CLINICAL STUDY PROTOCOL

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 for HIV Infection
Study Acronym:	PURPOSE 2
Plain Language Short Title:	Pre-Exposure Prophylaxis Study of Lenacapavir in Cisgender Men, Transgender Women, Transgender Men, and Gender Nonbinary People at Risk for HIV Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	153858 Not Applicable NCT04925752
Population Diagnosis or Condition:	Pre-Exposure Prophylaxis of HIV Infection
Protocol ID:	GS-US-528-9023
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date: **Amendment History::**	Amendment 4: 21 October 2024 Original: 01 March 2021 Original Version 2: 10 March 2021 Amendment 1: 08 June 2021 Amendment 2: 31 January 2022 Amendment 3: 25 October 2023 High-level summaries of the histories of amendments are provided in Appendix 8.
Country-specific Requirements:	Country-specific requirements, as applicable, are listed in Appendix 7.

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312).

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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333 Lakeside Drive
Foster City, CA 94404

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IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	153858 Not Applicable NCT04925752
Study Sites Planned:	Approximately 110 sites globally
Objectives:	The primary objective of this study is to evaluate the efficacy of lenacapavir (LEN) in preventing the risk of HIV-1 infection relative to the background HIV-1 incidence rate. Participants are cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender nonbinary people (GNB). The primary objective for the Incidence Phase of this study is to estimate the HIV-1 background incidence rate. The primary objective for the Randomized Blinded Phase of this study is as follows: • To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection

	The secondary objectives for the Randomized Blinded Phase of this study are as follows: • To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF) for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection • To evaluate the efficacy of LEN for HIV-1 PrEP in participants at risk of HIV-1 infection in participants adherent to LEN • To evaluate the safety and tolerability of LEN and F/TDF for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection • To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥ 16 to < 18 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection 
Study Design:	This is a Phase 3, double-blind, multi-site, randomized study to compare HIV-1 incidence in the LEN study drug group with the nonrandomized control of background HIV-1 incidence, defined as the estimated HIV-1 incidence without PrEP in the population studied. F/TDF will serve as the internal active control. This study includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-label Extension (OLE) Phase, and a Pharmacokinetic (PK) Tail Phase. Participants eligible for the Randomized Blinded Phase will be randomized in a 2:1 ratio to receive LEN or F/TDF, respectively.

	Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first data monitoring committee (DMC) review of the unblinded safety data and recommendation to continue the study. Gilead Sciences (Gilead) will notify sites when they may begin enrollment of adolescents.
Number of Participants Planned:	Approximately 3000 participants will be randomized in the Randomized Blinded Phase.
Target Population:	CGM, TGW, TGM, and GNB ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV infection.
Duration of Study Drug Administration:	Participants enrolled in the Randomized Blinded Phase will receive study drug for approximately 52 weeks. Participants transitioning to the LEN OLE Phase will receive SC LEN injections every 26 weeks (± 7 days) until either LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first. Participants eligible for the PK Tail Phase will receive up to 78 weeks of once daily oral F/TDF.
Diagnosis and Main Eligibility Criteria:	<u>Incidence Phase Key Criteria:</u> • 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 16 and 17 years of age) will commence following the first DMC review of the unblinded safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents. • HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months • Sexually active with ≥ 1 partner assigned male at birth (condomless receptive anal sex) in the last 12 months and 1 of the following: — Condomless receptive anal sex with ≥ 2 partners in the last 12 weeks — History of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks — Self-reported use of stimulants with sex in the last 12 weeks

	• Willing and able to comply with study procedures • Prior use of HIV PrEP (including F/TDF or F/TAF) or HIV postexposure prophylaxis (PEP) 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). <u>Randomized Blinded Phase Key Criteria:</u> • 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 • Body weight ≥ 35 kg • Participants of childbearing potential who engage in frontal (vaginal) intercourse must not intend to become pregnant during the study and must agree to utilize protocol-specified method(s) of contraception • 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, which is allowed and does not require medical monitor approval. • Hepatitis B virus (HBV) negative or immune • Participants with severe hepatic impairment are not allowed

Study Procedures/ Frequency:	**Screening Visit** 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 (only if local rapid HIV-1/2 test is positive), DBS storage sample, and plasma storage samples for virology, safety, and/or PK testing • Record serious adverse events (SAEs) and adverse events (AEs) related to protocol-mandated procedures • Obtain medical history, 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 external (penile) and internal (vaginal) condoms and lubricant If the local rapid fourth generation HIV-1/2 Ab/Ag test is positive, participants will undergo confirmatory testing and counseling as appropriate, and study participation will conclude. At the investigator's discretion, a positive local rapid fourth generation HIV-1/2 Ab/Ag test may be separately confirmed by following local testing guidelines in order to facilitate rapid antiretroviral therapy (ART) initiation. Participants who have a negative local rapid fourth generation HIV-1/2 Ab/Ag test and urine pregnancy test (for participants assigned female at birth who are of childbearing potential) and meet the Incidence Phase eligibility criteria will be offered participation in the Randomized Blinded Phase, and if interested, will complete a separate written informed consent (or assent with parental/guardian consent as applicable). After informed consent is provided, the following assessments will be performed: • Blood collection for HBV and hepatitis C virus (HCV) testing, chemistry and hematology profile, eGFR calculation, serum pregnancy test for participants assigned female at birth who are of childbearing potential, and local laboratory asymptomatic syphilis testing

	• Urine collection for urinalysis, urine protein, urine chemistry, and routine asymptomatic sexually transmitted infection (STI) testing for *Neisseria gonorrhoeae* (GC) and *Chlamydia trachomatis* (CT) (for participants assigned female at birth, central laboratory urine *Trichomonas vaginalis* [TV] testing may be performed at the investigator's discretion) • Record SAEs and AEs related to protocol-mandated procedures • Obtain medical history and any prior medications • Complete physical examination including vital signs, weight, height, and waist circumference • Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator. • HIV risk reduction counseling including provision of external (penile) and internal (vaginal) condoms and lubricant • Screening for intimate partner violence and appropriate referral when applicable • Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire Any participant diagnosed with HIV will receive counseling, be referred for local HIV-related care, and study participation will conclude. Eligible HIV-negative participants will return to the study site within 30 days of the screening visit for Day 1/Injection 1 assessments. **Randomized Blinded Phase** On Day 1/Injection 1, after confirmation that all HIV-1/2 tests from the Randomized Blinded Phase screening were negative, a local rapid fourth generation HIV-1/2 Ag/Ab test will be performed to confirm negativity, and participants will be screened for signs and symptoms of acute HIV infection. If rapid HIV-1/2 testing and acute HIV symptom screening are negative and all other eligibility criteria are fulfilled, participants will be randomized in a 2:1 (LEN:F/TDF) ratio to 1 of the following study drug groups: • LEN study drug group: subcutaneous (SC) LEN + placebo-to-match (PTM) F/TDF (N = 2000) • F/TDF study drug group: F/TDF + placebo SC LEN (N = 1000)

	On Day 1/Injection 1, SC LEN 927 mg or placebo SC LEN will be administered at the study site with a PK loading dose of oral LEN 600 mg (2 × 300 mg tablets) or PTM oral LEN tablets (2 tablets). In addition, 2 oral LEN tablets or PTM LEN tablets will be provided to participants to self-administer on Day 2. If a participant misses the Day 2 dose, the dose should be administered immediately upon realizing the dose was missed. Subsequently, SC LEN or placebo SC LEN will be administered at the study site every 26 weeks (± 7 days). Participants will also receive oral F/TDF (200/300 mg) or PTM F/TDF to self-administer daily starting on Day 1/Injection 1. The site staff will contact the participant 1 week (± 2 days) after injection to assess for any injection site reactions (ISRs) and to confirm the participant has administered the Day 2 dose. At each injection visit, participants will be observed for approximately 30 minutes after each SC injection administration. Participants will attend study visits on Day 1/Injection 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days) thereafter until all enrolled participants have completed at least 52 weeks of follow-up in the study and the primary analysis is completed. This will indicate the end of the Randomized Blinded Phase. On Day 1/Injection 1, the following assessments will be performed: • Urine collection for routine asymptomatic STI testing for GC and CT (for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion); urinalysis, urine proteins, and urine chemistry; urine storage sample; and urine pregnancy test for participants assigned female at birth who are of childbearing potential • Blood collection for chemistry, hematology, and metabolic assessments; eGFR calculation; local rapid fourth generation HIV-1/2 Ab/Ag test; central HIV-1/2 testing; HIV-1 RNA quantitative NAAT; HIV-1 recency assay (run as indicated based on HIV test results); CD4 cell count (only if local HIV-1/2 test is positive); DBS storage sample; plasma and serum storage samples for virology, safety, and/or PK testing; serum pregnancy testing (in the event of a positive urine pregnancy test), local laboratory asymptomatic syphilis testing • Targeted (symptom-directed) physical examination • Vital signs, height, weight, and waist circumference

	• Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator. • Questionnaires: — Integrated Sexual Behaviors and Alcohol and Substance Use — PrEP Impacts and Administration Preference Questionnaire - Day 1 — Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection) • Review and record AEs, including screening for any signs and symptoms of acute HIV infection or STIs, and changes in concomitant medications • Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and study retention • HIV risk reduction counseling including provision of external (penile) and internal (vaginal) condoms and lubricant • Screening for intimate partner violence and appropriate referral when applicable Any participant with signs or symptoms consistent with acute HIV infection will undergo Day 1/Injection 1 procedures but will not receive study drug until HIV negative status is confirmed by a central laboratory fourth generation HIV-1/2 Ab/Ag test and HIV-1 RNA quantitative NAAT. At Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days) thereafter in the Randomized Blinded Phase, the following assessments will be performed: • Urine collection for asymptomatic STI testing for GC and CT (for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion); urinalysis, urine proteins, and urine chemistry; urine storage sample; and urine pregnancy test for participants assigned female at birth who are of childbearing potential

	• Blood collection for chemistry and hematology profile; metabolic assessments and HBV and HCV testing (Week 26/Injection 2, Week 52, and every 26 weeks thereafter); eGFR calculation; local rapid fourth generation HIV-1/2 Ab/Ag test; central HIV-1/2 testing; HIV-1 RNA quantitative NAAT storage sample; DBS storage sample; plasma and serum storage samples for virology, safety, and/or PK testing; serum pregnancy test (in the event of a positive urine pregnancy test), local laboratory asymptomatic syphilis testing (Week 13 and every 13 weeks thereafter) • One week (± 2 days) after each injection, participants will be contacted for a postinjection follow-up assessment. • Questionnaires: — Adherence to Oral Study Product Questionnaire: Weeks 4, 8, 13, and every 13 weeks thereafter — Integrated Sexual Behaviors and Alcohol and Substance Use: Week 13 and every 13 weeks thereafter — Administration and Dosing Questionnaire for PrEP Medication: Weeks 13, 39, and 13 weeks after each injection visit thereafter — PrEP Impacts and Administration Preference Questionnaire: Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits — Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection): Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits • Targeted (symptom-directed) physical examination • Vital signs, height, weight, and waist circumference • Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing (Week 13 and every 13 weeks thereafter). Swabs may be self-collected by the participant at the discretion of the investigator. • Review and record AEs, including screening for any signs and symptoms of acute HIV infection or STIs, and changes in concomitant medications • Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and study retention

	• HIV risk reduction counseling including provision of external (penile) and internal (vaginal) condoms and lubricant • Screening for intimate partner violence and appropriate referral when applicable Participants assigned female at birth who are of childbearing potential are required to use effective contraception for the duration of the study. Any participant who becomes pregnant after randomization may remain in the study and continue to receive study drug after a reconsent process in which they will be informed of the benefits and risks of continuing receipt of study drug and the collection of birth outcomes for the child and lactation information. Participants who are taking testosterone and become pregnant during the study must discontinue testosterone if continuing the pregnancy and wish to continue on study drug. The outcome of the pregnancy should be reported to Gilead Patient Safety throughout the study, including the protocol-defined follow-up period. Participants randomized to LEN who decline to participate in the LEN OLE Phase will transition to the PK Tail Phase at this visit (ie, End of Randomized Blinded Phase visit will coincide with PK Tail Day 1 visit). Participants randomized to F/TDF who decline to participate in the LEN OLE Phase will complete the early study drug discontinuation (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 who prematurely discontinue blinded study drug during the Randomized Blinded 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. **Lenacapavir Open-Label Extension Phase** Following completion of the primary analysis, if LEN demonstrates acceptable safety and efficacy in the Randomized Blinded Phase, the study will proceed to the LEN OLE Phase. All participants who still remain on randomized blinded study drug at the time of the End of Randomized Blinded Phase visit will have the option to transition to the LEN OLE Phase at this visit (ie, End of Randomized Blinded Phase visit will coincide with LEN OLE Day 1 visit).

	Participants will receive SC LEN injections every 26 weeks (± 7 days) in the LEN OLE Phase until either LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first. LEN OLE Day 1 will coincide with the end of the Randomized Blinded Phase. Participants randomized to LEN in the Randomized Blinded Phase who choose to participate in the LEN OLE Phase will receive SC LEN every 26 weeks (± 7 days) and have study visits every 13 weeks (± 7 days). The SC LEN injection visits in the LEN OLE Phase will be determined by the previous LEN injection (ie, participants whose last LEN injection was 13 weeks before LEN OLE Day 1 will receive their first open-label LEN injections at the LEN OLE Week 13 visit; participants whose last LEN injection was 26 weeks before LEN OLE Day 1 will receive their LEN injections at the LEN OLE Day 1 and Week 26 visits) and every 26 weeks thereafter. Participants randomized to F/TDF in the Randomized Blinded Phase will switch to SC LEN and have study visits at LEN OLE Day 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days) thereafter. Subcutaneous LEN will be administered at the LEN OLE Day 1, Week 26, and every 26 weeks thereafter. These participants will also receive a loading dose of oral LEN on LEN OLE Days 1 and 2, as described in the Randomized Blinded Phase. If a participant misses the Day 2 dose, the dose should be administered immediately upon realizing the dose was missed. The site staff will contact the participant 1 week (± 2 days) after injection to assess for any ISRs and to confirm the participant has administered the Day 2 dose. Participants will complete the LEN OLE Phase once LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first. Upon completion of the LEN OLE Phase or discontinuation of the study, participants will transition to locally available PrEP, which may include lenacapavir or other available PrEP modalities as clinically indicated. If a participant chooses to end participation in the LEN OLE Phase prior to conclusion, then the participant will complete an ESDD visit, be referred to locally available PrEP services as clinically indicated, and will complete a 30-day follow-up visit. The following assessments will be performed at the LEN OLE Phase study visits: • Urine collection for routine asymptomatic STI testing for GC and CT (for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's

	discretion) (End of Randomized Blinded Phase visit/LEN OLE Day 1, and every 13 weeks thereafter); urinalysis; urine storage sample (End of Randomized Blinded Phase visit/LEN OLE Day 1 only); and urine pregnancy test for participants assigned female at birth who are of childbearing potential • Blood sample collection for chemistry (every 26 weeks) and hematology profile (every 26 weeks); metabolic assessments and HBV and HCV testing (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 52 weeks thereafter); eGFR calculation (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 26 weeks thereafter); local rapid fourth generation HIV-1/2 Ab/Ag test; central HIV-1/2 testing; HIV-1/2 RNA qualitative NAAT storage sample; DBS storage sample (End of Randomized Blinded Phase visit/LEN OLE Day 1 only); Anytime plasma PK sample; plasma and serum storage samples for virology, safety, and/or PK testing; serum pregnancy test (in the event of a positive urine pregnancy test); local laboratory asymptomatic syphilis testing (End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter) • Targeted (symptom-directed) physical examination • Vital signs, height, and weight • Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing (End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter). Swabs may be self-collected by the participant at the discretion of the investigator. • Review and record AEs, including screening for any signs and symptoms of acute HIV infection or STIs and changes in concomitant medications • Adherence counseling to encourage the importance of attending study visits in a timely fashion, adherence to study drug injections, and retention • HIV risk reduction counseling including provision of external (penile) and internal (vaginal) condoms and lubricant • Screening for intimate partner violence and appropriate referral when applicable • One week (± 2 days) after each injection participants will be contacted for a postinjection follow-up assessment. • Questionnaires (until and including LEN OLE Week 52):

	— Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire: End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter — Administration and Dosing Questionnaire for PrEP Medication: 13 weeks after each injection visit — Experienced Preference for PrEP Medication Questionnaire: every injection visit — Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection): every injection visit — Adherence to Oral Study Product Questionnaire: End of Randomized Blinded Phase visit/LEN OLE Day 1 only Upon completion of the LEN OLE or discontinuation of the study, participants will transition to locally available PrEP, which may include lenacapavir or other available PrEP modalities as clinically indicated. If a participant chooses to end participation in the LEN OLE Phase prior to conclusion, then the participant will complete an ESDD visit, be referred to locally available PrEP services as clinically indicated, and will complete a 30-day follow-up visit. **Pharmacokinetic Tail Phase** Participants who prematurely discontinue study drug in the Randomized Blinded Phase will transition to the PK Tail Phase to receive OL oral F/TDF once daily for up to 78 weeks to cover the PK tail and complete visits every 13 weeks (± 7 days). Upon unblinding, participants who were randomized to LEN in the Randomized Blinded Phase who decline to participate in the LEN OLE Phase will transition to the PK Tail Phase. Upon unblinding, participants who were randomized to F/TDF in the Randomized Blinded Phase who decline to participate in the LEN OLE Phase will complete the ESDD visit, transition to local HIV prevention services, and return for a 30-day follow-up visit. See Appendix 7 for US-specific text. The following assessments will be performed at the PK Tail Phase study visits: • Urine collection for routine asymptomatic STI testing for GC and CT (for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's

	discretion); urinalysis, urine proteins, and urine chemistry; and urine pregnancy test for participants assigned female at birth who are of childbearing potential • Blood collection for chemistry and hematology profile; metabolic assessments and HBV and HCV testing (PK Tail Day 1 and every 52 weeks thereafter); eGFR calculation; local rapid fourth generation HIV-1/2 Ab/Ag test; central HIV-1/2 testing; HIV-1 RNA quantitative NAAT storage sample; DBS storage sample (PK Tail Day 1 for participants who prematurely discontinue study drug during the Randomized Blinded Phase, Week 13, and every 13 weeks thereafter); anytime plasma PK sample; plasma and serum storage samples for virology, safety, and/or PK testing; serum pregnancy test (in the event of positive urine pregnancy test); local laboratory asymptomatic syphilis testing • Targeted (symptom-directed) physical examination • Vital signs, height, and weight • Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator. • Review and record AEs, including screening for any signs and symptoms of acute HIV infection or STIs and changes in concomitant medications • Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and retention • HIV risk reduction counseling including provision of external (penile) and internal (vaginal) condoms and lubricant • Screening for intimate partner violence and appropriate referral when applicable

	• Questionnaires: — Integrated sexual behaviors and alcohol and substance use: PK Tail Day 1, Week 13, and every 13 weeks thereafter — PrEP Impacts and Administration Preference Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase — Administration and Dosing Questionnaire for PrEP Medication: PK Tail Day 1 — Adherence to Oral Study Product Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase, Week 13, and every 13 weeks thereafter Participants who permanently discontinue study drug during the PK Tail Phase will complete an ESDD visit and a 30-day follow-up visit. See Appendix 7 for US-specific text
Test Product, Dose, and Mode of Administration:	**Randomized Blinded Phase** SC LEN 927 mg injection, 309 mg/mL (2 × 1.5 mL) administered every 26 weeks starting on Day 1/Injection 1 and oral LEN 600 mg (2 × 300 mg tablets) administered on Day 1/Injection 1 and Day 2. **Lenacapavir Open-Label Extension Phase** SC LEN 927 mg injection, 309 mg/mL (2 ´ 1.5 mL) administered every 26 weeks. Participants randomized to F/TDF in the Randomized Blinded Phase will also be administered oral LEN 600 mg (2 ´ 300 mg tablets) on LEN OLE Days 1 and 2.
Reference Therapy, Dose, and Mode of Administration:	**Randomized Blinded Phase** F/TDF fixed-dose combination (200 mg emtricitabine/300 mg tenofovir disoproxil fumarate), administered orally once daily with or without food. PTM F/TDF, administered orally once daily Placebo for SC LEN injection (2 × 1.5 mL) administered every 26 weeks and PTM oral LEN (2 tablets) administered on Day 1/Injection 1 and Day 2. **Pharmacokinetic Tail Phase** F/TDF, administered orally once daily
Criteria for Evaluation:	

Safety:	Occurrence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP.
Efficacy:	Diagnosis of HIV-1 infection is the primary endpoint for the Randomized Blinded Phase for both primary objectives of this study.
Pharmacokinetics:	LEN plasma levels
Adherence:	1) On-time LEN injection administration 2) Adherence to F/TDF assessed using intracellular TFV-DP levels in DBS
Questionnaires:	The following self-reported data will be assessed by questionnaires: 1) Adherence 2) Integrated sexual behaviors and alcohol and substance use 3) Numeric pain rating scale – injection pain 4) Administration and dosing for PrEP medication 5) PrEP impacts and administration preference
Statistical Methods:	The primary objective of the study will be achieved by showing that the HIV-1 incidence (per 100 person-years [PY]) in the LEN study drug group during the study is significantly lower than the background incidence rate with 1-sided alpha of 0.025. The background incidence rate will be calculated from the Incidence Phase based on the HIV-1 recency assay result using an HIV-1 incidence formula similar to Kassanjee, et al {Kassanjee 2012}. The incidence rate ratio of the LEN study drug group to the background, the associated 95% CI, and p-value will be calculated using the delta method {Gao 2021} or a likelihood-based method {Shao 2024} if the number of HIV-1 infections in the LEN group is zero. The primary analysis will be conducted when all enrolled participants have completed a minimum of 52 weeks (1 year) of follow-up in the study or prematurely discontinued from the study (whichever occurs first) after randomization. Key (α-controlled) secondary analyses will be 1) to assess whether the HIV-1 incidence rate ratio of the LEN study drug group is at least 20% lower than the background incidence rate and the point estimate of LEN/background HIV ≤ 0.5, 2) to assess whether the HIV-1 incidence in the LEN study drug group is at most 0.8 per 100 PY higher than the HIV-1 incidence in the F/TDF study drug group, and 3) to assess whether the HIV-1 incidence in the LEN study drug group is significantly lower than the HIV-1 incidence in the F/TDF study drug group. The overall type 1 error rate for these analyses will

	be controlled at $\alpha = 0.025$ (1-sided) by following a fixed-sequence gatekeeping approach in the sequential order listed in Section 8.7. A secondary analysis of the HIV-1 incidence rate will be the comparison with one-half of the lower bound of the 95% CI of the nonrandomized control background HIV-1 incidence rate reported as 3.49 (3.05, 3.92) {Mera 2020}. This analysis will estimate the HIV-1 incidence and its 95% CI for the LEN study drug group based on the Full Analysis Set and will conclude significance for the secondary analysis if the upper bound of the 95% CI is lower than 1.525 (half of 3.05). The concurrent background HIV-1 incidence rates will also be estimated by other methods. These will include prerandomization methods such as recent epidemiologic data, and postrandomization methods such as correlation of rectal gonorrhea rates with HIV-1 incidence. Descriptive statistics will summarize baseline characteristics, exposure to study drug, follow-up time, and all safety measures in the entire population and specifically in adolescents. A total sample size of 3000 is considered. With 2000 participants in the LEN study drug group, the study will have > 95% power to show at least a 20% reduction compared with the background HIV-1 incidence rate. The sample size estimate is based on the following assumptions and considerations: • Background HIV-1 incidence of 3.00/100 PY • LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 compared with the nonrandomized control of background HIV-1 incidence • 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 MDRI and FRR are based on the Sedia Lag assay {Kassanjee 2016}. These assay parameters are still under investigation and may be fine-tuned further. An external DMC (data monitoring committee) will evaluate the safety and efficacy of LEN in this population. The first data review meeting of the DMC will be convened 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 beyond 600 participants before the safety review is conducted and, if determined by the DMC, the study is allowed to continue. Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first DMC review of the unblinded safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents. Data monitoring committee safety review meetings will occur approximately annually thereafter during the Randomized Blinded Phase of the study. The DMC will formally evaluate efficacy data, only once, after 50% of participants enrolled have completed at least 52 weeks of follow-up in the study or prematurely discontinued from the study. The DMC may recommend stopping the study early if the prespecified evaluation criteria are met. If the Randomized Blinded Phase is stopped early due to an efficacy outcome, the interim analysis will serve as the primary analysis. The DMC will have access to treatment codes for all their reviews.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
%CV	percentage coefficient of variation
3TC	lamivudine
Ab	antibody
AE	adverse event
Ag	antigen
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the concentration versus time curve
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
$AUC_{x\text{-}xx}$	partial area under the concentration versus time curve from time “x” to time “xx”
BCRP	breast cancer resistance protein
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
BL	baseline
BLQ	below the limit of quantitation
bNAb	broadly neutralizing antibody
CA	capsid protein
CBC	complete blood count
CC_{50}	half maximal cytotoxic concentration
CD4	cluster determinant 4
CDC	Centers for Disease Control and Prevention
CGM	cisgender men
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
C_{min}	minimum observed concentration of drug
COBI, C, co	cobicistat (Tybost®)
COC	combination oral contraceptives

CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	*Chlamydia trachomatis*
C_{trough}	concentration at the end of the dosing interval
C_{Week26}	concentration at the end of the dosing interval at Week 26
CYP	cytochrome P450 enzyme
DAIDS	Division of AIDS
DBS	dried blood spot
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRV	darunavir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
E2	17β-estradiol
EC	ethics committee
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EE	ethinylestradiol
eCRF	electronic case report form
EDC	electronic data capture
EFV	efavirenz
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
ETV	etravirine
EU	European Union
F	relative bioavailability
F/TAF	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
FA	free acid
FAS	Full Analysis Set
FAM	famotidine
FDA	Food and Drug Administration
FDC	fixed-dose combination
FRR	false recency rate
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
GAHT	gender-affirming hormone therapy
GC	*Neisseria gonorrhoeae*
GCP	Good Clinical Practice
GFR	glomerular filtration rate

GGT	gamma glutamyltransferase
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GNB	gender nonbinary people
HbA_{1c}	hemoglobin A_{1c}
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HTE	heavily treatment-experienced
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug
ISR	injection site reaction
IQ	inhibitory quotient
IQR	interquartile range
IQ4	inhibitory quotient of 4
IQ6	inhibitory quotient of 6
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEN	lenacapavir
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MDRI	mean duration of recent infections
MDZ	midazolam
MSM	men who have sex with men
MTCT	mother-to-child transmission

NAAT	nucleic acid amplification test
NaS	LEN injection
NaSP	LEN injection with poloxamer
ND	not determined
NHP	nonhuman primate
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NVP	nevirapine
OATP	organic anion transporting polypeptide
OBR	optimized background regimen
OL	open-label
OLE	open-label extension
$paEC_{95}$	protein-adjusted 95% effective concentration
PEG	polyethylene glycol
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	principal investigator
PIT	pitavastatin
PK	pharmacokinetic(s)
PWH	people with HIV
PO	oral
POC	proof of concept
PopPK	population pharmacokinetic
PR (interval)	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PrEP	pre-exposure prophylaxis
PS	Patient Safety
PT	preferred term
PTM	placebo-to-match
PY	person-years
Q1	first quartile
Q3	third quartile
Q6MO	every 6 months
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formulation
RTV	ritonavir
RBP	randomized blinded phase

RIF	rifampin
RNA	ribonucleic acid
ROS	rosuvastatin
rSE	relative standard error
SAE	serious adverse event
SAHCS	Southern African HIV Clinicians' Society
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SDV	source data verification
SHIV	simian human immunodeficiency virus
SIV	simian immunodeficiency virus
SOC	system organ class
SOP	standard operating procedure
SSRs	special situation reports
STI	sexually-transmitted infection
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TAF	tenofovir alafenamide (Vemlidy®)
TDF	tenofovir disoproxil fumarate (Viread®)
TEAE	treatment-emergent adverse event
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TGM	transgender men
TGW	transgender women
T_{max}	time (observed time point) of C_{max}
TN	treatment naive
TPV	tipranavir
TV	Trichomonas Vaginalis
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
UNAIDS	Joint United Nations Programme on HIV/AIDS
UWDIS	University of Washington Drug Interaction Solutions
US	United States
VL	viral load
VORI	voriconazole
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there were 1.7 million new human immunodeficiency virus type 1 (HIV-1) infections in 2019, despite efforts to improve human immunodeficiency virus (HIV) testing, linkage to treatment, and prevention {UNAIDS 2020}. From 2008 through 2018, the rates of new HIV-1 infections in the United States (US) were consistently stable in the population as a whole, and stabilized at high rates in men who have sex with men (MSM) after more than a decade of increases {Centers for Disease Control and Prevention 2017}. However, notable disparities exist in the impact of the HIV epidemic on racial and ethnic minorities in the US, with Black and Hispanic/LatinX MSM being disproportionally affected {Hess 2017}. In 2018, Black Americans accounted for 13% of the US population but 42% of new HIV diagnoses {Becasen 2019}. Epidemiologic studies have estimated that 1 in 6 MSM, including 1 in 2 Black, 1 in 5 Latino, and 1 in 11 White MSM, will be diagnosed with HIV in their lifetime. The HIV epidemic has also disproportionally affected transgender women (TGW); in the US, an estimated 42% of TGW are living with HIV, with evidence of intersectional compounding of disproportionate risk, as the majority of TGW living with HIV are Black (62%) or Latina (35%) compared with less than 17% in White TGW {Centers for Disease Control and Prevention (CDC) 2021, Clark 2017}. Transgender men (TGM) and gender nonbinary people (GNB) are an understudied population and there are limited HIV incidence data; however, recent studies suggest ongoing HIV risk due to low HIV testing. In Brazil and Peru, the HIV epidemic also disproportionately affects MSM and TGW {Chow 2016, Saffier 2017}. In South Africa, there is a generalized HIV epidemic, with growing recognition of disproportionately higher HIV incidence in MSM and TGW {Sandfort 2021, Sullivan 2020}. There remains an important unmet medical need globally for improved approaches to HIV prevention, including new options for HIV pre-exposure prophylaxis (PrEP).

There are now 2 highly safe and efficacious options for HIV PrEP in MSM and TGW, Descovy® (DVY) and Truvada® (TVD), approved in 2019 and 2012, respectively. In locations where uptake of PrEP is high, there has been a significant population-level reduction in HIV incidence, demonstrating the potential for PrEP to contribute to population-wide HIV control {Grulich 2018, Sullivan 2018}. However, for many individuals at risk for HIV, the uptake of daily oral PrEP has been a challenge. In the US, it is estimated that 1.1 million persons are at risk for HIV, yet only 240,000 are on DVY or TVD, and another > 400,000 started but have stopped daily oral PrEP. The underutilization of PrEP is particularly striking in populations that are disproportionately affected by HIV incidence, particularly in Black TGW {Klein 2019}. Several reasons likely contribute to the suboptimal uptake of PrEP, including lack of health system accessibility, medical mistrust due to experiences of homophobia, transphobia, and stigma, lack of willingness to take daily oral PrEP, concerns about side effects, and low self-perception of risk {Centers for Disease Control and Prevention (CDC) 2017, Wood 2019}. Among TGW, additional concerns about drug interactions with gender-affirming hormones have been identified as a significant barrier to PrEP uptake, despite increasing PrEP awareness {Poteat 2019}. Similar challenges have been identified as barriers to PrEP adherence and persistence in those who begin

daily oral PrEP, including stigma, an unacceptable dosing regimen, side effects, and low-risk perception. Even among TGW with health insurance and access to health care, significant disparities exist in daily oral PrEP uptake compared with cisgender MSM {Liu 2018}. Among TGM and transmasculine individuals in the US in a 2019 survey, 25% met eligibility criteria for PrEP, and yet only 11% had been prescribed PrEP {Golub 2019, Reisner 2019}. Recent data from gay-identified TGM who have sex with cisgender male partners revealed a higher eligibility for PrEP (55%) and yet only 22% of this sample were currently using PrEP.

Taken together, persistent disparities exist in ongoing HIV incidence in Black, Hispanic/LatinX MSM and TGW populations, with the greatest disparities in Black TGW in the US, and with continued low uptake of PrEP in these disproportionately affected populations globally. These barriers clearly highlight the need for additional PrEP options that may address disparities to PrEP uptake. LEN (6-monthly subcutaneous [SC] injections) have the potential to provide an additional option for populations at risk of HIV acquisition. LEN can help address substantial existing PrEP barriers including 1) requirement for daily adherence, 2) stigma and concerns about disclosure and discrimination or other social harms, 3) oral medication-associated adverse events (AEs) including gastrointestinal tolerability, and 4) challenges with access to health care providers in overburdened health systems or in geographical PrEP deserts. Thus, LEN has the potential to increase the uptake of, adherence to, and thereby the scalability of PrEP in those populations most disproportionately affected by HIV-1 which will contribute to the overarching goal of ending the HIV-1 epidemic.

1.2. Study Drugs

1.2.1. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF; Truvada)

Truvada has been approved in 52 countries for PrEP in combination with safer sex practices in adults and in 34 countries for PrEP in combination with safer sex practices in adolescents.

Further information is available in the local prescribing information for F/TDF (Truvada).

1.2.2. Emtricitabine/Tenofovir Alafenamide (F/TAF; Descovy)

See Appendix 7 for US-specific text.

1.2.3. Lenacapavir

1.2.3.1. General Information

Lenacapavir (LEN) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function being developed for the treatment of HIV-1 infection. LEN inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production and proper capsid core formation. Virus produced in the presence of LEN display aberrantly shaped capsids. These malformed virus particles can still infect a new target cell but cannot replicate as they are unable to support reverse transcription without a properly formed capsid core.

LEN is characterized by potent antiviral activity, a novel resistance profile, low human clearance, and low aqueous solubility. These combined characteristics allow LEN to be well suited for an extended-release parenteral formulation that can potentially be used as a novel long-acting antiretroviral (ARV) treatment administered monthly or less frequently.

For further information on LEN, refer to the current investigator's brochure (IB) for LEN.

