Year
F/TDF	Low	Δ_{20}	t_{20}
F/TDF	Medium	Δ_{21}	t_{21}
F/TDF	High	Δ_{22}	t_{22}
F/TDF	Unknown	Δ_{2}	t_{2}
Without PrEP	Unknown	Δ_{0}	t_{0}

bHIV 1.3 Predicted HIV-1 Incidence by Bayesian Method

With the observed data summarized as above, the Bayesian posterior distribution for the predicted bHIV can be generated using the modeling approach developed by {Glidden 2021}. The Bayesian estimate (posterior median) and the 95% credible interval will be reported.

APPENDIX 6. ASSESSMENT OF ADHERENCE AND ITS ASSOCIATION WITH EFFICACY BASED ON DRIED BLOOD SPOT CONCENTRATION

DBS 1.1 Background

Drug exposure level has been identified as the key factor in optimizing efficacy of HIV-1 PrEP. Although drug exposure level is related to multiple factors, adherence to drug (consistent drug administration) is the most important factor.

The adherence on or prior to HIV diagnosis will be investigated for those diagnosed with HIV-1. Additionally, a cohort substudy to estimate the overall rate of adherence will be conducted.

Cards with dried blood samples (DBS) should be placed in a freezer within 1 day after blood draw and should be stored frozen for optimal stability. Samples put in a freezer later than one day after blood has been drawn or those with missing date for placement in the freezer will not be considered for these substudies and will not be sent to the analytical laboratory.

DBS 1.2 Exposure and Adherence

For these substudies, exposure is defined as tenofovir diphosphate (TFV-DP) concentration inside the red blood cells for the F/TDF study drug group) as assessed by the dried blood spot (DBS concentration). Concentrations of TFV-DP in DBS assessments reflect cumulative exposure to study drug prior to the sampling time and are not reflective of only the most recent daily dosing. Thus, as DBS concentration reflects long term exposure to study drug, it serves as an objective measure of overall or long-term adherence to study drug which is less affected by potential variability in daily drug administration (ie, missing a dose or doses, varying the time of day of drug administration).

TFV-DP concentrations are continuous measures and have been reported in units of femtomoles per punch (fmol/punch) or femtomoles per million viably cryopreserved peripheral blood mononuclear cells (f/M vPBMC). Previous work on DBS concentrations with F/TDF have been validated based on 3 mm punched disks.

Previous analyses {Anderson 2012} of data from directly observed therapy (DOT) study (STRAND) in healthy volunteers along with the data from the iPrEX study have shown that F/TDF PrEP efficacy is associated with TFV-DP and that optimal efficacy may be achieved with concentrations consistent with ≥4 doses/week (see Appendix Table 18).

Appendix Table 18. TFV-DP Concentrations after DOT Dosing of F/TDF (STRAND Study) and Associated Risk Reduction and Proportion of Participants Attaining TFV-DP EC90 in the iPrEx Study

Regimen	STRAND Study			iPrEX	
	Concentration (fmol/M vPBMC)				
(Doses / Week)	25 Percentile	Median	75 Percentile	HIV-1 Acquisition Risk Reduction	Participants Attaining TFV-DP EC_{90}
2	6	11	13	76%	14%
4	25	32	39	96%	90%
7	31	42	47	99%	100%

Source: Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men {Anderson 2012}

A 72 week open-label cohort study {Grant 2014} of men and transgender women who have sex with men in previously enrolled PrEP trials (ATN 082, iPrEx, and US Safety Study) reported consistent results, Appendix Table 19.

Appendix Table 19. Estimated Dose and F/TDF PrEP Protection Associated with DBS Concentration

DBS Concentration (fmol/punch)	<LLQ	LLQ-349	350-699	700-1249	≥1250
Estimate dose (tablets/week)	**None**	**<2**	**2–3**	**4–6**	**7**
Follow-up (% of visits)	25%	26%	12%	21%	12%
HIV-1 infections (n)	18	9	1	0	0
Person-years per infection	384	399	179	316	181
HIV-1 incidence (95% CI)	4.70 (2.99–7.76)	2.25 (1.19–4.79)	0.56 (0.00–2.50)	0.00 (0.00–0.61)	0.00 (0.00–1.06)

Source: Uptake of pre-exposure prophylaxis, sexual practices, and HIV-1 incidence in men and transgender women who have sex with men: a cohort study {Grant 2014}.

A more recent pharmacokinetic study of TFV-DP in DBS using DOT dosing of F/TDF (at daily dosing of 33%, 67%, or 100%) {Anderson 2018} has also shown consistent results. The modeling of data from this study has shown that the fitted (estimated) median (25 and 75 percentiles) TFV-DP DBS concentrations in men, were 375 (316, 444), 774 (653, 917) and 1389 (1173, 1646) fmol/punch for 2, 4 and 7 doses per week respectively {Anderson 2018}.

For participants diagnosed with HIV-1, impact of adherence as assessed by DBS on or prior to diagnosis will be assessed. DBS card at the time of diagnosis may not be collected for an infected participants or the sample may not meet specifications and be rejected by the analytical laboratory. In general, missing DBS concentration at the time of HIV-1 diagnosis will be imputed by considering:

1) the last known TFV-DP concentration (C) prior to diagnosis

2) days between the last dose date and HIV-1 diagnosis (HIV-1 diagnosis date – last dose date) where any negative days (last dose is after HIV-1 Dx) are set to 0

3) days between the last TFV-DP concentration (C) prior to diagnosis and HIV-1 diagnosis (HIV-1 diagnosis date – last DBS date)

4) the decay rate, k, of TFV-DP concentration in RBC calculated based on half-life, $t_{1/2}$, of each study drug group, where $k=0.693/t_{1/2}$.

The imputed concentration, $C_i = C \times e^{-k \times t}$, where t is the min of 2) and 3) above.

TFV-DP has shown the median (range) half-life of 17 (14 to 23) days for F/TDF in previous DOT studies of F/TDF {Anderson 2018}.

DBS 1.3 The Cohort Substudy

DBS 1.3.1 Study Design

In order to estimate the rate of adherence based on the DBS concentration, a cohort of approximately 10% of the participants who were randomized were randomly pre-selected. The participants were selected early during study conduct based on the planned participant number ranges for the study. The selection for the Cohort substudy, randomly selected 1 out of every 10 participant numbers expected to be used for enrollment (Section 1.4.2).