1.2.3.2. Preclinical Pharmacology and Toxicology

1.2.3.2.1. Preclinical Pharmacology

LEN is a novel, potent, and highly selective multistage inhibitor of HIV-1 replication in the MT-4 T-cell line, in primary human cluster determinant (CD)4 positive T-lymphocytes, and in monocyte-derived macrophages, with half-maximal effective concentration (EC_{50}) and selectivity index (half-maximal cytotoxic concentration [CC_{50}]/EC_{50}) values ranging from 0.030 to 0.19 nM and 140,000 to > 1,670,000, respectively. LEN exhibits consistent antiviral activity against multiple HIV-1 clinical isolates with EC_{50} values ranging from 0.02 to 0.16 nM. LEN also shows potent antiviral activity against HIV-2 isolates but was at least 15-fold less active relative to HIV-1. The antiviral activity of LEN is affected by the level of infection in a manner similar to other ARVs but was still 5- to > 100-fold more potent relative to other ARVs at the highest multiplicity of infection tested.

LEN acts by inhibiting the proper functioning of HIV-1 capsid. LEN binds with high affinity and specificity to recombinant HIV-1 capsid protein and is a potent inhibitor of both early- and late-stage capsid-mediated processes essential for HIV-1 replication. LEN interferes with late-stage virus production and capsid core formation events and with an early-stage process occurring after reverse transcription but before the integration of viral DNA. LEN interferes with HIV-1 nuclear entry as measured by the accumulation of integration products and abortive 2-LTR-containing circles, both of which form exclusively in the nucleus. The LEN binding site is highly conserved and is shared by host proteins implicated in HIV-1 nuclear entry.

Resistance studies indicated that LEN will be clinically active against HIV-1 variants with reduced susceptibility to other ARV classes. LEN shows synergistic antiviral activity and no antagonism in combination with agents from other ARV classes. LEN shows low cytotoxicity in primary human hepatocytes and in several nontarget human cell lines of different tissue origin (CC_{50} values > 44 to 50 μM). Resistance selection assays suggest that the target clinical plasma exposure for LEN (plasma concentrations > 16 nM, corresponding to an inhibitory quotient [IQ] of > 4) is expected to provide sufficient barrier to drug resistance development relative to other ARVs presently used in the clinic.

1.2.3.2.2. Preclinical Toxicology

LEN was considered not genotoxic in either in vitro or in vivo assays. The potential for LEN to be phototoxic is low. The lack of systemic toxicity after LEN oral and SC administration is not unexpected based on the specific viral target. Expected local injection site reactions (ISRs) (granulomatous inflammation) were observed histologically after SC administration in rats, dogs,

and rabbits. The chronic granulomatous inflammation reaction at the injection site in rats and dogs is a foreign body response to the LEN SC depot and is an expected host response. Granulomatous inflammation has been observed after SC and intramuscular implantation of bioactive material, including those for HIV treatment {Anderson 1997, Shah 2017, Van't Klooster 2010}.

No adverse effects occurred in a male and female fertility study in rats that evaluated potential effects in the reproductive process resulting from SC administration of a long-acting LEN formulation. Endpoints included evaluation of estrous cycling, tubal transport, implantation, development of the preimplantation stages of the embryo in the female, and functional reproductive effects (alterations in libido and epididymal sperm maturation) in the male.

Embryo-fetal toxicity studies were conducted with LEN in rats via oral administration and in rabbits via intravenous (IV) administration. No adverse effects occurred upon external, visceral, and skeletal examination.

LEN was well tolerated after 6 months of exposure in rats when administered as a single 100-mg/kg SC dose via polyethylene glycol (PEG) 300/ethanol/water solutions. No systemic toxicity was observed. LEN-related nonadverse edema, macroscopic thickening and/or tan discoloration, and correlative granulomatous inflammation were present at the SC injection site. LEN was also well tolerated after 9 months of exposure in dogs when administered as monthly SC doses of 20 or 40 mg/kg via PEG 300/ethanol/water solutions. No systemic toxicity was observed. LEN-related nonadverse edema and erythema and correlative microscopic observations of necrosis, granulomatous inflammation, mixed cell inflammation, and/or hemorrhage were present at the SC injection sites of animals administered LEN. Adverse SC injection site necrosis was noted in animals administered 20 mg/kg/dose with sodium hydroxide or 40 mg/kg/dose without sodium hydroxide in the vehicle.

1.2.3.3. Efficacy of HIV Capsid Inhibitor in Nonhuman Primate PrEP Model

1.2.3.3.1. Nonhuman Primate Proof of Concept for PrEP Efficacy

Proof-of-concept (POC) data to support evaluation of ARV drugs for HIV-1 prophylaxis were provided by the nonhuman primate (NHP) model for simian immunodeficiency virus (SIV)/simian human immunodeficiency virus (SHIV) transmission {Tsai 1995}. The model uses a repeat rectal challenge in rhesus macaques that has demonstrated prophylactic efficacy of tenofovir (TFV) (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) ± emtricitabine (FTC), and has been further validated with correlative positive data from the highly-adherent participants in PrEP clinical studies receiving daily PrEP regimens (eg, iPrEx, IPERGAY, and DISCOVER).

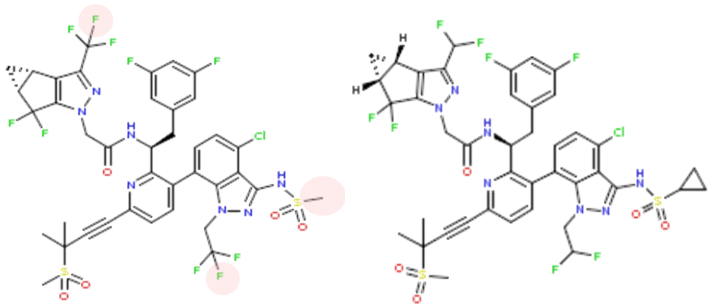
1.2.3.3.2. HIV Capsid Inhibitor Lenacapavir

Lenacapavir (LEN, formerly GS-6207) is the first clinically validated HIV capsid inhibitor with a unique, multistage mechanism of action {Link 2020}. Lenacapavir binds at a highly conserved interface between capsid protein (CA) monomers, thereby disrupting multiple late-stage and early-stage CA-mediated processes essential during viral replication. A long-acting formulation of LEN has demonstrated potent antiviral activity (up to 2.3 $\log_{10}$ decline in HIV-1 RNA after 9 days of monotherapy) and a potential for twice-yearly SC dosing in a Phase 1b study (GS-US-200-4072){Link 2020}. Additionally, LEN has demonstrated potent antiviral activity in a Phase 2/3 study (GS-US-200-4625) in heavily treatment-experienced (HTE) people with HIV (PWH) failing their current regimen {Segal-Maurer 2021}.

1.2.3.3.3. GS-CA1, A Close Analog of Lenacapavir

GS-CA1, a close analog of LEN, is an HIV-1 capsid inhibitor with high antiviral efficacy and long-acting potential as an injectable drug (Figure 1, Table 1). GS-CA1 was used for NHP studies as the compound has demonstrated similar inhibition of HIV and SHIV replication in vitro {Yant 2019}.

Figure 1. Similarity of LEN and GS-CA1 Chemical Structures



GS-6207 GS-CA1

GS-6207 = Lenacapavir (LEN)

Table 1. Comparison of LEN and GS-CA1

Parameter	Analysis	LEN	GS-CA1
In Vitro Antiviral Activity	EC50, MT-4, HIV-1IIIb (nM)	0.100	0.240
	Human paEC95, MT-4, HIV-1IIIb (nM)	4.02	8.26
	EC50, human PBMCs, HIV-1, n=23 (nM)	0.050	0.130
	EC50, rhesus PBMCs, SHIV-SF162P3 (nM)	0.569	0.748
	Rhesus-paEC95, rhPBMCs, SHIV-SF162P3 (nM)	ND	31.5
Compound MoA	Inhibits early or late stages of HIV replication	both	both
In Vitro Cytotoxicity	CC50, Primary Human CD4+ T Cells (μM)	> 50	> 50
Predicted Hepatic Clearance (^{3}H)	Rat/dog/rhesus/ cyno/human (L/h/kg)	0.02/0.06/0.16/ 0.05/0.01	0.06/0.15/0.07/ 0.04/0.02
In Vivo Clearance	Rat/dog/rhesus/cyno (L/h/kg)	0.06/0.11/0.26/0.24	0.08/0.33/0.30/0.21

CC_{50} = half-maximal cytotoxic concentration; CD = cluster determinant; EC_{50} = half-maximal effective concentration; LEN = lenacapavir; MoA = mechanism of action; ND = not determined; paEC95 = protein-adjusted 95% effective concentration; PBMC = peripheral blood mononuclear cell; rh = rhesus; SHIV = simian human immunodeficiency virus

1.2.3.3.4. Efficacy of GS-CA1 in Nonhuman Primate Rectal Challenge PrEP Study

An NHP study was designed to determine the prophylactic efficacy of the capsid inhibitor GS-CA1, an analog of LEN with potent activity against both HIV and SIV capsids, in the preclinical macaque model of HIV/AIDS prevention.

Male and female treatment-naive rhesus macaques (n = 24) were given a single injection of GS-CA1 at 2 dose levels, 150 mg/kg and 300 mg/kg (n = 8 for each dose level), followed by repeat, escalating-dose weekly intrarectal challenges with SHIV. An SC injection of vehicle control, GS-CA1 (150 mg/kg), or GS-CA1 (300 mg/kg) was given to 8 macaques per group, 1 week before virus exposure and followed by up to 15 weekly SHIV162p3 rectal challenges escalating from 10 (n = 8) to 33 (n = 2) to 100 (n = 5) median tissue culture infectious dose.

During the study, 100% (8/8) of placebo-control animals became SHIV RNA positive after a median of 6.5 (range: 1-14) challenges. In contrast, all GS-CA1–dosed animals (150 mg/kg group) remained negative through Week 10 (9 challenges), with 6 of 8 becoming SHIV positive between Weeks 11 and 16. Similarly, all GS-CA1–dosed animals (300 mg/kg group) remained negative through Week 16 (15 challenges), with 3 of 8 becoming SHIV positive after Week 16. Cox regression analysis translated into 86% and 96% per-exposure risk reduction for the low and high dose groups, respectively, and both were highly significant ($p = 0.0061$ and $p = 0.0002$, respectively).

Notably, infections were detected in the GS-CA1–dosed groups only after the drug exposures began to fall below the protein-adjusted 95% effective concentration ($paEC_{95}$) (IQ = 1) when the GS-CA1 concentrations had fallen to 31.5 nM (Table 1).

1.2.3.3.5. Efficacy of GS-CA1 in Nonhuman Primate Vaginal Challenge PrEP Study

Female treatment-naive rhesus macaques (n = 24) were given a single injection of GS CA1 at 2 dose levels, 150 mg/kg and 300 mg/kg (n = 8 for each dose level), followed by repeat weekly vaginal challenges with SHIV. An SC injection of vehicle control, GS-CA1 (150 mg/kg), or GS-CA1 (300 mg/kg) was given to 8 macaques per group, 1 week before virus exposure and followed by up to 10 weekly SHIV162p3 challenges.

During the study 100% (8/8) of placebo control animals became SHIV RNA positive after a median of 4 (range 3 to 8) challenges. The GS-CA1–dosed animals (150 mg/kg group) remained negative through Week 9 (8 challenges), with 6 of 8 becoming SHIV positive between Weeks 10 and 18. The GS-CA1–dosed animals (300 mg/kg group) remained negative through Week 20 (10 challenges) {Bekerman 2021}.

1.2.3.4. Clinical Studies of Lenacapavir

A summary of the relevant available data from studies not yet included in the IB at the time of the development of the GS-US-528-9023 protocol is presented. These data are from 4 Phase 1 clinical studies in healthy volunteers (GS-US-200-4071, GS-US-200-4538, GS-US-200-5709 and GS-US-200-4333), a Phase 1b study in PWH (GS-US-200-4072), an ongoing Phase 2/3 study of LEN together with an optimized background regimen (OBR) in HTE PWH with multidrug resistant infection (GS-US-200-4625), and an ongoing Phase 2 study of LEN in combination with other ARV agents in ARV-naive PWH (GS-US-200-4334).

1.2.3.4.1. Study GS-US-200-4071

GS-US-200-4071 is a completed Phase 1 study in healthy volunteers evaluating the safety, tolerability, and pharmacokinetics (PK) of single and multiple ascending doses of oral LEN as an oral liquid (solution)-filled capsule (50 or 100 mg/mL) or tablet (50 or 300 mg).

Pharmacokinetic Results

The PK results presented here are from a database finalization date of 04 February 2020. As of this date, a total of 50 unique participants have received LEN or placebo capsules and 56 unique participants have received LEN or placebo tablets. Single- and multiple-dose PK data from the 50-mg/mL solution-filled capsule and single-dose PK data from the tablets are presented below.

This study was originally designed as a single ascending dose/multiple ascending dose evaluation of solution in capsule formulations, with 10 days of washout between the single-dose and multiple-dose periods (Part A; Cohorts 1 and 2). Following receipt of PK data from these 2 cohorts suggesting the $t_{1/2}$ was longer than predicted from nonclinical studies, the study design was altered to single ascending dose (Parts B to D).

Within each cohort in Parts A to C, participants were randomized to receive LEN (N = 8) or placebo (N = 2); all treatments were administered under fasted conditions. In Cohorts 1, 2, and 5, capsules containing 50 mg/mL solution were evaluated at doses of 30, 100, and 300 mg, respectively. Following development of a tablet formulation, 50- and 300-mg tablets were evaluated at doses of 300, 900, 1800, and 50 mg in Cohorts 7, 8, 9, and 10, respectively. In Part D, 2 cohorts received OL 300-mg LEN tablets (N = 8) given with a high-fat, high-calorie meal (Cohort 12) or with a low-fat, low-calorie meal (Cohort 13). A brief description of these cohorts is presented in Table 2.

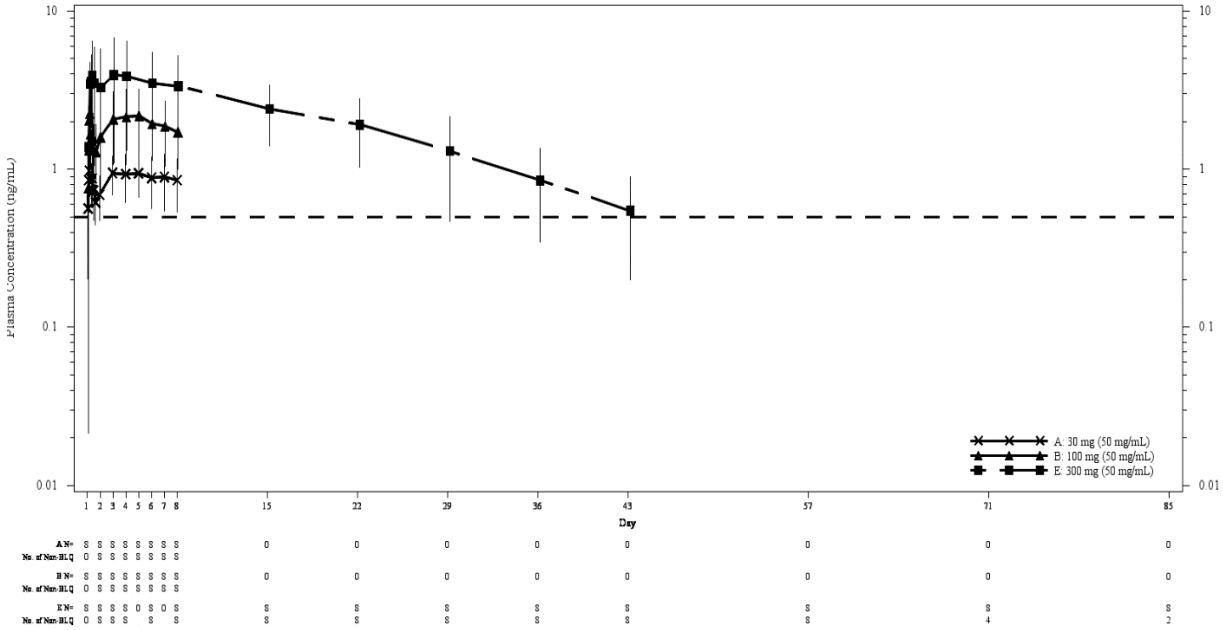
Table 2. GS-US-200-4071: LEN Formulations and Doses Evaluated

Formulation Description	Cohort	Dose (Number of capsules, fasting status)
Single-dose solution in capsule		
50 mg/mL	Cohort 1 Cohort 2 Cohort 5	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted) 300 mg (8 capsules, fasted)
Multiple-dose (10 days, once-daily administration) solution in capsule		
50 mg/mL	Cohort 1 Cohort 2	30 mg (1 capsule, fasted) 100 mg (3 capsules, fasted)
Single-dose tablet		
50 mg	Cohort 10	50 mg (1 tablet, fasted)
300 mg	Cohort 7 Cohort 8 Cohort 9 Cohort 12 Cohort 13	300 mg (1 tablet, fasted) 900 mg (3 tablets, fasted) 1800 mg (6 tablets, fasted) 300 mg (1 tablet, high fat)[a] 300 mg (1 tablet, low fat)[a]

LEN = lenacapavir
High-fat meal included high calorie count (~1000 kcal, ~50% fat); low-fat meal included low calorie count (~400 kcal, ~25% fat).

LEN concentration-time profiles and PK parameters after administration of single oral doses of LEN oral solution (50 mg/mL) in capsules are presented in Figure 2 and Table 3, respectively. Maximum plasma concentrations of LEN (C_{max}) occurred between 7 and 29 hours (median T_{max}), and the median $t_{1/2}$ of LEN was approximately 13 days. Within each increase in dose, the increase in LEN exposure was less than dose proportional, suggesting that it exhibits solubility limited absorption (Table 3).

Figure 2. GS-US-200-4071: Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral LEN Solution in Capsule (50 mg/mL; N = 8 per Cohort)



BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation
Treatments: A: LEN 30 mg (50-mg/mL solution-filled capsule); B: LEN 100 mg (50-mg/mL solution-filled capsule); E: LEN 300 mg (50-mg/mL solution-filled capsule)
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
Lower limit of quantitation is defined as 0.5 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figure was set to include all lower bar and mean/median values > 0 on the Y-axis.

Table 3. GS-US-200-4071: Plasma Pharmacokinetic Parameters of LEN Following Single-Dose Oral Administration of 50 mg/mL Solution in Capsule (N = 8 per Cohort)

Parameter	Cohort 1; 30 mg (N = 8)	Cohort 2; 100 mg (N = 8)	Cohort 5; 300 mg (N = 8)
C_{max} (ng/mL)	1.16 (23.9)	2.70 (55.4)	4.75 (52.4)
T_{max} (h)[a]	29.0 (4.00, 108.00)	26.0 (4.00, 96.0)	7.00 (4.00, 28.00)
AUC_{last} (h*ng/mL)[b]	145 (30.1)	318 (46.0)	2230 (52.9)
AUC_{inf} (h*ng/mL)	ND	ND	2300 (51.3)
AUC_{exp} (%)	ND	ND	3.76 (59.7)
$AUC_{0\text{-}24h}$ (h*ng/mL)	16.8 (26.9)	34.4 (47.4)	ND
T_{last} (h)[a]	168 (168, 168)	168 (168, 168)	1540 (1340, 1850)
$t_{1/2}$ (h)[a] [days][b]	ND	ND	318 (293, 346) [13.3]

LEN = lenacapavir; ND = not determined; Q1 = first quartile; Q3 = third quartile
a Median (Q1, Q3).
b Median t1/2 is presented in days to 3 significant digits.
Pharmacokinetic parameters are presented as mean and percentage coefficient of variation (%CV) and shown to 3 significant digits.

LEN PK parameters after 10 daily oral doses of LEN (50 mg/mL solution in capsule) are presented in Table 4. Consistent with its $t_{1/2}$, following 10 days of multiple dosing, the mean LEN C_{max} and $AUC_{0\text{-}24h}$ were at least 10-fold higher than those after a single dose (Table 3 and Table 4).

Table 4. GS-US-200-4071: Plasma Pharmacokinetic Parameters of LEN Following Multiple-Dose Oral Administration of 30 mg and 100 mg Solution in Capsule (50 mg/mL) (N = 8 per Cohort)

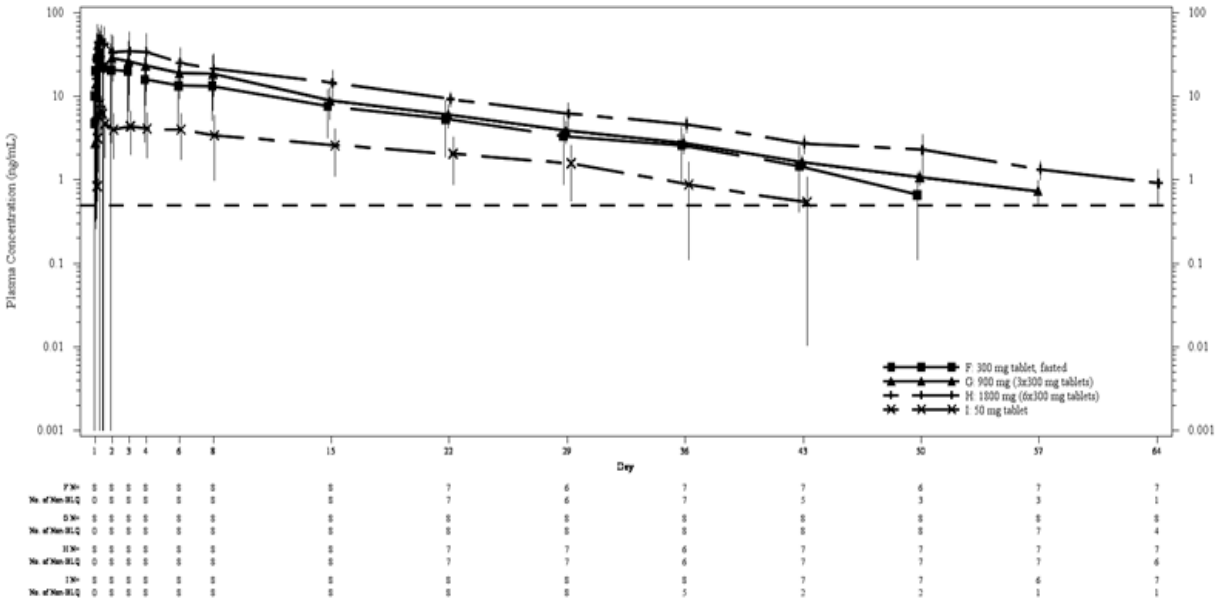
Parameter	Cohort 1; 30 mg (N = 8)	Cohort 2; 100 mg (N = 8)
	50 mg/mL solution in capsule	
C_{max} (ng/mL)	12.2 (17.1)	41.2 (53.8)
T_{max} (h)[a]	3.50 (1.75, 10.0)	4.00 (4.00, 11.0)
$AUC_{0\text{-}24h}$ (h*ng/mL)	232 (17.9)	842 (56.5)

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
a Median (Q1, Q3).
Pharmacokinetic parameters are presented as mean and percentage coefficient of variation (%CV) and shown to 3 significant digits.

LEN concentration-time profiles and PK parameters after administration of single doses of LEN oral tablets administered either under fasted conditions or with a high-fat or low-fat meal are presented in Figure 3, Figure 4, and Table 5. As observed with the oral solution in capsule, LEN exposures increased in a less than dose-proportional manner over the range of 50 to 1800 mg following administration of LEN oral tablets. Maximal concentrations (C_{max}) of LEN were achieved approximately 4 to 8 hours postdose (T_{max}), and LEN median $t_{1/2}$ ranged from 10 to 13 days (Table 5). In comparison with the oral solution in capsule, LEN 300-mg tablet AUC_{inf} was approximately 3.5-fold higher than that observed following a 300-mg dose of 50 mg/mL solution in capsule (Table 3 and Table 5).

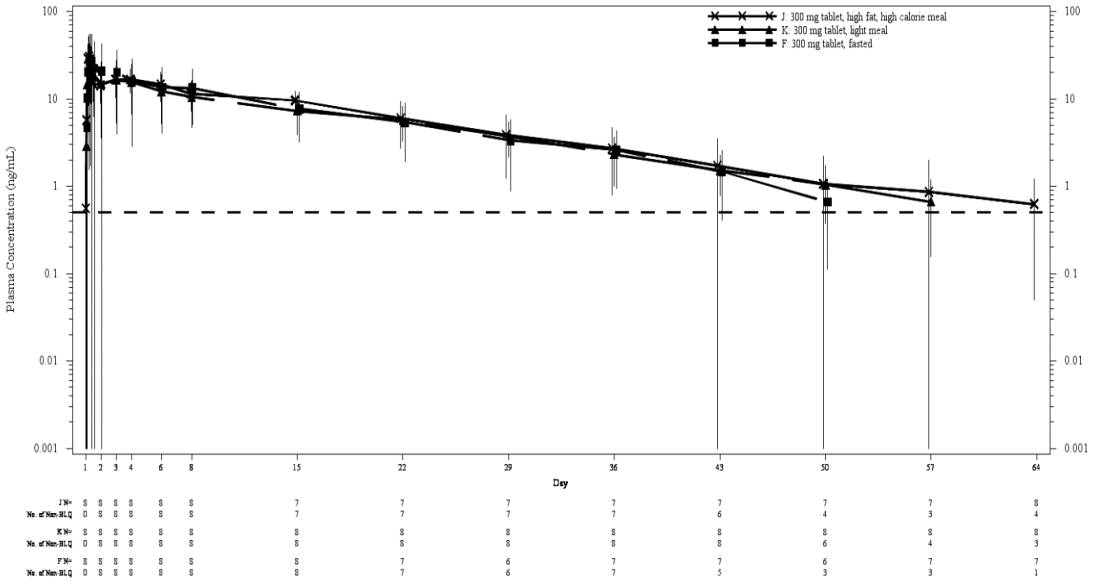
CCI [redacted]

Figure 3. GS-US-200-4071: Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Fasted Administration of Oral LEN Tablets (N = 8 per Cohort)



BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation
Treatments: F: LEN 300 mg (1 × 300-mg tablet); G: LEN 900 mg (3 × 300-mg tablets); H: LEN 1800 mg (6 × 300-mg tablets); I: LEN 50 mg (1 × 50-mg tablet)
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
Lower limit of quantitation is defined as 0.5 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figure was set to include all lower bar and mean/median values > 0 on the Y-axis.

Figure 4. **GS-US-200-4071: Mean (SD) LEN Plasma Concentration-Time Profiles Following Single-Dose Administration of Oral LEN 300 mg Tablets, Administered Fasted or with a High-Fat or Low-Fat Meal (N = 8 per Cohort)**



BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation
Treatments: F: LEN 300 mg (1 × 300-mg tablet) (fasted); J: LEN 300 mg (1 × 300-mg tablet) with high-fat, high-calorie meal; K: LEN 300 mg (1 × 300-mg tablet) with light meal
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
Lower limit of quantitation is defined as 0.5 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figure was set to include all lower bar and mean/median values > 0 on the Y-axis.

Table 5. **GS-US-200-4071: Plasma Pharmacokinetic Parameters Following Single-Dose Oral Administration of LEN Tablets, Fasted, or Following a High- or Low-Fat Meal (N = 8 per Cohort)**

Parameter	50 mg (1 × 50-mg tablet) (N = 8)	300 mg (1 × 300-mg tablet) (N = 8)	900 mg (3 × 300-mg tablets) (N = 8)	1800 mg (6 × 300-mg tablets) (N = 8)	300 mg + High-Fat Meal (N = 8)	300 mg + Low-Fat Meal (N = 8)
AUC_{inf} (h*ng/mL)	2650 (61.0)	7690 (57.8)	9790 (45.5)	14,100 (37.5)	8060 (39.8)	7290 (49.6)
C_{max} (ng/mL)	8.24 (48.3)	33.7 (96.3)	43.9 (73.3)	53.8 (48.0)	35.0 (33.0)	32.6 (62.4)
T_{max} (h)[a]	4.00 (4.00, 5.00)	4.00 (4.00, 6.00)	4.00 (3.00, 16.0)	8.00 (6.00, 8.00)	5.00 (4.00, 6.00)	6.00 (4.00, 8.00)
$t_{1/2}$ (h)[a] [days][b]	299 (270, 415) [12.5]	243 (204, 281) [10.1]	289 (255, 327) [12.0]	311 (262, 362) [13.0]	267 (244, 357) [11.1]	287 (255, 322) [12.0]

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
a Median (Q1, Q3).
b Median $t_{1/2}$ is presented in days to 3 significant figures.
Pharmacokinetic parameters are presented as mean and percentage coefficient of variation (%CV) and shown to 3 significant digits.

Safety Results

Final safety results are available from a database finalization date of 04 February 2020 for the study. A total of 106 participants were randomized or enrolled into the study. Of the 106 participants, 40 participants received LEN as capsules (50 mg/mL solution-filled capsules or 100 mg/mL solution-filled capsules), 10 participants received placebo as solution-filled capsules, 48 participants received LEN as tablets (50 mg or 300 mg), and 8 participants received placebo as tablets.

LEN was generally safe and well tolerated across all treatment groups. A total of 40 participants received LEN capsules, and 48 participants received LEN tablets, and 18 participants received placebo (capsules or tablets). The median duration of follow-up was 85 days for participants who received LEN or placebo as capsules and 64 days for participants who received LEN or placebo as tablets.

Adverse events were reported for 12 of 40 participants (30.0%) who received LEN capsules, 14 of 48 participants (29.2%) who received LEN tablets, 5 of 18 participants (27.8%) who received placebo (capsules or tablets). For participants who received LEN either as capsules or tablets, the most commonly reported AE was headache (2 of 40 participants [5.0%] who received LEN capsules, 4 of 48 participants [8.3%] who received LEN tablets, and 1 of 18 participants [5.6%] who received placebo [capsules or tablets]). For participants who received placebo, the most commonly reported AE was back pain (2 of 18 participants [11.1%]).

Overall, Grade 1 AEs were reported for 12 of 40 participants (30.0%) who received LEN capsules, 14 of 48 participants (29.2%) who received LEN tablets, and 4 of 18 participants (22.2%) who received placebo (capsules or tablets). One participant who received placebo tablets, had Grade 2 AEs (limb abscess and staphylococcal infection). Overall, 4 participants (10.0%), who received LEN capsules, had AEs considered related to study drug. All treatment-related AEs were Grade 1 in severity and the only treatment-related AE occurring in more than 1 participant was headache (2 participants). No Grade 3 or 4 AEs, deaths, serious adverse event (SAEs), pregnancy, or AEs leading to permanent discontinuation of study drug were reported in any treatment group.

There were no clinically relevant changes from predose in median values for hematology or clinical chemistry (including metabolic parameters) across study parts. One participant who received LEN capsule (Cohort 4, 75 mg) had Grade 2 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations on Day 29 (without graded laboratory abnormalities in other liver function tests) which were reported as a Grade 1 AE of hepatic enzyme increased and was considered related to study drug. The AE resolved by Day 57 at which time both ALT and AST values returned to predose values. There were no Grade 3 or 4 liver function test abnormalities or other hepatic AEs in the study.

The maximum abnormality grade for most of the participants was Grade 1 or Grade 2. Grade 3 laboratory abnormalities reported for more than 1 participant were occult urine blood (3 participants who received LEN capsules, 7 participants who received LEN tablets and 2 participants who received placebo as capsules) and elevated fasting low-density lipoprotein

(LDL) (2 participants who received LEN capsules and 2 participants who received placebo as tablets). Grade 4 laboratory abnormalities were reported for 1 participant who received LEN capsule (increase in triacylglycerol lipase) and 1 participant who received LEN tablet (increase in creatine kinase [CK]); both Grade 4 laboratory abnormalities were isolated events that returned to normal by the end of the study.

No notable changes from predose in vital signs (systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiration rate) were observed in the study. No clinically significant electrocardiogram (ECG) abnormalities were reported during the study.

1.2.3.4.2. Study GS-US-200-4538

GS-US-200-4538 (completed) was a blinded, Phase 1 study in healthy volunteers evaluating the safety, tolerability, and PK of single-ascending SC doses of LEN solution formulations. 100 unique participants received single doses of either SC LEN formulations or placebo (4:1 ratio) (Table 8).

Table 6. GS-US-200-4538: Solution Formulations and Doses

Formulation	Dose of LEN (volume injected)
300 mg/mL, free acid (300 mg/mL FA)	300 mg (1 × 1 mL)
309 mg/mL, LEN injection (309 mg/mL NaS)	309 mg (1 × 1 mL)
	927 mg (3 × 1 mL)
	927 mg (2 × 1.5 mL)
155 mg/mL, LEN injection (155 mg/mL NaS)	309 mg (1 × 2 mL)
	927 mg (3 × 2 mL)
300 mg/mL, LEN injection with poloxamer (300 mg/mL NaSP)	900 mg (3 × 1 mL)
75 mg/mL, LEN injection with poloxamer (75 mg/mL NaSP)	75 mg (1 × 1 mL)
	225 mg (2 × 1.5 mL)
50 mg/mL, LEN injection with poloxamer (50 mg/mL NaSP)	50 mg (1 × 1 mL)

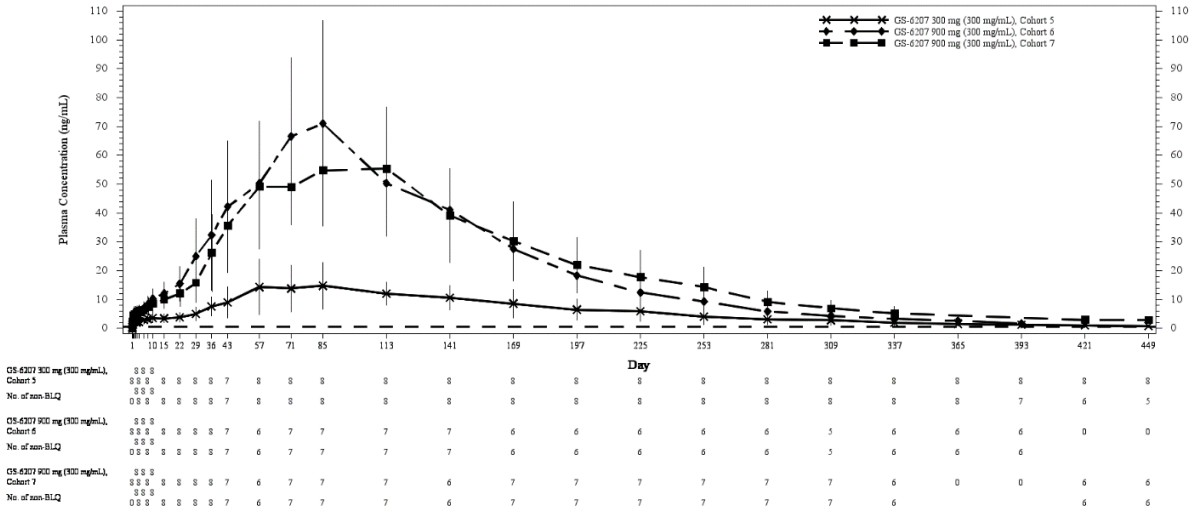
FA = free acid; LEN = lenacapavir; NaS = LEN injection; NaSP = LEN injection with poloxamer

Pharmacokinetic samples were collected for up to 449 days; safety and PK analyses are ongoing. Data from select formulations are presented below.