DBS 1.3.2. Objective

The primary objective of the cohort substudy is to characterize the overall adherence for each study drug group.

DBS 1.3.3. Implementation

In order to lower the burden on the laboratory analyzing DBS cards, subsets of DBS cards will be sent to the analytic laboratory. This will be done by sending subsets of Week 4 samples first. Week 8 subsets of samples will be sent when Week 4 samples have been analyzed and etc. as participants complete the study visits. The size of the batch will depend on the logistics at the analytic laboratory. Further details are provided in the charter for DBS sample analysis project plan conducted at Colorado Antiviral Pharmacology Laboratory (University of Colorado).

The unblinded statistician supporting the external DMC will execute a SAS program to select, for each batch, the accession numbers in the cohort substudy and will:

1) Provide the accession number of the selected DBS cards to LabCorp (central warehousing lab for DBS cards) for transfer to the analytic lab (University of Colorado). LabCorp will receive the following information: Investigator ID, Participant ID, Lab Date, Accession Number and Container Number (of sample storage at LabCorp).
2) The analytic lab will receive the following information: Investigator ID, Participant ID, Lab Date, Study drug group and Accession Number.

DBS 1.3.4. Statistical Analysis

Summary tables, similar to those for the main study, will characterize the Cohort substudy for demographics and baseline characteristics, baseline HIV risk characteristics, and participant disposition.

Descriptive statistics (n, mean, standard deviation, median, quartiles, minimum and maximum) for DBS TFV-DP concentration levels will be provided by study drug group and visit.

Median (Q1, Q3) of DBS concentration across visit time (horizontal axis) overlaid by horizontal lines corresponding to adherence thresholds for each study drug group, will be generated by study drug group.

APPENDIX 7. ADVERSE EVENTS CATEGORY

An adverse event record will be flagged for an AE category for analysis in the raw Adverse Events dataset if its MedDRA PT is included in the pre-specified SMQ or MST list for the corresponding AE category, under MedDRA Version 27.0.

AE Category (variable name)	**SMQ Name (Scope)**
COVID-19 (COVID19N)	COVID-19 (SMQ) – Narrow
Hypersensitivity (HYPERSNN)	Hypersensitivity (SMQ) - Narrow

AE Category MST Name (Variable Name)	**Preferred Terms**
Proximal Renal Tubulopathy Proximal Renal Tubulopathy (RENALTUB).	• Aminoaciduria • Beta-N-acetyl-D-glucosaminidase increased • Isosthenuria • Nephropathy toxic • Renal glycosuria • Renal papillary necrosis • Renal tubular acidosis • Renal tubular atrophy • Renal tubular disorder • Tubulointerstitial nephritis • Renal tubular dysfunction • Hyperphosphaturia • Fanconi syndrome acquired • Urine phosphorus increased • Urine retinol binding protein increased • Tubulointerstitial nephritis and uveitis syndrome • Acquired aminoaciduria
Renal Insufficiency Renal Failure Events (RENALFEV.)	• Renal failure • Renal impairment • Acute kidney injury • Subacute kidney injury

AE Category **MST Name** **(Variable Name)**	**Preferred Terms**
Specific COVID-19 Adverse Event COVID-19_DIAGNOSIS-FOCUSED COVID19D	• Coronavirus infection • Coronavirus test positive • COVID-19 • SARS-CoV-2 test positive • COVID-19 pneumonia • Coronavirus pneumonia • Occupational exposure to SARS-CoV-2 • Suspected COVID-19 • Exposure to SARS-CoV-2 • COVID-19 immunisation • COVID-19 prophylaxis • COVID-19 treatment • SARS-CoV-2 carrier • SARS-CoV-2 test false negative • SARS-CoV-2 antibody test positive • SARS-CoV-2 sepsis • SARS-CoV-2 viraemia • Multisystem inflammatory syndrome in children • Congenital COVID-19 • Vaccine derived SARS-CoV-2 infection • SARS-CoV-2 RNA increased • SARS-CoV-2 RNA decreased • SARS-CoV-2 RNA fluctuation • Post-acute COVID-19 syndrome • Multisystem inflammatory syndrome in adults • Multisystem inflammatory syndrome • Thrombosis with thrombocytopenia syndrome • Breakthrough COVID-19

APPENDIX 8. MEDICATIONS OF INTEREST

Gender affirming hormones were identified by the Standard Medication Name (WHOGEN) below based on WHODrug BMAR23 for hormone PK sampling purpose.

Standard Medication Name (WHOGEN) for Testosterone
TESTOSTERONE
TESTOSTERONE CIPIONATE
TESTOSTERONE DECANOATE
TESTOSTERONE ENANTHATE
TESTOSTERONE ISOCAPROATE
TESTOSTERONE PHENYLPROPIONATE
TESTOSTERONE PROPIONATE
TESTOSTERONE UNDECANOATE

Standard Medication Name (WHOGEN) for Estradiol
ESTRADIOL
ESTRADIOL CIPIONATE
ESTRADIOL ENANTATE
ESTRADIOL HEMIHYDRATE
ESTRADIOL VALERATE
ESTROGENS CONJUGATED
ETHINYLESTRADIOL
ESTRADIOL VALERATE;LEVONORGESTREL
ESTRADIOL VALERATE;NORETHISTERONE ENANTATE
ETHINYLESTRADIOL;NORELGESTROMIN

APPENDIX 9. PROGRAMMING SPECIFICATION

14.1. Derivation Specifications

14.1.1. Derivation of Age

If the age from the Day 1 eCRF is not available, age will be calculated as follows:

Only year is provided for the date of birth (DOB). For the month and day of DOB for the purposes of calculating age, use the month and day from (1) the Day 1 date for treated participants, (2) the randomization date for participants that were not dosed or (3) the Incidence Phase Screening informed consent date for participants not randomized in RBP.

a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

c) Divide the result in (b) by 12,

AGE = the integer of the result in (c),

Age for laboratory test reference range will be based on the age at the sample collection date.

14.2. Definition of Study Dates

Last Dose Date for the RBP or Last Dose Date for OLOP is defined for participants who permanently discontinued study drug according to Study Drug Completion eCRF (ie, SDRGCOMP) for each study phase, respectively.

- For participants randomized to SC LEN injection in the RBP, the last dose date is defined as the latest nonmissing end date of randomized active SC LEN or oral LEN study drug in the RBP (in EX_IV eCRF).
- For participants not randomized to SC LEN injection (in EX_IV eCRF) in the RBP, the last dose date for the RBP is defined as the last dose date of randomized active F/TDF in the RBP. For participants receiving OLOP after permanent discontinuation of RBP study drug, the last dose date for OLOP is defined as the last dose date of OLOP administered via the PK Tail Phase (in EX eCRF).
  - Additionally, for participants not randomized to SC LEN injection (in EX_IV eCRF) in the RBP and for participants receiving OLOP whom have partial missing last dosing date, the last dosing date will be imputed using dates from the RBP (based on RBP study drug) or OLOP (based on OLOP administered via the PK Tail Phase), respectively:

The derivations below are for the RBP and based on RBP study drug. Similar derivations will be done for OLOP using OLOP administered via the PK Tail Phase.

If study drug start date or end date are partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

For participants with a partial last dosing date (ie, month and year of last dose are known), use the max (the dispensing dates of active F/TDF study drug bottles for RBP , study drug start dates and end dates, imputed end date of last dose [day imputed as 15]) as the final imputed last dose date for the study phase. (However, if dispensing date's month is after last dose date's month, data query is needed.)

For participants where only the year of the last dosing date is known), then impute the last dose date based on the below:

Condition	Last dose date (year only) is imputed as
The year of the last dose is equal to the year of the last visit*	Maximum of active F/TDF study drug start dates and end dates, clinic visit dates and laboratory visit dates excluding the follow-up visits
The year of the last dose is before the year of the last visit*	December 31st of the last dose year
The year of the last dose is after the year of the last visit*	Data query is needed. If this remains unchanged after query, impute as: January 1st of the last dose year

* Last visit is defined as the maximum of clinic visit dates and laboratory visit dates excluding the follow-up visits.

If the date of last dose is completely missing, use the maximum of active F/TDF study drug start dates and end dates, clinic visit dates, and laboratory visit dates excluding the follow-up visits to impute the last dose date.

If participant died and the death date is complete (ie, not partial date) and before the imputed last dose date, the complete death date should be used as the imputed last dose date.

If participant has been diagnosed with HIV-1 infection before the imputed last dose date (year only or month/year only known with the same year or month/year of the date of HIV-1 diagnosis), the date of HIV-1 diagnosis should be used as the imputed last dose date. Per study design, participants that have been diagnosed with HIV-1 infection must immediately discontinue study drug.

Additionally, for participants whom the last dose date for the RBP is after the first dose date for OLOP after permanent discontinuation of RBP study drug, data query is needed.

Last Dose Date Imputation for Ongoing Participants (Participants who either do not receive SC LEN injection in the RBP and for participants in OLOP, for the purpose of duration of exposure)

Last dose date is not defined for participants still on study drug in the SAP. However, for the calculation of the duration of exposure to oral study drug, for participants who have not permanently discontinued study drug at the data cutoff date, the estimated last dose date will be the maximum of nonmissing F/TDF study drug (active or placebo) start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding any follow-up visits from the RBP or OLOP, respectively. The same imputation rules used for last dose date will be applied to the partial missing study drug stop date.)

Last Dose Date for the First OLOP is defined as the last dose date of only the first OLOP study drug (in EX eCRF) in the PK Tail Phase. If participants switch OLOP study drug multiple times (eg, from OL F/TDF to OL F/TAF and back to OL F/TDF), the interruption in the OLOP study drug will be ignored if it is less than 7 days.

If participants do not switch OLOP study drug for 7 or more days in the PK Tail Phase, the last dose date for the first OLOP is the same as the last dose date for OLOP (see above for imputations for partial dates.)

If participants switch OLOP study drug for 7 or more days in the PK Tail Phase and the last dose date for the first OLOP study drug is partially missing (ie, month and year of last dose are known), then impute the last dose date for the first OLOP as the max (the dispensing dates of study drug bottles, study drug start dates and end dates, imputed end date of last dose [day imputed as 15]) prior to the date of first switch of OLOP (in EX eCRF) in the PK Tail Phase after permanent discontinuation of RBP study drug.

If the date of first switch of OLOP study drug is a partial date impute based on the below:

Condition	Last dose date (year only) is imputed as
month and year (or year if only year is known) are the same as the date of the first dispensation of switch OL study drug	date of the first dispensation of switch OL study drug
month and year (or year only if only year is known) is after the date of the first dispensation of switch OL study drug	1st of month / January 1st if only year is known
month and year (or year only if only year is known) is before the date of the first dispensation of switch OL study drug	Data query is needed.

Last Study Date is the latest of the study drug (active or placebo) start dates and end dates, the clinic visit dates, the laboratory visit dates, the AE onset date and end dates, including any follow-up visits and post-injection follow-up visits, for participants who prematurely discontinued study or who completed study according to the Study Completion eCRF. If study drug start dates or end date is partially missing (ie, only year and month are known), the day will be imputed as 15 for the purpose of this analysis.

— If participant died and the death date is complete (ie, not partial date) and before the imputed last study date, the complete death date should be used as the imputed last study date.

Last Study Date Imputation for Ongoing Participants (for the purpose of duration of exposure)

Last study date is not defined for participants still on study in the SAP. However, for programing purposes, the latest of study drug (active or placebo) start dates and end dates, the clinic visit dates, the laboratory visit dates, and the AE onset date and end dates including any follow-up visits (and post-injection follow-up visit dates for RBP only), will be used to impute the last study date for participants still on study.

Last Exposure Date for the RBP, OLOP or first OLOP Imputation for Ongoing Participants (for the purpose of duration of exposure)

Last exposure dates are not defined for participants still on study in the SAP. However, for programing purposes, use the last exposure date definitions defined above (Section 3.8.2.2) with the Last Dose Date Imputation (for the respective study phase) and Last Study Date Imputation for Ongoing Participants defined above.