Pharmacokinetic Results

Data following administration of single doses of SC LEN injection, 309 mg/mL (the SC LEN formulation intended to be used in the PrEP study) are presented below (Figure 5 and Table 7). Based on the PK data, a slow initial release of LEN was observed; however, concentrations exceeding an inhibitory quotient of 4 (IQ4; 4-fold higher than the paEC$_{95}$ from MT-4 cells; 3.87 ng/mL) were observed for at least 26 weeks following a single 927-mg dose (Figure 5 and Table 7). Similar PK profiles were observed following SC administration of a 927-mg dose administered as either 3 × 1.0 mL or 2 × 1.5 mL SC injections.

Figure 5. GS-US-200-4538: Mean (SD) Plasma Concentration Versus Time (Part B) (LEN PK Analysis Set)



BLQ = below the limit of quantitation; LEN = lenacapavir; LLOQ = lower limit of quantitation; PK = pharmacokinetic(s); SD = standard deviation
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries. LLOQ was defined as 0.5 ng/mL for LEN.
Postdose concentration values ≤ LLOQ are not presented on the figure.
Figures on the linear scale in which lower bars were negative were truncated to 0 on the Y-axis.

Table 7. GS-US-200-4538: Summary Statistics of Plasma Pharmacokinetic Parameters LEN, 309 mg/mL NaS (LEN PK Analysis Set)

Parameter (Unit)	Cohort 5 (309 mg, 309 mg/mL 1 × 1 mL)	Cohort 6 (927 mg, 309 mg/mL 3 × 1 mL)	Cohort 7 (927 mg, 309 mg/mL 2 × 1.5 mL)
AUC_{6month} (h*ng/mL)	44,083.9 (33.2)	183,820.6 (39.3)	165,735.5 (27.6)
AUC_{last} (h*ng/mL)	63,414.1 (28.6)	186,428.8 (52.9)	196,592.6 (49.2)
AUC_{inf} (h*ng/mL)	66,173.0 (27.6)	226,534.1 (32)	232,382.4 (28.7)
AUC_{exp} (%)	4.4 (43.8)	2.1 (112.5)	4.0 (44.5)
C_{max} (ng/mL)	17.7 (50.3)	67.0 (54.8)	61.2 (43.5)
T_{max} (h)	2352.22 (1405.14, 3336.09)[a]	1848.00 (1680.00, 2016.00)[a]	2016.94 (1680.00, 2629.08)[a]
T_{last} (h)	10,716.63 (10,202.20, 10,910.43)[a]	9407.78 (6431.48, 9432.14)[a]	10,756.65 (9183.46, 10,756.97)[a]
$t_{1/2}$ (h)	1859.94 (1665.30, 2386.67)[a]	1277.39 (1184.33, 1334.53)[a]	1939.25 (1486.68, 2354.08)[a]

%CV = percentage coefficient of variation; LEN = lenacapavir; NaS = LEN injection; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile
PK parameters are reported as mean (CV%)
a Median (Q1, Q3)

Safety Results

Adverse events were reported for 69 of 80 participants (86.3%) who received 1 of the SC LEN formulations (155 mg/mL NaS injection or 309 mg/mL [NaS] or 300 mg/mL with poloxamer [NaSP] or 50 mg/mL [NaSP] or 75 mg/mL [NaSP]), and 17 of 20 participants (85.0%) who received placebo (Table 8). No deaths or Grade 4 AEs were reported.

The most frequently reported AEs in all LEN cohorts were injection site induration (n = 52, 65.0%), injection site pain (n = 41, 51.3%), and injection site erythema (n = 37, 46.3%). Two participants (2.5%) who received LEN had Grade 3 AEs: 1 with tibia fracture and the other with limb abscess (the participant with the limb abscess also had Grade 2 AEs of cellulitis, localized infection, gastroenteritis, and headache). None of the SAEs were attributed to study drug.

Overall, 22 participants (27.5%) who received LEN and 6 participants (30.0%) who received placebo had maximum Grade 3 laboratory abnormalities. Grade 3 laboratory abnormalities reported for more than 1 participant in either overall treatment group were occult blood in urine (11 participants [13.8%] who received LEN and 4 participants [20.0%] who received placebo; all were due to menses or considered not clinically significant by the investigator); LDL cholesterol and fasting LDL cholesterol (each in 6 participants [7.5%] who received LEN and 1 participant [5.0%] who received placebo; all 7 participants had Grade 1 or 2 LDL abnormalities at predose); CK (2 participants [2.5%] who received LEN and 2 participants [10.0%] who received placebo; these were either abnormal predose and/or due to exercise); and lymphocytes (2 participants [2.5%] who received LEN; 1 participant had a viral infection at the time and the other participant was asymptomatic).

Isolated Grade 4 laboratory abnormalities were reported for 2 participants (2.5%) who received LEN (exercise-related increased CK in 1 participant, and increases in fasting triglycerides in another) and 1 participant (5.0%) who received placebo (increases in AST, CK, and lipase, with alternative etiologies).

Table 8. GS-US-200-4538: Adverse Events Reported for at Least 4 Participants in Either Overall Treatment Group (Safety Analysis Set)

Preferred Term	Overall LEN (All Cohorts) (N = 80)	Overall Placebo (All Cohorts) (N = 20)
Number (%) of Participants with Any Treatment-Emergent Adverse Event	69 (86.3%)	17 (85.0%)
Injection site induration	52 (65.0%)	6 (30.0%)
Injection site pain	41 (51.3%)	5 (25.0%)
Injection site erythema	37 (46.3%)	0
Injection site swelling	27 (33.8%)	2 (10.0%)
Headache	20 (25.0%)	5 (25.0%)
Injection site bruising	14 (17.5%)	8 (40.0%)
Injection site nodule	10 (12.5%)	0
Upper respiratory tract infection	6 (7.5%)	3 (15.0%)
Oropharyngeal pain	6 (7.5%)	1 (5.0%)
Back pain	4 (5.0%)	0

AE = adverse event; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the study drug start date, or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
PTs were presented by descending order of total frequencies.

No notable changes from predose in vital signs (systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiration rate) have been observed in the study. No clinically significant ECG abnormalities have been reported during the study.

1.2.3.4.3. Study GS-US-200-5709

GS-US-200-5709 is a Phase 1, open-label, multiple-cohort study in healthy participants assessing the safety, tolerability, and PK of multiple-dose oral (tablet) and SC (309 mg/mL NaS) LEN.

In Cohorts 1 and 2 of this study, safety and PK of potential clinical regimens were evaluated.

Cohort 3 of this study characterized the safety and PK of LEN administered at clinically relevant therapeutic and supratherapeutic exposures; this regimen included oral LEN 600 mg administered twice daily for 11 days, with the last dose given in the morning on the 11th day.

Preliminary Pharmacokinetic Results

Cohort 1 (Phase 2/3 Regimen)

Lenacapavir plasma PK parameters and concentration-time profiles based on interim analysis up to Day 197 are presented in Table 9 and Figure 6.

Following oral LEN administration, mean concentration and its lower bound 90% CI were consistently maintained above IQ4 (15.5 ng/mL) from 2 hours postdose on Day 2 to Day 197. Following SC administration on Day 15, median T_{max} occurred approximately 85 days postdose. Mean concentration (lower 90% CI) at Day 197 was 23.9 ng/mL (20.4 ng/mL). From Days 0 to 196, mean (%CV) $AUC_{0\text{-}196\ days}$ was 134,000.5 h*ng/mL (55.9%).

Table 9. GS-US-200-5709: Summary Statistics of LEN Plasma Pharmacokinetic Parameters (Cohort 1) (LEN PK Analysis Set)

PK Parameter Mean (%CV)	Cohort 1			
	Day 1[a] (N = 31)	Day 2[a] (N = 31)	Day 8[a] (N = 31)	Day 15-Day 197[a] (N = 30)
C_{max} (ng/mL)	22.0 (45.5)	40.4 (43.4)	39.3 (44.7)	58.7 (58.1)
T_{max} (h)[b] [days]	4.00 (4.00, 6.00) [0.17]	6.00 (4.00, 8.00) [0.25]	6.00 (4.00, 8.00) [0.25]	2028.0 (1682.5, 2688.2) [84.5]
C_{last} (ng/mL)	11.8 (57.2)	19.1 (40.0)	19.9 (40.4)	29.8 (67.6)
T_{last} (h)[b] [days]	24.0 (24.0, 24.0) [1.0]	144.0 (144.0, 144.0) [6.0]	168.0 (168.0, 168.0) [7.0]	4319.5 (2689.0, 4365.8) [180.0]
$AUC_{0\text{-}196\ days}$ (h•ng/mL)	134,000.5 (55.9)			

%CV = percentage coefficient of variation; LEN = lenacapavir; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous

a 600 mg oral LEN (2 × 300 mg tablets) on Day 1 and Day 2, followed by 300 mg oral LEN (1 × 300 mg tablet) on Day 8, and 927 mg SC LEN (2 × 1.5 mL, 309 mg/mL NaS) on Day 15.

b Median (Q1, Q3).

Cohort 2 (Simplified Regimen)

Lenacapavir plasma PK parameters and concentration-time profiles based on interim analysis up to Day 197 are presented in Table 10 and Figure 6.

Mean concentration and its lower bound 90% CI exceeded IQ1 ($paEC_{95}$ from MT-4 cells; 3.87 ng/mL) within 4 hours of dosing on Day 1 and were maintained above IQ1 through Day 2. Following 600 mg oral dose on Day 2, mean concentration and its lower bound 90% CI exceeded IQ4 (15.5 ng/mL) within 2 hours. Following SC administration on Day 1, median T_{max} occurred approximately 70 days postdose. Mean LEN concentrations were consistently maintained above the efficacious target of IQ4 for the dosing interval. Mean concentrations (lower 90% CI) at Days 183 and 197 were 19.0 ng/mL (14.0 ng/mL) and 16.1 ng/mL (11.5 ng/mL), respectively. From Days 0 to 196, mean (%CV) $AUC_{0\text{-}196\ days}$ was

152,884.0 h*ng/mL (56.4%). Lenacapavir C_{max} and $AUC_{0\text{-}196\ days}$ were within ± 8% and ± 15%, respectively, when compared with Cohort 1 exposures. From Days 0 to 182 (26 weeks postdose), mean (%CV) $AUC_{0\text{-}182\ days}$ was 148,284.1 h*ng/mL (56.6%). Lenacapavir exposures for the dosing interval as assessed by $AUC_{0\text{-}196\ days}$ for Cohort 1 and $AUC_{0\text{-}182\ days}$ for Cohort 2 were within ± 11%.

Table 10. GS-US-200-5709: Summary Statistics of LEN Plasma Pharmacokinetic Parameters (Cohort 2) (LEN PK Analysis Set)

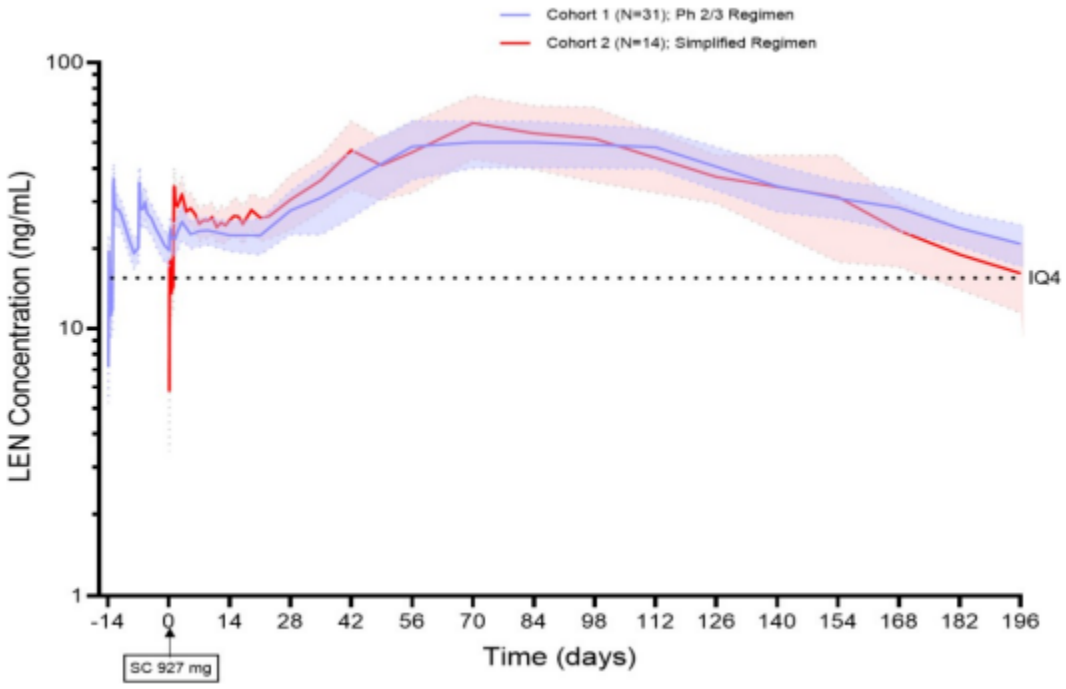
PK Parameter Mean (%CV)	Cohort 2	
	Day 1[a] (N = 14)	Day 2-Day 197[a] (N = 14)
C_{max} (ng/mL)	20.1 (34.5)	67.1 (47.2)
T_{max} (h)[b]	6.00 (4.00, 8.00)	1653.9 (985.0, 1991.2)
T_{max} (days)	0.25	68.9
C_{last} (ng/mL)	14.4 (36.9)	21.4 (93.1)
T_{last} (h)[b]	24.0 (24.0, 24.0)	4679.4 (4678.9, 4679.9)
T_{last} (days)	1.0	195.0
$AUC_{0\text{-}182\ days}$ (h•ng/mL)	148,284.1 (56.6)	

%CV = percentage coefficient of variation; LEN = lenacapavir; NaS = sodium salt; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous

a 927 mg SC LEN (2 × 1.5 mL, 309 mg/mL NaS) + 600 mg oral LEN (2 × 300 mg tablets) on Day 1 followed by 600 mg oral LEN (2 × 300 mg tablets) on Day 2.

b Median (Q1, Q3).

Figure 6. GS-US-200-5709: Comparison of Mean (90% CI)[a] LEN Plasma Concentration-time Profiles Between Cohorts 1 and 2 (LEN PK Analysis Set)



CI = confidence interval; IQ4 = inhibitory quotient of 4; LEN = lenacapavir; PK = pharmacokinetic(s); SC = subcutaneous
Cohort 1 (Phase 2/3 regimen) was oral LEN 600 mg on Days 1 and 2, oral LEN 300 mg on Day 8, and SC LEN 927 mg on Day 15.
Cohort 2 (simplified regimen) was SC LEN 927 mg and oral LEN 600 mg on Day 1 and oral LEN 600 mg on Day 2.
a Blue and pink shaded areas represent 90% CI band for the mean profile for Cohort 1 and Cohort 2, respectively; Horizontal dotted line shows IQ4 of 15.5 ng/mL.
On X-axis, values −14 to 0 represent 14-day oral lead-in period for Cohort 1.

Cohort 3

Final PK data from Cohort 3 after administration of oral LEN 600 mg twice daily (Days 1 through 10), followed by an oral LEN 600 mg dose in the morning on Day 11, are presented in Table 11. Intensive PK sampling (from 0 to 12 hours) was conducted on Days 1, 2, and 11 with sparse sampling on Days 3, 4, 8, 9, and 10. As shown, LEN exhibited significant accumulation over the course of 11 days of dosing, which is consistent with its long $t_{1/2}$. Overall, C_{max} observed in Cohort 3 was approximately 10-fold above the anticipated C_{max} in the Phase 3 PrEP study.