14.3. General Definitions

14.3.1. Study Completion

Through the time of the primary analysis and until the end of the RBP/start of the LEN OLE phase, participants cannot complete the study or study drug in the RBP. Only 1 study completion form is collected for the entire study. Therefore, study disposition in the RBP of the study is defined as follows for dosed participants:

PK Tail Phase entry eCRF		PK Tail Phase first dose date		Study completion form	Discontinued Study?
No or .	AND	.		--	No, continuing in RBP
No or .	AND	.	AND	No	Yes, in RBP
Yes	OR	Yes		--	No, discontinued RBP but continuing study in OLOP
Yes	OR	Yes	AND	No	Yes, in OLOP

Note OLOP is collected from eCRFs as the PK Tail Phase and disregards temporary interruption of SC LEN injection study drug due to the clinical hold.

14.3.2. Background HIV Estimation

The bHIV estimation is based on central lab HIV tests from the first Incidence Phase screening visit.

Split visit: There are participants who took the local rapid test at the first Incidence Screening visit, but took the central lab HIV tests at a later date due to various reasons (eg, unable to draw blood). If it was confirmed by the site that the local rapid test and the central HIV tests taken on different dates were solely due to operational reasons at the site and are both part of the

Incidence Screening procedures, we would consider these "split visit", and require sites to enter in the General Comments CRF page a comment containing the key word "split visit". Such central labs are considered as the Incidence Screening results for determination of HIV-1 status in the Incidence Phase.

Participants whose delayed central lab results are not assessed as "split visit", and were not diagnosed with HIV-1 and were randomized and dosed in RBP are considered as HIV-1 negative at the Incidence Screening (included in the All Screened Set).

14.3.3. Adherence

On-Time SC Injection via Adherence to Prescribed SC Injection Schedule in RBP

To determine the number of participants expected to receive an SC injection, calculate the number of days on study as follows:

- For participants who prematurely discontinued RBP study phase, **the number of days on RBP study phase** is
  - first dose of OLOP due to permanent discontinuation of RBP study drug - the first dose date +1, for participants that were dosed with OLOP due to permanent discontinuation of RBP study drug
  - last study date - the first dose date +1, for participants that were not dosed with OLOP due to permanent discontinuation of RBP study drug
- For participants who are on-going in the RBP study phase (ie, without first dose of OLOP due to permanent discontinuation of RBP study drug), **the number of days on RBP study phase** is the last study date - the first dose date +1.

14.3.4. Body Mass Index

Height may be collected multiple times in this study for participants < 20 years of age. Body mass index (BMI) is calculated using the latest height collected on or prior to the date of the weight collection.

BMI will be calculated as follows:

- BMI = (weight [kg]) / (height [meters]^2)

14.3.5. HIV Tests and Diagnosis

LabCorp HIV Laboratory Tests

HIV Test Description	HIV-1 Positive results	HIV-1 Negative results	LBTSTNAM	LBTESTCD/Original Central Lab
HIV-1/HIV-2 Ag/Ab screening test (4th generation)	Repeatedly Reactive	Non-reactive	'HIV 1/2 Ag/Ab Screen, Siemens' Or 'HIV1/2Ag/AbScreen,SiemensEXPPS'	HIV12P24 CNT449 or CNT573 (express)
HIV-1/HIV-2 Ag/Ab screening test (4th generation): plasma	Repeatedly Reactive	Non-reactive	HIV1/2Ag/AbScrAbtEDTApl(-70)CL	HIV12P24 ATT52
HIV-1/HIV-2 Differentiation Ab test	HIV-1 Positive, HIV2 Pos-HIV1 Cross-Reactive, HIV Positive Untypable	HIV Antibody Negative, HIV-1 Indeterminate, HIV-2 Indeterminate, HIV Indeterminate, HIV-2 Positive*	'HIV Ab Interpretation, Geenius'	HIVAB IMT1948
HIV-1/HIV-2 Differentiation Ab test: plasma	HIV-1 Positive, HIV2 Pos-HIV1 Cross-Reactive, HIV Positive Untypable	HIV Antibody Negative, HIV-1 Indeterminate, HIV-2 Indeterminate, HIV Indeterminate, HIV-2 Positive*	'HIVAbIntrprtGeeniusEDTApl(-70)'	HIVAB IMT2800
HIV-1/HIV-2 Differentiation Ab test (CE version, for LabCorp Singapore)	HIV-1 Positive, HIV2 Pos (With HIV 1 Cross-Reactive), HIV Positive Untypable	HIV Negative, HIV-1 Indeterminate, HIV-2 Indeterminate, HIV Indeterminate, HIV-2 Positive*	'HIVAbIntrprtGeeniusEDTApl(-70)'	HIVAB IMT2397
HIV SUPPL/CONFIRMATION (SGH)	HIV 1 Positive, Positive**	Inconclusive, HIV 2 Positive	HIV Ab Confirmation-340	HIVAB ORT31501
HIV SUPPL/CONFIRMATION (SGH)	Reflex to HIV Ab Confirmation**	Negative, Indeterminate	HIV Supplementary test-340	HIVAB ORT31507
HIV-1 RNA Qualitative (available before December 6, 2021)	Positive	Negative or Invalid	'HIV-1 RNA Qual,EDTApl-335QT'	HIV1RNA ERT608
HIV-1 RNA Qualitative (available starting December 6, 2021)	Reactive Abnormal	Non Reactive	'HIV-1 RNA, EDTApl-335-PNL'	HIV1RNA ERT6386
HIV-2 RNA Qualitative (available starting December 6, 2021)		Reactive Abnormal*, Non Reactive	'HIV-2 RNA, EDTApl-335-PNL'	HIV2RNA ERT6387
HIV-1 RNA Quantitative (available before December 6, 2022)	<20 cp/mL HIV-1 RNA Detected or numeric value	No HIV-1 RNA detected	'HIV RNA TaqMan-2.0-EDTA-CL'	HIV1RNA GET1816

HIV Test Description	HIV-1 Positive results	HIV-1 Negative results	LBTSTNAM	LBTESTCD/Original Central Lab
HIV-1 RNA Quantitative (available starting December 6, 2022)	<20 cp/mL HIV-1 RNA Detected or numeric value	No HIV-1 RNA detected	'HIV RNA Cobas 6800-EDTA-CL'	HIV1RNA GET2053

* HIV-2 positive will not be summarized with HIV-1 incidence.
** Singapore General Hospital (SGH) labs do not contribute to the determination of HIV-1 diagnosis in the Incidence Screening / baseline HIV-1 incidence.

14.4. Efficacy - Program Codes

14.4.1. Comparing Experimental Arm to bHIV

For comparison of bHIV with the HIV-1 incidence in the randomized groups, the test statistic

$$Z = \frac{\log \hat{R} - \log R_0}{\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}}$$

will be used for hypothesis testing, where R_0 will be set to 1 for testing H_{01} and set to 0.8 for testing H_{02}. Denote R_{obs} as the observed rate ratio (ie, LEN/bHIV), then the observed test statistic will be calculated as

$$Z_{obs} = \frac{\log R_{obs} - \log R_0}{\sqrt{\hat{\sigma}^2_{\log(\hat{\lambda}_0)} + \hat{\sigma}^2_{\log(\hat{\lambda}_1)}}}.$$

The 1-sided p-value will be calculated as the lower-tail probability for a quantile of Z_{obs} for a standard normal distribution, using SAS function: CDF('NORMAL', Z_{obs}).

The following example SAS code will be used to compute these CIs and p-values for the primary efficacy evaluation:

```
data rrbhiv;

      _x1 = 12; /*Number of HIV-1 Infections in study for treatment A*/
      bhiv = 1.76; /*bhiv per 100 PY by recency assay*/
      hat1 = 12/1455.1; /*hiv incidence rate for treatment A*/
      bhivsdr = 0.027; /*Variance of log(lambda_0_hat)*/

      alpha = 0.05;
      zval = -quantile("Normal", alpha/2);
      rr1=(hat1/bhiv)*100;
      if _x1 ^=0 then do;
            l1 = hat1/bhiv*exp(-zval*sqrt(bhivsdr + (1/sqrt(_x1))**2));
            u1 = hat1/bhiv*exp(zval*sqrt(bhivsdr + (1/sqrt(_x1))**2));
      end;
```

```
      *test z for r0=1;
      if rr1 ^=0 then do;
            testz1=(log(rr1)-log(1))/sqrt(bhivsdr + (1/sqrt(_x1))**2);
            pval1=cdf("Normal",testz1);
      end;
      else do;
            testz1=.;
            pval1=.;
      end;

      *test z for r0=0.8;
      if rr1 ^=0 then do;
            testz4=(log(rr1)-log(0.8))/sqrt(bhivsdr + (1/sqrt(_x1))**2);
            pval4=cdf("Normal",testz4);
      end;
      else do;
            testz4=.;
            pval4=.;
      end;
run;
```

If the number of HIV-1 infections diagnosed in the LEN group is zero, the estimated HIV-1 incidence $\hat{\lambda}_1$ will be zero, and the methods specified above would fail. In this case, the CI and the p-value will be calculated based on a likelihood ratio test. The following example SAS code will be used to compute CIs and p-values when the HIV-1 incidence in the experimental arm is 0:

```
proc iml;

N_screened = 3000; *Number of volunteers screened for HIV;
N_hiv = 150; * Number of HIV positive cases at screening;
N_testR = 150; * Number of HIV positive cases who take the recency test;
N_R = 10; /*Number of HIV positive cases identified as recent infections by
the RITA algorithm;*/
N_event = 0; * Number of HIV infections in the active arm;
fupy = 3000; /* Total follow up time for HIV negative cases who are enrolled
into the active arm */
margin = 0.8; * The specified incidence ratio in null hypothesis;

assay_mdri = 147.7; /*Mean duration of recent infection (MDRI) of the recency
assay (days)*/
assay_rse_mdri = 0.1169; * rSE for MDRI;
assay_frr = 0.0131; * False recency rate (FRR) of the recency assay;
assay_rse_frr = 0.888; * rSE for FRR;
assay_bigT = 2; /* Infection cutoff time to define whether an infection is
recent, the unit is year */

start logL(hr, param) global(N_screened, N_hiv, N_testR, N_R,
            assay_mdri, assay_frr, assay_rse_mdri, assay_rse_frr, assay_bigT,
            N_event, fupy);
      /*    1: lambda0
            2: p
            3: MDRI
            4: FRR
      */
```

```
      p5 = N_testR / N_hiv;
      result = 0;
      pnr = (1 - param[2]) * param[1] * param[3] + (param[2] - (1 - param[2])
* param[1] * assay_bigT) * param[4];
      if (pnr <= 0 | param[2] <= 0 | param[2] >= 1 | param[1] <= 0) then
return(-1e100);
      if (N_testR > N_R & param[2] - pnr <= 0) then return(-1e100);
      result = (N_screened - N_hiv) * log(1 - param[2]) + N_R * log(pnr *
p5);
      if (N_testR > N_R) then result = result + (N_testR - N_R) *
                                    log((param[2] - pnr) * p5);
      result = result - param[1] * hr * fupy;
      if (param[1] * hr > 0) then result = result + N_event * log(param[1] *
                                         hr * fupy);
      result = result - (param[3] - assay_mdri / 365.25)##2 / 2 /
               (assay_rse_mdri * assay_mdri / 365.25)##2;
      result = result - (param[4] - assay_frr)##2 / 2 / (assay_rse_frr *
               assay_frr)##2;
      if (N_hiv > N_testR) then result = result + (N_hiv - N_testR) *
                                      log(param[2] * (1 - p5));
      return(result);
      finish;

      hr2 = .;
      start tp1(param) global(hr2, assay_bigT, N_R, N_testR);
          x2 = {. . . .};
          x2 = param;
          x2[1] = exp(x2[1]);
          x2[2] = exp(x2[2]) / (1 + exp(x2[2]));
          x2[3] = exp(x2[3]) + param[4] * assay_bigT;
          x2[4] = param[4];
          return(-logL(hr2, x2));
      finish;

      start LikelihoodRecencyPvalue(hr) global(N_screened, N_hiv, N_testR,
            N_R, assay_mdri, assay_frr, assay_rse_mdri, assay_rse_frr,
            assay_bigT, N_event, fupy, hr2);
      if (N_R > N_testR | N_testR > N_hiv | N_hiv > N_screened) then abort;
      lambda0 = (N_R / (N_testR / N_hiv) - assay_frr * N_hiv) / ((N_screened
                - N_hiv) * (assay_mdri / 365.25 - assay_frr * assay_bigT));
      if (lambda0 <= 0) then return(1);
      hr1 = N_event / fupy / lambda0;
      if (hr1 < 1e-8) then hr1 = 1e-8;
      tp2 = {. . . .};
      tp2[1] = lambda0;
      tp2[2] = N_hiv / N_screened;
      tp2[3] = assay_mdri / 365.25;
      tp2[4] = assay_frr;
      logL1 = logL(hr1, tp2);
      con=repeat(.,2,4);
      *opt = {0 2};
      opt = {0 0};
      tp3 = {. . . .};
      tp3[1] = log(tp2[1]);
      tp3[2] = log(tp2[2] / (1 - tp2[2]));
```

```
      tp3[3] = log((tp2[3] - tp2[4] * assay_bigT));
      tp3[4] = tp2[4];
      hr2 = hr;
      call nlpnms(rc, p_MLE, "tp1", tp3, opt, con);
      /*
      if (rc < 0) then do;
            opt2 = {0 5};
            call nlpnms(rc, p_MLE, "tp1", tp3, opt2, con);
            print hr N_testR N_R;
            pause;
      end;
      */
      logL2 = tp1(p_MLE);
      chistat = (logL2 + logL1) * 2;
      pval = sdf('ChiSq', chistat, 1);
      if (N_event / fupy / lambda0 < hr) then pval = pval / 2;
      else pval = 1 - pval / 2;
      return(pval);
      finish;

      start LikelihoodRecencyCi(alpha) global(N_event);
      if (N_event <= 0 & alpha > 0.50) then return(0);
      lower = 1e-6;
      upper = 1e6;
      f_lower = LikelihoodRecencyPvalue(lower);
      f_upper = LikelihoodRecencyPvalue(upper);
      tol = 1e-8;
      if (f_lower < alpha + tol) then return(0);
      if (f_upper > alpha - tol) then return(upper);
      nIter = 0;
      do until(f_upper > alpha - tol | nIter > 100);
            midp = sqrt(lower * upper);
            f_midp = LikelihoodRecencyPvalue(midp);
            if (f_midp > alpha) then do;
                  lower = midp;
                  f_lower = f_midp;
            end;
            else do;
                  upper = midp;
                  f_upper = f_midp;
            end;
            nIter = nIter + 1;
      end;
      return(upper);
      finish;

lrt_pval = LikelihoodRecencyPvalue(margin);
lrt_upper = LikelihoodRecencyCi(0.025);
lrt_lower = LikelihoodRecencyCi(0.975);
print lrt_pval lrt_lower lrt_upper;
varNames = {"lrt_pval" "lrt_lower" "lrt_upper"};
create lrt_result var varNames;
append;
close lrt_result;
quit;
```