Table 11. GS-US-200-5709: Summary Statistics of LEN Plasma Pharmacokinetic Parameters (Cohort 3) (LEN PK Analysis Set)

	LEN							
	600 mg oral LEN (2 × 300 mg tablets; AM dose) and 600 mg oral LEN (2 × 300 mg tablets; PM dose)							600 mg oral LEN (2 × 300 mg tablets; AM dose)
PK Parameter Mean (%CV)	Day 1 (N = 15)	Day 2 (N = 15)	Day 3 (N = 15)	Day 4 (N = 15)	Day 8 (N = 15)	Day 9 (N = 15)	Day 10 (N = 15)	Day 11 (N = 15)
$AUC_{0\text{-}12h}$ (h•ng/mL)	135.4 (30.7)	894.4 (47.2)	NC	NC	NC	NC	NC	9706.9 (28.2)
C_{max} (ng/mL)	19.0 (24.0)	96.4 (49.5)	NC	NC	NC	NC	NC	1012.1 (26.2)
T_{max} (h)[a]	5.00 (4.00, 5.00)	8.00 (5.00, 11.97)	NC	NC	NC	NC	NC	4.00 (4.00, 5.00)
C_{last} (ng/mL)	11.1 (39.9)	88.4 (45.2)	241.6 (41.2)	376.9 (31.7)	604.8 (32.6)	680.5 (28.2)	751.9 (25.7)	787.7 (31.3)
T_{last} (h)[a]	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)	11.97 (11.97, 11.97)
C_0 (ng/mL)	BLQ (BLQ)	42.0 (47.2)	152.6 (49.7)	342.4 (39.6)	558.5 (36.8)	699.9 (33.2)	693.1 (35.0)	788.8 (32.1)

BLQ = below the limit of quantitation; %CV = percentage coefficient of variation; LEN = lenacapavir; LLOQ = lower limit of quantitation; NC = not calculated due to insufficient PK sampling; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile
a Median (Q1, Q3).
C_0 represents concentration at time 0 hours.
Values BLQ were treated as 0 for predose and one-half the LLOQ for postdose summaries.
LLOQ was defined as 0.5 ng/mL for LEN.

Preliminary Safety Results

In Cohort 1, a total of 31 participants received at least 1 dose of study drug. The median (Q1, Q3) duration of follow-up was 264 (145, 372) days. No deaths, pregnancies, or SAEs were reported. Adverse events were reported for 27 of 31 participants (87.1%). Adverse events considered related to study drug were reported for 22 participants (71.0%). The most commonly reported AEs in Cohort 1 were injection site induration (16 of 31 participants, 51.6%), injection site pain (12 of 31 participants, 38.7%), and injection site erythema (10 of 31 participants, 32.3%). All the AEs were Grade 1 or 2 in severity. No Grade 3 or 4 AEs were reported. One of 31 participants (3.2%) prematurely discontinued study due to an AE (SARS-CoV-2 test positive). Graded laboratory abnormalities were reported for 23 of 31 participants (74.2%). The maximum abnormality grade for most of the participants was Grade 1 or 2. Five participants had Grade 3 laboratory abnormalities (increased creatine kinase, increased creatinine, increased fasting triglycerides, and glycosuria) and 1 participant had a Grade 4 laboratory abnormality (increased fasting triglycerides). None of the graded laboratory abnormalities were reported as AEs.

In Cohort 2, a total of 14 participants received at least 1 dose of study drug. The median (Q1, Q3) duration of follow-up was 136 (136, 150) days. No deaths, pregnancies, SAEs, AEs for confirmed or suspected COVID-19, or AEs leading to permanent discontinuation of study or study drug were reported. Adverse events were reported for all participants (14 of 14 participants, 100.0%). The most commonly reported AEs were injection site induration (14 of 14 participants, 100%), injection site erythema (5 of 14 participants, 35.7%), and injection site pain (4 of 14 participants, 28.6%). All AEs were Grade 1 or 2 in severity. No Grade 3 or 4 AEs were reported. Treatment-related AEs were reported for all participants (100.0%). All ISRs were considered related to study drug and accounted for all the treatment-related AEs. Graded laboratory abnormalities were reported for 7 of 14 participants (50.0%). The maximum abnormality grade for most of the participants was Grade 1 or 2. Three of 14 participants (21.4%) had Grade 3 laboratory abnormalities (increased creatine kinase, increased fasting LDL, fasting hypercholesterolemia, and increased fasting triglycerides) and no participants had Grade 4 laboratory abnormalities. None of the graded laboratory abnormalities were reported as AEs.

No participant in Cohort 1 or 2 had notable changes in vital signs (systolic blood pressure, diastolic blood pressure, pulse, and temperature) or clinically significant ECG abnormalities.

In Cohort 3, a total of 15 participants received at least 1 dose of study drug. The median (Q1, Q3) duration of follow-up was 71 (71, 71) days. No Grade 3 or 4 AEs, deaths, SAEs, treatment-related AEs, AEs for confirmed or suspected COVID-19, or AEs leading to permanent discontinuation of study or study drug were reported. The only AE reported was dyspepsia (6.7%, 1 of 15 participants). This AE was Grade 1 and not treatment related. Graded laboratory abnormalities were reported for 11 of 15 participants (73.3%). The maximum abnormality grade for the majority of participants was Grade 1 or 2, and there were no Grade 4 laboratory abnormalities. One participant had Grade 3 increased fasting triglycerides. None of the graded laboratory abnormalities were reported as AEs. No notable changes from predose values in vital signs (systolic blood pressure, diastolic blood pressure, pulse, and temperature) were observed during the study. No clinically significant ECG abnormalities were reported. Minimal changes were observed in baseline values for time-matched change from baseline in PR interval, QRS interval, QT interval, QTcF interval, and heart rate. These were not considered clinically relevant.

1.2.3.4.4. Study GS-US-200-4333

GS-US-200-4333 was a Phase 1 open-label, parallel design, single and multiple dose, multiple cohort study in healthy volunteers to evaluate the drug-drug interaction (DDI) potential of LEN. Available preliminary data for LEN capsules administered in combination with known strong cytochrome P450 enzyme (CYP)3A/P-glycoprotein (P-gp) inhibitors, darunavir (DRV)/cobicistat (COBI) and COBI, or LEN tablets administered in combination with a strong CYP3A/UGT/P-gp inducer, rifampin (RIF), an acid reducing agent, famotidine (FAM), and organic anion transporting polypeptide (OATP), breast cancer resistance protein (BCRP), P-gp or CYP3A substrates, pitavastatin (PIT), rosuvastatin (ROS), TAF, and midazolam (MDZ), respectively are presented below.

Cohort 1 served as a reference arm for Cohorts 2 and 3; participants received a single dose of LEN 300 mg alone (N = 30). Participants in Cohorts 2 and 3 received up to 90 days of COBI 150 mg once daily, or DRV/COBI 800/150 mg once daily, respectively, with a single dose of LEN 300 mg coadministered in the morning on Day 11 (N = 29 per cohort). All doses were administered in the morning under fed conditions. PK samples were obtained up to Day 63 (Cohort 1) and up to Day 35 (Cohorts 2 and 3) to characterize the PK of LEN in each treatment..

Preliminary PK data are presented below (Table 12). The median times at which maximum plasma concentrations of LEN were achieved ranged from 6 to 8 hours postdose (T_{max}), and the median $t_{1/2}$ of LEN administered alone was 12.3 days, and ranged from 16.8 to 18.8 days following administration with DRV/COBI or COBI. Coadministration of DRV/COBI or COBI with LEN resulted in an approximate 2-fold increase in C_{max} and AUC_{inf}. This 2-fold increase in LEN exposure was not deemed clinically relevant based on safety data from ongoing Phase 1 studies at or above exposures anticipated to be achieved following administration of LEN with strong CYP3A/P-gp inhibitors. Accordingly, the use of strong CYP3A and P-gp inhibitors is permitted with LEN.

Table 12. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of LEN 300 mg Oral Capsule Following Administration Alone or with DRV/COBI (800/150 mg QD) or COBI (150 mg QD) (N = 29-30 per Cohort)

Parameter	LEN Alone 300 mg (N = 30)	LEN 300 mg + COBI (N = 29)	LEN 300 mg + DRV/COBI (N = 29)
C_{max} (ng/mL)	30.6 (74.4)	57.8 (53.6)	61.5 (43.4)
AUC_{last} (h•ng/mL)	10,400 (77.7)	16,100 (61.3)	14,200 (47.3)
AUC_{inf} (h•ng/mL)	10,700 (76.8)	22,700 (62.5)	19,500 (48.7)
T_{max} (hours)	8.00 (6.00, 48.0)	8.00 (6.00, 48.0)	6.00 (6.00, 8.00)
$t_{1/2}$ (days)	12.3 (9.97, 15.9)	18.8 (15.9, 24.2)	16.8 (14.5, 19.3)

%CV = percentage coefficient of variation; COBI = cobicistat; DRV = darunavir; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; QD = once daily
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2,}$ and $T_{last,}$ which are presented as median (Q1, Q3), and shown to 3 significant digits

Cohort 4 served as a reference arm for Cohorts 8 and 10; in Cohort 4, participants received a single dose of LEN 300 mg tablet alone (N = 27). Participants in Cohort 8 received 25 days of RIF (600 mg once daily), with LEN administered on Day 14, and participants in Cohort 10 received a single dose of FAM (40 mg) 2 hours prior to LEN on Day 1 (N = 25 per cohort). All LEN doses were administered in the morning under fasted conditions. Pharmacokinetic samples were obtained up to Day 23 post-LEN dose (Cohorts 4 and 10) and up to Day 12 postdose (Cohort 8) to characterize the PK of LEN in each treatment..

The median $t_{1/2}$ of LEN administered alone was 13.4 days (Table 13). Following coadministration with RIF, LEN C_{max} and AUC_{inf} were approximately 2.5-fold and 5-fold lower, respectively, with a corresponding ~5-fold decrease in $t_{1/2}$. These data support the existing recommendations to disallow the use of strong CYP3A4/UGT1A1/P-gp inducers with LEN.

Following coadministration with FAM, no change in LEN exposure or $t_{1/2}$ was observed; accordingly, administration of FAM and other acid reducing agents with LEN is therefore permitted.

Table 13. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of LEN 300 mg Tablet Following Administration Alone or with RIF (600 mg QD) or FAM (40 mg) (N = 25-27 per cohort)

Parameter	LEN Alone 300 mg (N = 27)	LEN 300 mg +RIF (N = 25)	LEN 300 mg +FAM (N = 25)
C_{max} (ng/mL)	20.4 (102)	8.17 (59.6)	18.6 (60.2)
AUC_{last} (h•ng/mL)	3880 (65.3)[a]	745 (48.1)[b]	4610 (58.3)
AUC_{inf} (h•ng/mL)	5430 (58.0)[a]	786 (47.7)	6360 (52.9)
$\%AUC_{exp}$	30.0 (24.6)	5.20 (50.7)	28.5 (24.7)
T_{max} (hours)	4.00 (4.00, 6.00)	24.0 (24.0, 48.0)	10.0 (4.00, 48.0)
$t_{1/2}$ (hours)[days]	321 (261, 374) [13.4][a]	63.8 (59.5, 71.1) [2.66][b]	270.0 (250, 331) [11.3]
T_{last} (days)	23.0 (23.0, 23.0)	12.0 (12.0, 12.0)	23.0 (23.0, 23.0)

%CV = percentage coefficient of variation; FAM = famotidine; LEN = lenacapavir; RIF = rifampin; Q1 = first quartile; Q3 = third quartile; QD = once daily
a N = 25
b N = 24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, t1/2, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

In Cohort 11, participants received PIT, ROS, TAF, and MDZ alone, or coadministered with oral GS-LEN. Agents were either coadministered with oral LEN to evaluate the worst-case (coadministration; PIT, ROS, TAF, and MDZ), or up to 3 days after the last dose of LEN (PIT, MDZ) to evaluate the systemic drug interaction liability of LEN. Mean concentrations of LEN were at, or above clinically relevant C_{max} concentrations (> 100 ng/mL) throughout the drug interaction evaluation (data not shown). Preliminary PK data are presented in Table 14, Table 15, Table 16, and Table 17..

Table 14. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of PIT (2 mg) Following Administration Alone or With LEN (N = 30-31)

Parameter	PIT Alone (N = 31)	PIT+ LEN (Day 15; Coadministration) (N = 30)	PIT + LEN (Day 27; 3 Days Post LEN Dose) (N = 30)
C_{max} (ng/mL)	31.4 (52.8)	31.0 (48.1)	26.8 (50.5)
AUC_{last} (h•ng/mL)	85.7 (44.9)[a]	96.8 (47.8)	76.2 (37.7)[b]
AUC_{inf} (h•ng/mL)	90.9 (43.7)[a]	102 (46.9)	81.5 (36.1)[b]
T_{max} (hours)	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)
$t_{1/2}$ (hours)	11.7 (8.56, 13.5)[a]	10.9 (7.41, 14.7)	14.1 (10.2, 16.5)[b]
T_{last} (hours)	36.0 (24.0, 48.0)	36.0 (24.0, 48.0)	36.0 (24.0, 48.0)

%CV = percentage coefficient of variation; LEN = lenacapavir; PIT = pitavastatin; Q1 = first quartile; Q3 = third quartile
a N = 25
b N =24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2}$, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 15. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of ROS (5 mg) Following Administration Alone or With LEN (N = 30)

Parameter	ROS Alone (N = 33)	ROS+ LEN (Day 18; Coadministration) (N = 30)
C_{max} (ng/mL)	1.06 (39.5)	1.87 (65.8)
AUC_{last} (h•ng/mL)	10.8 (34.2)a	14.2 (48.1)b
AUC_{inf} (h•ng/mL)	12.3 (33.9)a	16.1 (43.8)b
T_{max} (hours)	5.00 (5.00, 5.00)	4.00 (2.00, 4.00)
$t_{1/2}$ (hours)	13.1 (9.13, 17.8)a	17.3 (13.9, 20.8)b
T_{last} (hours)	36.0 (24.0, 48.0)	48.0 (36.0, 48.0)

%CV = percentage coefficient of variation; LEN = lenacapavir; ROS = rosuvastatin; Q1 = first quartile; Q3 = third quartile
a N = 25
b N = 24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, $t_{1/2}$, and T_{last}, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 16. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of TAF (25 mg) and its Metabolite, TFV, Following Administration Alone or With LEN (N = 28-30)

Parameter	TAF Alone (N = 30)	TAF+ LEN (Day 21; Coadministration) (N = 30)
TAF		
C_{max} (ng/mL)	248 (52.5)	322 (52.6)
AUC_{last} (h•ng/mL)	256 (54.3)	328 (35.3)
AUC_{inf} (h•ng/mL)	262 (54.4)[a]	361 (27.8)[b]
T_{max} (hours)	1.00 (0.50, 1.13)	1.00 (0.50, 1.50)
$t_{1/2}$ (hours)	0.38 (0.34, 0.42)[a]	0.41 (0.35, 0.43)[b]
TFV		
C_{max} (ng/mL)	6.29 (30)	7.97 (34.2)
AUC_{last} (h•ng/mL)	171 (26.3)	259 (22.2)[c]
AUC_{inf} (h•ng/mL)	206 (25.9)	322 (21)

%CV = percentage coefficient of variation; LEN = lenacapavir; TAF = tenofovir alafenamide; TFV = tenofovir; Q1 = first quartile; Q3 = third quartile
a N = 25
b N =24
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

Table 17. GS-US-200-4333: Preliminary Plasma Pharmacokinetic Parameters of MDZ (2.5 mg) and its Metabolite, 1-OH-MDZ, Following Administration Alone or with LEN (N = 30-31)

Parameter	MDZ Alone (N = 31)	MDZ+ LEN (Day 24; Coadministration) (N = 30)	MDZ + LEN (Day 25; 1 Day Post LEN Dose) (N = 30)
MDZ			
C_{max} (ng/mL)	9.46 (29.1)	17.7 (22.7)	19.7 (23.8)
AUC_{last} (h•ng/mL)	50.5 (35.1)	129 (24.9)	171 (27.7)
AUC_{inf} (h•ng/mL)	52.9 (36.3)	170 (30.6)	208 (34.5)
T_{max} (hours)	2.00 (1.00, 2.00)	2.00 (1.25, 4.00)	2.00 (1.00, 2.00)
$t_{1/2}$ (hours)	5.18 (3.96, 7.2)	7.05 (6.06, 9.05)	9.38 (7.04, 11.4)
1-OH-MDZ			
C_{max} (ng/mL)	2.64 (44.4)	1.39 (34.9)	1.33 (36.5)
AUC_{last} (h•ng/mL)	13.1 (39.2)	8.12 (28.6)	9.7 (35.9)
AUC_{inf} (h•ng/mL)	13.9 (38.9)	9.56 (30)	11.5 (43)

%CV = percentage coefficient of variation; LEN = lenacapavir; MDZ = midazolam; Q1 = first quartile; Q3 = third quartile
Pharmacokinetic parameters are presented as mean (%CV) except T_{max}, and $t_{1/2}$, which are presented as median (Q1, Q3), and shown to 3 significant digits.

PIT AUC and C_{max} were not affected following administration with LEN, suggesting LEN does not inhibit OATP transporters (Table 14). ROS AUC and C_{max} were approximately 1.3 to 1.6-fold higher following coadministration with LEN (Table 15), suggesting LEN weakly inhibits BCRP transporters. TAF and TFV AUC and C_{max} were 1.2- to 1.6- fold higher following coadministration with LEN (Table 16), suggesting LEN is a weak inhibitor of P-gp transporters. MDZ AUC and C_{max} were approximately 2- to 4- fold higher, and 1-OH-MDZ AUC and C_{max} were correspondingly lower following coadministration with LEN (Table 17), suggesting LEN is a moderate inhibitor of CYP3A. Coadministration of a single dose of LEN with strong UGT1A1/CYP3A4/P-gp inhibitor (ATV+COBI) resulted in increases in LEN AUC_{inf} of 306%. The larger effect observed with ATV+COBI relative to COBI alone suggests that UGT1A1 is an elimination pathway for LEN. Strong and moderate inducers of CYP3A4/P-gp decreased LEN exposures by 84% and 56% (RIF and efavirenz [EFV], respectively) and may result in loss of virologic response; therefore, concomitant use of strong and moderate inducers of CYP3A4/P-gp with LEN should be avoided (Please refer to Section 5.4 for prior and concomitant medications that are prohibited).