14.4.2. Comparing Experimental Arm to F/TDF

The HIV-1 incidence between LEN and F/TDF and its 95% CIs are calculated using the rate ratio method. To test superiority, the p-value from a Poisson model will be used, where trtgrp is the treatment, sero is the number of HIV-1 diagnosis and ln is the natural log of the summation of all participants' person years follow-up time. The following example SAS code will be used to compute the HIV-1 incidence and p-value.

```
data rate;
   input ptyr sero trtgrp$;
   ln = log(ptyr);
   datalines;
   1500  17  LEN
   1500  16  FTDF
    ;
proc genmod data=rate;
   class trtgrp (ref='FTDF');
   model sero = trtgrp / dist=poisson link=log offset=ln;
   lsmeans trtgrp / ilink diff exp cl alpha=0.05;
run;
```

If the number of infections is zero in LEN or F/TDF, then the following example SAS code will be used to compute the 95% CI and 1-sided p-value.

```
data rate;
  input ptyr sero trtgrp$;
  ln = log(ptyr);
  datalines;
  1500  0  LEN
  1500  16  FTDF
  ;
  run;

  ods trace on;
  ods output ExactParmEst=Diffm;
  proc genmod data=rate;
     class trtgrp (ref='FTDF');
     model sero = trtgrp /dist = poisson link=log offset=ln;
     exact trtgrp/ estimate onesided;
  run;
  ods trace off;

  data Diffm; set Diffm;
    if UpperCL = .I then UpperExp = UpperCL;
    else UpperExp = exp(UpperCL);
    if LowerCL = .M then LowerExp = 0;
    else LowerExp = exp(LowerCL);
   run;

  data rate_LEN;
       set rate;
       if trtgrp = "LEN";
  run;
```

```
proc sql; create table Diffm as select * from Diffm, rate_LEN; quit;

data Diffm; set Diffm;
   if sero = 0 then do;
       one_side_PValue = PValue;
       ExpEstimate = 0;
   end;
   else do;
       one_side_PValue = 1;
       ExpEstimate = .I;
   end;
run;
```

HIV-1 incidence in randomized group LEN and F/TDF and its 95% exact CIs are calculated using the method proposed by Ulm 1990. The 95% CI of the rate difference will be calculated using a hybrid approach {Li 2011} The following example SAS code will be used for calculating these CIs:

```
/*Hybrid CI*/
data test;
   alpha=0.05;
   zval = -quantile("Normal", alpha);

   x1=42; *Number of HIV Infections in LEN arm;
   x2=101; *Number of HIV Infections in F/TDF arm;
   f1=500; *Total Person-Years Follow Up in LEN arm;
   f2=400; *Total Person-Years Follow Up in F/TDF arm;

    hat1 = x1/f1;
    hat2 = x2/f2;
    diff = hat1 - hat2;

      /*Rate Difference: Hybrid CI*/
    l1 = quantile("CHISQ", alpha/2, 2*x1)/(2*f1); *Ulm lower exact CI;
    u1 = quantile("CHISQ", 1-alpha/2, 2*x1+2)/(2*f1); *Ulm upper exact CI;
    l2 = quantile("CHISQ", alpha/2, 2*x2)/(2*f2); *Ulm lower exact CI;
    u2 = quantile("CHISQ", 1-alpha/2, 2*x2+2)/(2*f2); *Ulm upper exact CI;
    hybriddifflower = hat1 - hat2 - sqrt((hat1 - l1)**2 + (u2 - hat2)**2);
*Lower CI of Rate Difference (LEN-F/TDF);
    hybriddiffupper = hat1 - hat2 + sqrt((hat1 - u1)**2 + (l2 - hat2)**2);
*Upper CI of Rate Difference (LEN-F/TDF);
run;
```