No SAEs, Grade 4 AEs, or deaths were reported during the study. A total of 8 participants had AEs that led to premature discontinuation of study drug, of which only 1 was considered related to LEN treatment (transaminases increased). Across all cohorts, most AEs reported were Grade 1 or Grade 2 in severity. Grade 3 AEs and Grade 3 laboratory abnormalities were reported most frequently after treatment with ATV+COBI and ATV+COBI with LEN; most of these findings were associated with transient elevations in total bilirubin concentrations that were expected with ATV+COBI treatment. No other clinically relevant changes for clinical laboratory evaluations or vital signs were observed, and no clinically significant ECG abnormalities were reported.

1.2.3.4.5. Study GS-US-200-4072

GS-US-200-4072 is a completed, Phase 1b, randomized, double-blinded, placebo-controlled, multicohort, dose-ranging study evaluating the safety, tolerability, PK, and short-term antiviral activity of monotherapy with SC doses of a LEN free-acid suspension (100 mg/mL) in PWH who were either ARV therapy (ART) naive or ART experienced but capsid inhibitor naive.

This study enrolled 5 cohorts to receive LEN (20, 50, 150, 450, and 750 mg) or placebo. Within each cohort (n = 8), participants were randomized in a 3:1 ratio to receive active LEN (n = 6) or placebo (n = 2). A single dose of LEN or placebo was administered as SC injection(s) on Day 1.

Disposition and Baseline Characteristics

Of the 41 randomized participants, 29 participants received a single dose of LEN (6 participants each in the LEN 20, 50, 150, and 450 mg groups and 5 participants in the LEN 750 mg group), and 10 participants received a single dose of placebo. Two randomized participants did not receive study drug due to withdrawal of consent. Of the 39 randomized participants who received study drug, 38 participants completed the study, and 1 participant (LEN 450 mg group) prematurely discontinued the study due to being lost to follow-up.

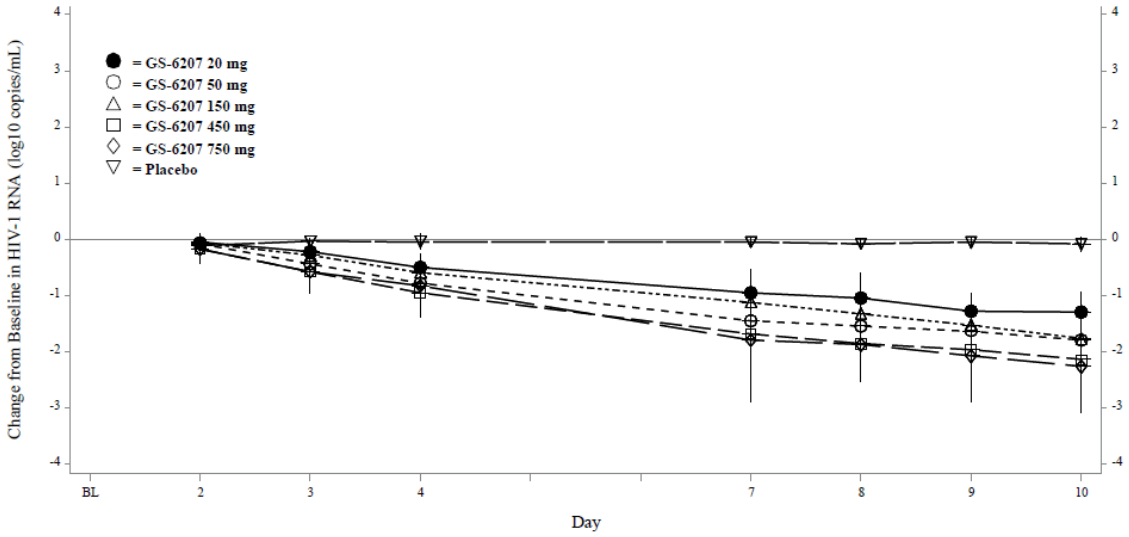
The median study duration (number of days between Day 1 and the last study date) was 226 days and ranged from 169 to 233 days across the 5 LEN cohorts.

The majority of participants were male (89.7%, 35 participants), White (53.8%, 21 participants), and not Hispanic or Latino (84.6%, 33 participants). The median age was 33 years (range: 19 to 65 years). The median (first quartile [Q1], third quartile [Q3]) baseline HIV-1 RNA was 4.53 (4.30, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) CD4 cell count was 463 (359, 614) cells/µL. The majority of participants were ART naive (82.1%).

Virologic Efficacy Results

Levels of HIV-1 RNA decreased following initiation of study drug (Figure 7). The mean (SD) maximum HIV-1 RNA reductions from baseline through Day 10 were 1.35 (0.318), 1.79 (0.476), 1.76 (0.203), 2.20 (0.468), and 2.26 (0.662) $\log_{10}$ copies/mL at doses of LEN 20, 50, 150, 450, and 750 mg, respectively. All participants who received ≥ 50 mg LEN had a > 1 $\log_{10}$ copies/mL reduction in their HIV-1 RNA through Day 10. Overall, antiviral activity was comparable across the dose range of 50 to 750 mg but lower at the 20 mg dose.

Figure 7. GS-US-200-4072: Mean and 95% CI Change from Baseline in HIV-1 RNA ($\log_{10}$ copies/mL) (Full Analysis Set)



GS-6207 20 mg (n=):	6	6	6	6	6	6	6
GS-6207 50 mg (n=):	6	6	6	6	6	6	6
GS-6207 150 mg (n=):	6	6	6	6	6	6	6
GS-6207 450 mg (n=):	6	6	6	6	6	6	6
GS-6207 750 mg (n=):	5	5	5	4	5	5	5
Placebo (n=):	10	10	10	9	10	10	10

BL = baseline; CI = confidence interval; HIV-1 = human immunodeficiency virus type 1; GS-6207 = lenacapavir (LEN)

Pharmacokinetic Results

The median T_{max} of LEN ranged between approximately 6 and 21 days postdose across treatment groups. The median $t_{1/2}$ values of LEN ranged between approximately 36 and 45 days and were comparable across the doses evaluated.

Following single-dose administration of LEN 20, 50, 150, 450, and 750 mg, mean LEN plasma concentrations on Day 10 were 2.6, 4.4, 12.9, 38.2, and 79.2 ng/mL, respectively. These values correspond to approximately 0.7-, 1.1-, 3.3-, 9.9-, and 20.5-fold higher, respectively, than the protein-adjusted 95% effective concentration for wild-type HIV-1 (3.87 ng/mL) in MT-4 cells.

Safety Results

Up to Day 10, AEs were reported for 21 of 29 participants (72.4%) who received LEN across the LEN treatment groups and 4 of 10 participants (40.0%) who received placebo. There were no notable differences in the number of participants who had AEs up to Day 10 across the increasing doses of LEN for doses > 20 mg. For participants who received LEN, the most commonly reported AEs were injection site pain (55.2%, 16 participants), injection site erythema (34.5%, 10 participants), and injection site induration (24.1%, 7 participants). The only AEs reported for > 1 participant in the placebo group were injection site pain (30.0%, 3 participants) and headache (20.0%, 2 participants).

No deaths, Grade 4 AEs, or AEs leading to study drug discontinuation were reported.
One participant experienced a Grade 3 SAE of atrial fibrillation, which occurred following methamphetamine use and was not considered related to study drug by the investigator. After the data cut, the same participant with a history of hypertension, hyperlipidemia, and tobacco abuse experienced Grade 4 SAEs of coronary artery disease and acute myocardial infarction, Grade 3 AE of unstable angina and angina pectoris, and Grade 3 SAE of noncardiac chest pain. All AEs and SAEs were considered not related to study drug by the investigator. Another participant experienced a Grade 2 SAE of small intestinal obstruction which was considered not related to study drug by the investigator.

A total of 5 participants (17.2%) who received LEN and 3 participants (30.0%) who received placebo had a Grade 3 or Grade 4 laboratory abnormality reported. The only Grade 3 or 4 abnormalities reported for more than 1 participant in the LEN group were transient CK elevations (n = 2 participants), attributed to recent strenuous exercise. No Grade 3 or 4 laboratory abnormality was reported for more than 1 participant in the placebo group during the study.

1.2.3.4.6. Study GS-US-200-4625

Study GS-US-200-4625 is a Phase 2/3, placebo-controlled, multicenter study of LEN together with an OBR in HTE PWH with multidrug resistant infection.

Participants in Cohort 1 were randomized to receive either oral LEN or placebo, while also continuing their failing regimen during a 14-day Functional Monotherapy Period. After this period, participants who received oral LEN switched to SC LEN (972 mg; 309 mg/mL;

2 × 1.5 mL) and OBR, and participants who had received placebo then received oral LEN and OBR for 14 days prior to switching to SC LEN (972 mg; 309 mg/mL; 2 × 1.5 mL) and OBR. Participants in Cohort 2 received oral LEN and OBR for 14 days before switching to SC LEN and OBR. Cohort 2 includes participants that did not meet the criteria for randomization in Cohort 1 or who joined the study after Cohort 1 was fully enrolled.

Disposition and Baseline Characteristics

Overall in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: LEN, 24 participants; placebo, 12 participants; Cohort 2: LEN + OBR, 36 participants). All 72 participants completed the Functional Monotherapy (Cohort 1, 36 participants) or Oral Lead-in Period (Cohort 2, 36 participants), and all received Day 1 SC LEN.

Of the 72 participants who received Day 1 SC LEN, 32 participants (all from Cohort 2) are continuing study drug in the Main Phase, and 37 participants completed study drug in the Main Phase (Week 52). Three participants discontinued study drug during the Main Phase. Reasons for premature discontinuation were lost to follow-up, investigator's discretion, and death (1 participant each, 1.4%). One participant who decided not to receive SC LEN at Week 52 and not to continue the study completed the study at the Week 52 visit. Thirty-six participants entered into the Extension Phase (Cohort 1: 34 participants; Cohort 2: 2 participants). Of the 36 participants who entered the Extension Phase, 34 participants are continuing study drug. Two participants discontinued study drug during the Extension Phase. Reasons for premature discontinuation were AE and lost to follow-up (1 participant each, 2.8%).

In Cohort 1, demographic and baseline characteristics were generally similar between the LEN and placebo groups. The majority of participants were male (72.2%; 26 of 36 participants), White (45.7%, 16 participants) or Black (45.7%, 16 participants), and not Hispanic or Latino (71.4%, 25 participants). Median age was 54 years (range: 24 to 71 years). Baseline disease characteristics were consistent with the profile of the HTE population, with a median (range) number of prior ARV medications of 9 (2, 24), and 75% of participants with CD4 cell count < 200 cells/μL (a hallmark of severe immune suppression and the criterion to diagnose AIDS). Differences were seen between the LEN and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage.

In Cohort 2, the majority of participants were male (77.8%; 28 of 36 participants), White (36.1%, 13 participants) or Asian (33.3%, 12 participants), and not Hispanic or Latino (86.1%, 31 participants). Median age was 49 years (range: 23 to 78 years). The baseline disease characteristics, prior ARVs, failing regimens, OBR regimen, and resistance characteristics for Cohort 2 were consistent with the profile of the HTE population.

Primary Virologic Efficacy Results

A significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period than those receiving placebo (87.5% vs 16.7%; $P < 0.0001$). To address the imbalance in baseline HIV-1 RNA between the LEN and placebo groups, a post hoc analysis of the primary efficacy endpoint with adjustment for baseline HIV-1 RNA using rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant: 87.5% versus 16.7%; $P = 0.0003$. To address the imbalance in baseline CD4 cell count between the LEN and placebo groups, post hoc analyses of the primary efficacy endpoint were conducted in participants with comparable or clinically relevant CD4 cell counts. These analyses showed that the difference between groups remained statistically significant for the comparison between participants in the LEN group with a low baseline CD4 cell count (median: 98.5 cells/μL; n = 12) and participants in the placebo group (median: 84.5 cells/μL; n = 12) ($P = 0.0008$) and between participants in the LEN and placebo groups with a baseline CD4 cell count < 200 cells/μL ($P < 0.0001$).

Secondary Efficacy Endpoints

At Week 26, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 80.6% (58 of 72 participants) and 87.5% (63 of 72 participants), respectively.

At Week 52, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants), respectively.

Preliminary Pharmacokinetic Results

Lenacapavir plasma PK parameters and concentration-time profiles based on interim analysis at Week 52 are presented in Table 18 and Figure 8. The key findings were:

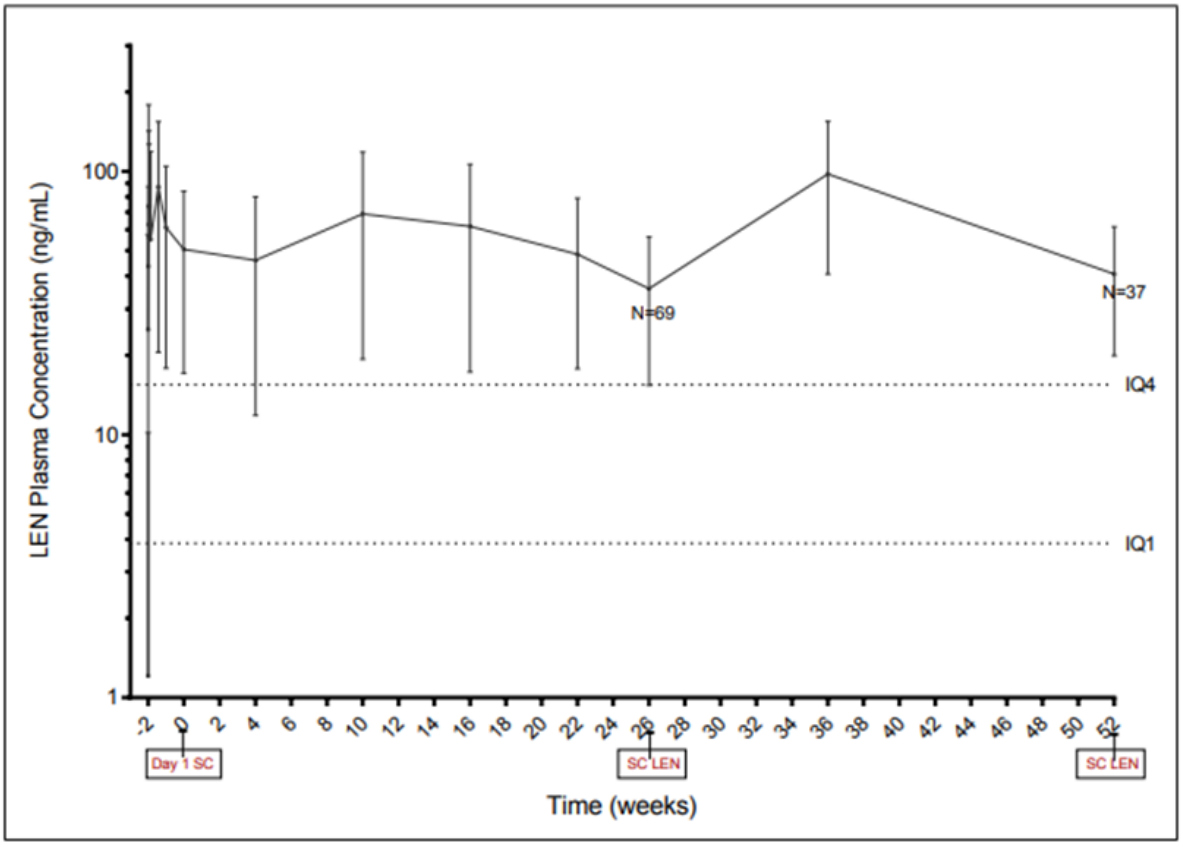
- Mean LEN concentrations and the lower bound 90% CI reached IQ4 (15.5 ng/mL) in approximately 1 hour postdose on Day 1 with majority of the participants (> 80%) achieving concentrations above IQ4 at 4 hours postdose on Day 1 and continued to be above IQ4 through the end of dosing intervals at Week 26 and Week 52.
- For the Oral Lead-in Period, mean (%CV) predose concentrations, and the lower bound 90% CI, on Day 2 (55.0 ng/mL [116%]; lower 90% CI = 42.3 ng/mL), on Day 8 (61.0 ng/mL [70.9%]; lower 90% CI = 52.5 ng/mL), and Day 1 SC (50.5 ng/mL [66.1%]; lower 90% CI = 44.0 ng/mL) exceeded IQ4.
- For the maintenance period, mean (%CV) predose concentrations, and the lower bound 90% CI, at Week 26 (35.9 ng/mL [57.1%]; lower 90% CI = 31.8 ng/mL) and at Week 52 (40.8 ng/mL [51.0%]; lower 90% CI = 35.0 ng/mL) exceeded IQ4.
- C_{trough} at Week 52 was 1.14-fold higher compared with Week 26 indicating minimal accumulation over the dosing period of 52 weeks.