The following example SAS code will be used for calculating the 1-sided p-value for the hypothesis H03: LEN – TVD >= 0.8/100 PY:

```
proc fcmp;

function pvalue(alpha);
y1 = 7; /* number of infections in arm1 */
y2 = 15; /* number of infections in arm2 */
d1 = 4369.7; /*total follow-up person-years in arm1*/
d2 = 4386.2; /*total follow-up person-years in arm2*/
lambda1 = y1/d1*100; /* estimated incidence in arm1 */
lambda2 = y2/d2*100; /* estimated incidence in arm2 */
l2 = cinv(alpha/2, 2*y2)/(2*d2)*100;
```

```
u1 = cinv(1-alpha/2, 2*(y1+1))/(2*d1)*100;
u_big = lambda1 - lambda2 + sqrt((u1-lambda1)**2+(lambda2-l2)**2); /* upper
bound (U)*/
return(u_big);
endsub;

alpha= solve('pvalue', {.}, 0.8, .)/2; /* U(alpha) = 0.8/100PY */
put 'p-value (U = 0.8): ' alpha;
run;
```

14.4.3. Predicted HIV-1 Incidence Based on Rectal Gonorrhea Rates

For the exploratory analyses, the predicted HIV-1 incidence based on rectal gonorrhea rates and 95% prediction intervals will be calculated using the following SAS code:

```
data meta;
   infile datalines delimiter=',' missover;
   input RecGCrate HIVrate    Source $    Location $;
   datalines;
3.5   ,     2.5   ,     Morris CID 2006              ,     US
2.3   ,     0.9   ,     Jin JAIDS 2010               ,     Australia
9.3   ,     35.2  ,     Sanders AIDS 2013            ,     Kenya
15.5  ,     6.6   ,     Molina IPERGAY NEJM 2015     ,     France
Canada
10.1  ,     3.6   ,     Castillo JAIDS 2015          ,     Peru
6.2   ,     3.8   ,     Kelley AIDS 2015             ,     US
16.1  ,     6.4   ,     McGowan PLOS One 2016        ,     US
33.1  ,     9.0   ,     McCormak PROUD Lancet 2016   ,     UK
33.0  ,     8.3   ,     Girometti Sex TransmInfect 2017,   UK
; run;

proc plot data=meta;
   title 'Removing Sanders';
   plot HIVrate*RecGCrate;
   where source ne 'Sanders';
run;
proc reg data=meta;
   model HIVrate = RecGCrate / CLB r cli clm;
   where source ne 'Sanders';
run;
```

The exact 95% confidence interval for the observed HIV-1 incidence for study participants receiving LEN will be calculated using the exact CIs for the single Poisson parameter method proposed by Ulm (1990) in Section 14.4.2 (SAS code for l1, u1, l2 and u2).

14.5. Safety

14.5.1. Injection site reaction (ISR) to study SC injection

To summarize ISRs by injection visit, each ISR to study SC injection will be associated with one injection visit (eg, Day 1 SC injection, Week 26 SC Injection, Week 52 SC injection, injections every 26 weeks) based on the start date of the ISR. If the start date of the ISR is on or after a given injection visit date and prior to the next injection visit date, if available, the ISR will be associated with that injection visit. Each injection visit consists of 2 SC injections and the first injection date will be used for that visit if injections were split over different dates. An exception is for AEPT of 'injection site nodule' and 'injection site induration' to study SC injection which will be associated with the injection visit collected on the Injection Site Reaction eCRF page.

14.5.2. Pregnancy Related Details

Study Phase (RBP or OLOP) of Pregnancy:

To determine whether pregnancy occurred in either the RBP or OLOP, the following field will be used:

1) If last menstrual period data (LMPD) is not missing, use LMPD to determine the phase;

2) If only the day of LMPD is missing, study phase of pregnancy is determined based on the month;

3) If LMPD is completely missing, or both month and day are missing, use pregnancy confirmed date to determine the phase;

4) If LMPD is prior to TR03SDT (if available), then it is considered as RBP, otherwise, it is considered OLOP.

14.5.3. Laboratory Tests

Lab Tests with Character Values

For lab tests with character results that are not used for summary tables, the scheduled visit record will be flagged at baseline if there are multiple records collected at the same date and time. All records will be displayed in listings (if applicable).

Conversion Factors for Local Laboratory Tests

Local Lab (LBTEST)	Local Lab Reported Conventional Unit	Central Lab Conventional Unit Equivalent
Basophils, Eosinophils Lymphocytes Monocytes Neutrophils, Segmented Platelets Leukocytes	x10^9/L	x10^3/uL
CD4	/mm3	/uL
Erythrocytes	x10^12/L	x10^6/uL

Graded Laboratory Abnormalities

The following labels will be used for treatment-emergent laboratory abnormalities and treatment emergent Grade 3 or higher laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Lymphocytes	Decrease	Lymphocytes (Decreased)*
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Creatinine Clearance	Decrease	Creatinine Clearance (Decreased)
	Direct Bilirubin	Increase	Direct Bilirubin (Hyperbilirubinemia)
	Lipase	Increase	Lipase (Increased)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)**
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
Urinalysis	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative)

* Note: DAIDs toxicity grades for lymphocytes and CD4 are only available for participants without HIV. Lymphocyte grading will not be included on or after the date of HIV infection diagnosis. As CD4 collection begins after HIV infection, CD4 will not be included in the toxicity table summaries.
** Maximum postbaseline grade will be summarized for nonfasting glucose for hyperglycemia (including glucose results without a known fasting status), as nonfasting glucose was not assessed at baseline for many of the participants; therefore, whether an abnormality is treatment-emergent or not cannot be determined for these participants.

Renal related laboratory evaluation (Gilead- computed values)

To calculate laboratory ratios (ie, urine protein to creatinine ratio), the lab value of each test in the ratio needs to be from the same accession number; if any test value used for the ratio calculation from the same accession number is missing, then the ratio is not calculable (ie, missing). For urine creatinine, a value of "< 1" is handled as a missing value in the calculation of related ratios. For urine protein, a value of "< 4.0" is handled as a missing value in the calculation of UPCR.

Summary tables will be based on Gilead-calculated ratios.

Listings will include both Gilead-calculated and LabCorp-calculated ratios.

HCV and HBV Laboratory Test Results

The following table presents the HBV and HCV tests with all possible values. Values that have an asterisk after them denote a "positive" (or "quantifiable" for HBV DNA and HCV RNA) result while all others denote a "negative" result.

Label	LBTESTCD	LBTEST	Possible Values
HBsAg	CNT550	Hepatitis B Virus Surface Antigen	"Positive"*, "Positive, Confirmed"*,"Negative"
HBsAb	CNT353	anti-Hep B Surface Ag2 Qual	"Positive"*, "Negative"
HBcAb	CNT68	Hepatitis B Core Total	"Positive"*, "Negative"
HBV DNA	GET1883	HBV DNA CAP/CTM 2.0-EDTA-CL	"No HBV DNA detected", "<20 IU/mL HBV DNA detected", ">170000000"*, *NUMERICAL VALUE**
HBV DNA	GET2052	Hepatitis B Virus DNA	No HBV DNA Detected, <10 IU/mL HBV DNA Detected, *NUMERICAL VALUE**
HCVAb	CNT534	Hepatitis C Virus Antibody	"Positive"*, "Equivocal", "Negative"
HCV RNA	GET1881	HCV RNA CAP/CTM 2.0EDTA-CL	"No HCV RNA detected", "<15 IU/mL HCV RNA detected", *NUMERICAL VALUE**
HCV RNA	GET2054	HCV RNA Cobas 6800-EDTA-CL	No HCV RNA detected, *NUMERICAL VALUE**

For baseline infection, when considering the different laboratory tests, the latest, non-missing record on or prior to the first dose date for each test (eg, HBsAg, HBsAb, HBcAb, and HBV DNA) are considered.

Participants with HCV infection based on central lab data at baseline are defined as participants with positive HCV antibody (HCVAb) and quantifiable HCV RNA (ie, HCV RNA ≥ 15 IU/mL)

Participants with HBV infection based on central lab data at baseline are defined as participants meet any of the following two criteria:

i) Positive HBsAg on or prior to the first dose date, or

ii) Negative HBsAg, negative HBsAb, positive HBcAb, and quantifiable HBV DNA (ie, HBV DNA ≥ 20 IU/mL) on or prior to the first dose date.

The following tables provide combinations of HBV and HCV tests and the corresponding baseline infection status

HBsAg	HBsAb	HBcAb	HBV DNA	Infection Status
Positive	-	-	-	Y
Negative	Positive	-	-	N
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
	Missing	Positive	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
		Negative	-	N
		Missing	Quantifiable	Null
			Not Quantifiable	N
			Missing	Null
Missing	Positive	-	-	Null
	Negative	Positive	Quantifiable	Y
			Not Quantifiable	Null
			Missing	Null
		Negative	-	Null
		Missing	-	Null
	Missing	-	-	Null

APPENDIX 10. DATA COLLECTION OF COVID-19 DATA

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

1) Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

2) Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Appendix Table 20). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit will be assigned as follows:

a) If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

b) If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same participant and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this participant and this visit will be categorized as "Virtual Visit"

c) Otherwise result is missing

Appendix Table 20. Example Search Terms for "COVID-19" and "Virtual" Used to Identify Missed/Virtual Visits.

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

APPENDIX 11. PREP IMPACTS AND ADMINISTRATION PREFERENCE, ADMINISTRATION AND DOSING, AND NUMERIC PAIN RATING SCALE QUESTIONNAIRES

PrEP Impacts and Administration Preference Questionnaire

PrEP Administration Preference Question

The number and percentage of participants with each PrEP medication preference (daily pill, no preference, injection) will be summarized by visit and by baseline PrEP medication preference.

Question	Coding for Categories
PrEP medication preference (This question merges two questions: 1. If I could take just one kind of PrEP medication, knowing they both worked equally well, I would prefer to take PrEP medication: (a) By injection every six months, (b) I have no preference one way or the other, (c) By a daily pill. 2. I would rate my preference for the PrEP medication I prefer as: (a) Slight preference, (b) Moderate preference, (c) Strong preference.)	3 = Injection, strong preference 2 = Injection, moderate preference 1 = Injection, slight preference 0 = No preference -1 = Pill, slight preference -2 = Pill, moderate preference -3 = Pill, strong preference

PrEP Impact Questions

Question	Coding for Categories
• COVID-19 impact on the preference of take PrEP medication preference	2 = Significantly more preference for an injection every six months 1 = Slightly more preference for an injection every six months 0 = No impact -1 = Slightly more preference for a daily pill -2 = Significantly more preference for a daily pill
• Future expectation to take PrEP medication without missing a dose if mode of administration • Future expectation to feel more protected from HIV if PrEP medication mode of administration	1 = By injection every six months 2 = By a daily pill 3 = No difference; either by injection every six months or by a daily pill,

Question	Coding for Categories
• Bothered by thoughts about my risk of HIV during past week • Worried about judgement from people knowing take PrEP medication, during past week • Worried about judgement from people knowing take PrEP daily pill, during past week • Worried about judgement from people knowing take PrEP injection every six months, during past week • Felt need to hide PrEP medication from others, during past week • Trouble remembering to take PrEP daily pill, during past week • Worried about running out of PrEP daily pill, during past week • Felt protected from getting HIV because of daily pill, during past week • Felt protected from getting HIV because of earlier injection, during past week • Burden taking PrEP daily pill, over last 6 months • Convenient taking PrEP daily pill for my lifestyle, over the last 6 months • Burden taking PrEP injection, over the last 6 months • Convenient taking PrEP injection for my lifestyle, over the last 6 months • Bothered by thoughts about my risk of HIV, during past week • Bothered by thoughts about my risk of HIV by daily pill, during past week • Bothered by thoughts about my risk of HIV by last injection, during past week	-2 = Strongly Disagree -1 = Disagree 0 = Neither Agree nor Disagree 1 = Agree 2 = Strongly Agree

Administration and Dosing Questionnaire

Question	Coding for Categories
• Experienced redness, itching, swelling or bruising around most recent injection • Experienced Pain after injection	0 = Not at all acceptable 1 = A little acceptable 2 = Moderately acceptable 3 = Acceptable 4 = Very acceptable 5 = No

Question	Coding for Categories
• Overall acceptability of most recent injection	0 = Not at all acceptable 1 = A little acceptable 2 = Moderately acceptable 3 = Acceptable 4 = Very acceptable

Numeric Pain Rating Scale Questionnaire

Question	Coding for Categories
• Injection pain rating	This question has numeric response only, ranges from 0 (no pain) to 10 (worst pain imaginable)