Table 18. GS-US-200-4625: Plasma Pharmacokinetic Parameters of LEN Following Oral 600 mg Daily Dosing (Days 1 and 2) and 300 mg (Day 8), With SC LEN Injection Every 26 Weeks Starting From Day 15 (Day 1 SC)

PK Parameter Mean (%CV)	Day 2[a] (N = 70)	Day 8[a] (N = 72)	Day 1 SC (N = 72)	Week 26 (N = 69)	Week 52 (N = 37)
C_{trough} (ng/mL)	55.0 (116)	61.0 (70.9)	50.5 (66.1)	35.9 (57.1)	40.8 (51.0)
Lower 90% CI of C_{trough} (ng/mL)	42.3	52.5	44.0	31.8	35.0

%CV = percentage coefficient of variance; LEN = lenacapavir; SC = subcutaneous
a For Cohort 1B, Days 16 and 22 reflect Days 2 and 8 respectively, relative to the start of oral LEN.

Figure 8. GS-US-200-4625: Mean (SD) LEN Plasma Concentration-time Profiles (Semilogarithmic Scale) Following Oral 600 mg Daily Dosing (Days 1 and 2) and 300 mg (Day 8), With SC LEN Injection Every 26 Weeks Starting From Day 15 (Day 1 SC)



IQ = inhibitory quotient; LEN = lenacapavir; SC = subcutaneous; SD = standard deviation
On the X-axis, −2 to 0 represents 2-Week Oral Lead-in Period

Preliminary Safety Results

Functional Monotherapy Period

During the Functional Monotherapy Period, the percentages of participants who experienced AEs were: LEN 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants). Nausea was the only AE reported in > 1 participant (LEN 12.5%, 3 participants).

The only AE considered related to study drugs that was reported in > 1 participant was nausea (8.3%, 2 participants; LEN group).

No deaths, SAEs, AEs leading to discontinuation of study drug, or Grade 3 or higher AEs, were reported in either the LEN or placebo group.

All LEN Analysis

The percentage of participants who received LEN in Cohorts 1 and 2 and experienced AEs was 93.1% (67 of 72 participants). The 3 most commonly reported AEs were injection site pain (37.5%, 27 of 72 participants), injection site swelling (33.3%, 24 participants), and injection site erythema (27.8%, 20 participants). Some ISRs were attributed to enfuvirtide.

The majority of AEs were Grade 1 or 2 in severity. Grade 3 or higher AEs were reported for 16 participants (22.2%). Grade 3 or higher AEs that were reported for ≥ 2 participants were injection site erythema (5.6%, 4 participants), injection site edema, injection site pain, and injection site swelling (2.8%, 2 participants each). Four participants experienced Grade 3 or higher AEs that were considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and immune reconstitution inflammatory syndrome (1 participant each). The AE of abdominal abscess was an abscess at the injection site due to secondary infection most likely because the participant scratched the injection site.

Overall, 66.7% (48 of 72 participants) experienced treatment-related AEs. The most commonly reported treatment-related AEs were injection site pain and injection site swelling (30.6%, 22 participants), injection site erythema (25.0%, 18 participants), and injection site nodule (23.6%, 17 participants).

Serious adverse events were reported for 11.1% (8 of 72 participants). The only SAE that was reported for more than 1 participant was COVID-19. None of these events led to discontinuation of study drug. No SAEs were considered related to study drug. One SAE of cancer resulted in death, which was also reported as an AE leading to premature discontinuation from the study. This participant in Cohort 2 died on Study Day 90, and the cause of death was reported as cancer. The event was previously reported in the Week 26 analysis and was considered not related to study drug.

While no participant discontinued study drug due to AE at the Week 26 analysis, 1 participant (1.4%) in Cohort 1 experienced a Grade 1 AE of injection site nodule during the Extension Phase, leading to premature discontinuation from the study after receiving the Week 52 SC LEN injection. The event was considered related to study drug.

Overall, 45 participants (62.5%) experienced a study drug-related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR that resolved after a few days. No Grade 3 or 4 ISRs were reported beyond Week 26. The median (Q1, Q3) total duration of any study drug-related ISR was 8 (3, 67) days. The most frequently reported study drug-related ISRs (reported in ≥ 10% of participants overall) and duration in median (Q1, Q3) days were as follows:

- Injection site swelling (30.6%, 22 participants), 12 (6, 30) days
- Injection site pain (30.6%, 22 participants), 3 (2, 7) days
- Injection site nodule (23.6%, 17 participants), 180 (111, 330) days
- Injection site erythema (25%, 18 participants), 6 (3, 8) days
- Injection site induration (15.3%, 11 participants), 118 (15, 182) days

A numerically lower percentage of participants had ISRs after the second LEN injection compared with the first injection.

Overall, 17 participants experienced study drug-related injection site nodule, and 11 participants experienced study drug-related injection site induration. All events were Grade 1 or 2. Outcomes of injection site nodule and induration events reported due to Day 1 SC injection were as follows:

- Nodules: Ongoing (9/23 [39.1%]); Resolved (14/23 [60.9%])
- Indurations: Ongoing (1/8 [12.5%]); Resolved (7/8 [87.5%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to Day 1 SC injection was 107 (70, 227) days and 43 (15, 196) days, respectively.

Outcomes of injection site nodule and induration events reported due to the second LEN injection at Week 26 were as follows:

- Nodules: Ongoing (12/14 [85.7%]); Resolved (2/14 [14.3%])
- Indurations: Ongoing (3/7 [42.9%]); Resolved (4/7 [57.1%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration due to the second LEN injection at Week 26 was 92 (3, 180) days and 38 (9, 123) days, respectively.

1.2.3.4.7. Study GS-US-200-4334

Study GS-US-200-4334 is a Phase 2, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of LEN in combination with other ARV agents in ARV-naive PWH. Participants were randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups (Table 19).

Table 19. GS-US-200-4334: Study Treatments

Treatment Group	Time Period	Study Treatments
1	Induction (Day 1 through Week 27)	Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[a] SC LEN 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	SC LEN 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter Oral daily TAF (25 mg)
2	Induction (Day 1 through Week 27)	Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 300 mg (1 × 300 mg tablet) on Day 8 Oral daily F/TAF (200/25 mg) from Day 1 onwards for a total of 28 weeks[b] SC LEN 927 mg (3 mL of 309 mg/mL) on Day 15
	Maintenance (Week 28 through Week 80)	SC LEN 927 mg (3 mL of 309 mg/mL) at Week 28 and every 26 weeks thereafter Oral daily BIC (75 mg)
3	Day 1 through Week 80	Oral LEN 600 mg (2 × 300 mg tablet) on Days 1 and 2; 50 mg (1 × 50 mg tablet) daily from Day 1 onwards Oral daily F/TAF (200/25 mg)
4	Day 1 through Week 80	Oral daily B/F/TAF (50/200/25 mg)

BIC, B = bictegravir; F = emtricitabine; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide
a Treatment Group 1 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily TAF.
b Treatment Group 2 participants with < 50 copies/mL of HIV-1 RNA at Week 16 and Week 22 stopped F/TAF at Week 28 and initiated oral daily BIC.

Participants are treated for at least 80 weeks. Participants in Treatment Group 4 will complete the study at Week 80.

Disposition and Baseline Characteristics

Of the 249 participants screened, 183 were randomized, and 182 received at least 1 dose of study drug. Of these 182 participants, 22 participants (12.1%) prematurely discontinued the study drug during the Main Phase (ie, data collected on or before Week 80): 17 of 105 participants (16.2%) in the SC LEN total group, 4 of 52 participants (7.7%) in the oral LEN group, and 1 of 25 participants (4.0%) in the bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy®) group. The reasons for premature study drug discontinuation in the SC LEN total group were participant decision and lost to follow-up (each 4 participants [3.8%]), investigator's discretion, lack of efficacy, and AE (each 3 participants [2.9%]). The reasons for premature study drug discontinuation in the oral LEN group were lost to follow-up (3 participants [5.8%]) and participant decision (1 participant [1.9%]) and in the B/F/TAF group it was participant decision (1 participant [4.0%]).

As of the Week 54 data cut date, 8 participants entered into the Extension Phase (SC LEN total group, 5 participants; oral LEN group, 3 participants) and were continuing study drug. Demographic and baseline characteristics were similar across the treatment groups. Most participants were male (93.4%), cisgender (92.3%), and gay (69.8%). Median age was 29 years (range: 19 to 72 years). Race was balanced between Black versus non-Black (52.2% vs 47.8%, respectively), as was ethnicity between Hispanic or Latino versus not Hispanic or Latino (45.1% vs 54.9%, respectively). Baseline disease characteristics were similar across the treatment groups. Overall, the median (Q1, Q3) baseline HIV-1 RNA value was 4.37 (3.86, 4.74) $\log_{10}$ copies/mL, and the median (Q1, Q3) baseline CD4 cell count was 437 (332, 599) cells/µL.

Among the 182 participants, most had HIV-1 RNA ≤ 100,000 copies/mL (85.2%, 155 participants) and a CD4 cell count range of ≥ 350 to < 500 cells/µL (31.9%, 58 participants) or ≥ 500 cells/µL (37.4%, 68 participants).

Virologic Efficacy Results

The primary efficacy endpoint was HIV-1 RNA < 50 copies/mL at Week 54 using the US FDA-Defined Snapshot Algorithm. The primary analysis at Week 54 demonstrated similar results in each treatment group, with no significant difference between each of the LEN-containing groups and the B/F/TAF group, as follows:

- LEN total: 136 of 157 participants (86.6%)
- SC LEN + (DVY → TAF): 47 of 52 participants (90.4%)
- SC LEN + (DVY → BIC): 45 of 53 participants (84.9%)
- Oral LEN + DVY: 44 of 52 participants (84.6%)
- B/F/TAF: 23 of 25 participants (92.0%)

Preliminary Pharmacokinetic Results

Based on the interim analysis, for both the SC LEN treatment groups (SC LEN + [F/TAF → TAF] and SC LEN + [F/TAF → BIC]), mean LEN concentrations and the lower bound 90% CI were consistently maintained above IQ4 (15.5 ng/mL) from Day 2 onwards to Week 54. For SC LEN, mean predose concentrations at Week 54 for Treatment Groups 1 and 2 were 1.22-fold and 1.15-fold higher, respectively, compared with Week 28, indicating minimal accumulation over the dosing period of 54 weeks.

For oral LEN 50 mg once daily (oral LEN + F/TAF treatment group), mean LEN single anytime concentrations and the lower bound 90% CI reached IQ4 (15.5 ng/mL) by Day 2 and were maintained at Weeks 28 and 54 for this interim analysis. For oral LEN, accumulation was not apparent after Week 4, indicating steady state is achieved by Week 4. Mean predose concentration at Week 54 was consistent with that at Week 28.

Preliminary Safety Results

By Week 54, 89.2% of participants in the LEN total group (140 of 157 participants) and 96.0% of those in the B/F/TAF group (24 of 25 participants) had been exposed to study drug for at least 54 weeks. Overall, SC and orally administered LEN were generally safe and well tolerated. No deaths were reported by Week 54. Serious AEs were reported for 6.4% (10 of 157 participants) in the LEN total group. None of the SAEs were reported for > 1 participant, and all were considered not related to the study drugs.

Adverse Events

Similar percentages of participants in the LEN total (total of 157 participants) and B/F/TAF (total of 25 participants) groups had any AE by Week 54 (LEN total 87.9%, 138 participants; B/F/TAF 84.0%, 21 participants). The most commonly reported AEs were as follows:

- LEN total (157 participants), excluding ISRs: headache and nausea (each 13.4%, 21 participants), COVID-19 (9.6%, 15 participants), and syphilis and lymphadenopathy (each 8.9%, 14 participants)

- SC LEN total (105 participants), only ISRs: injection site erythema (31.4%, 33 participants), injection site swelling (27.6%, 29 participants), and injection site pain (23.8%, 25 participants)

- Oral LEN + DVY (52 participants): headache (13.5%, 7 participants), nausea and lymphadenopathy (each 11.5%, 6 participants), and COVID-19, syphilis, diarrhea, and influenza (each 9.6%, 5 participants)

- B/F/TAF (25 participants): syphilis and arthralgia (each 16.0%, 4 participants) and headache, COVID-19, back pain, weight increased, upper respiratory tract infection, and insomnia (each 12.0%, 3 participants)

The majority of the AEs reported in the 4 treatment groups were Grade 1 or 2 in severity. The percentage of participants with AEs of Grade 3 or higher was 8.3% (13 of 157 participants) in the LEN total group and 8.0% (2 of 25 participants) in the B/F/TAF group. No AEs of Grade 3 or higher were reported for > 1 participant in any treatment group. Since the Week 28 analysis, 2 additional AEs of Grade 3 or higher were reported in the LEN total group (SC LEN + [DVY → TAF] group: 1 participant; SC LEN + [DVY → BIC] group: 1 participant]) and 1 additional AE of Grade 3 or higher was reported in the B/F/TAF group (1 participant).

The percentages of participants with treatment-related AEs were as follows:

- LEN total (157 participants): 43.9% (69 participants)
- SC LEN total (105 participants): 58.1% (61 participants)
- Oral LEN + DVY (52 participants): 15.4% (8 participants)
- B/F/TAF (25 participants): 16.0% (4 participants)

The higher frequency of treatment-related AEs in the SC LEN total group was mainly because of ISRs, as reflected in the most common AEs considered related to study drugs:

- LEN total group (157 participants), excluding ISRs: nausea (5.1%, 8 participants), diarrhea and headache (each 2.5%, 4 participants), and fatigue (1.9%, 3 participants)
- SC LEN total group (105 participants), only ISRs: injection site erythema (26.7%, 28 participants), injection site swelling (22.9%, 24 participants), injection site pain (19.0%, 20 participants)
- Oral LEN + DVY (52 participants): nausea and diarrhea (each 3.8%, 2 participants), fatigue, headache, dyspepsia, flatulence, vomiting, weight increased, influenza, overdose, and hot flush (each 1.9%, 1 participant)
- B/F/TAF (25 participants): dyspepsia, salivary hypersecretion, insomnia, and weight increased (4.0%, 1 participant)

Overall, 57 of 103 participants (55.3%) who received SC LEN had a study drug-related ISR; all were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule. The most frequently reported ISRs (≥ 15% in the SC LEN total group) and their duration in median (Q1, Q3) days were as follows:

- Injection site erythema (27.2%, 28 participants), 5 (2, 11) days
- Injection site swelling (23.3%, 24 participants), 11 (6, 29) days
- Injection site pain (19.4%, 20 participants), 4 (1, 9) days

Overall, 15 of 103 participants had an AE of injection site nodule and 13 of 103 participants had an AE of injection site induration. All were Grade 1 or Grade 2, except for 1 participant with a Grade 3 injection site nodule. Outcomes of injection site induration and nodule events after the first (Day 15) SC LEN injection were as follows:

- Nodules: Ongoing (1 of 13 [7.7%]); Resolved (12 of 13 [92.3%])
- Indurations: Ongoing (6 of 9 [66.7%]); Resolved (3 of 9 [33.3%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 278 (136, 366) days and 202 (101, 213) days, respectively.

Outcomes of injection site induration and nodule events after the second (Week 28) SC LEN injection were as follows:

- Nodules: Ongoing (5 of 8 [62.5%]); Resolved (3 of 8 [37.5%])
- Indurations: Ongoing (3 of 6 [50.0%]); Resolved (3 of 6 [50.0%])

The median (Q1, Q3) duration of resolved injection site nodule and injection site induration was 152 (123, 240) days and 145 (4, 258) days, respectively.

1.2.4. Nonclinical Studies in Pregnancy or Lactation

This study may enroll participants assigned female at birth with reproductive potential and as such, available preclinical and clinical pregnancy and lactation studies are summarized below.

1.2.4.1. Pregnancy

Emtricitabine

Reproductive studies were conducted in rats, mice, and rabbits. Animal studies (performed at 60- to 120-fold human exposure) did not indicate harmful effects of FTC with respect to fertility, pregnancy, fetal parameters, parturition, or postnatal development. FTC is not considered to be genotoxic (DESCOVY IB).

Tenofovir Disoproxil Fumarate

Reproductive studies were conducted in rats and rabbits. Animal studies do not indicate direct or indirect harmful effects of TDF with respect to pregnancy, fetal development, parturition, or postnatal development. There were no effects on mating or fertility parameters {BIKTARVY 2021}.

Tenofovir Alafenamide

See Appendix 7 for US-specific text.

Lenacapavir

Animal studies do not indicate direct or indirect harmful effects of LEN on fertility, pregnancy, embryonal and fetal development, parturition, or postnatal development. Animal study TX-200-2043 was conducted to determine the potential adverse effects on male and female fertility. Lenacapavir was administered at doses of 0 (77% PEG 200, 10% ethanol, and 13% sterile water for injection), 20, or 100 mg/kg once via SC injection to male and female Crl:CD (SD) rats (N = 25/sex/group) via 200 mg/mL LEN (0.5, 0.1, and 0.5 mL/kg, respectively). Assessment of toxicity was based on mortality, clinical signs, body weights, body weight gains, food consumption, estrous cycles, reproductive performance, intrauterine survival, gross necropsy findings, sperm parameters, and organ weights. A dose level of 100 mg/kg, the highest dose level evaluated, was considered to be the no observed effect level (NOEL) for male and female systemic toxicity, male and female reproductive toxicity, and embryonic toxicity of LEN. At the NOEL (100 mg/kg), the C_{max} and $AUC_{0\text{-}1008h}$ values were 577 ng/mL and 441,000 h•ng/mL, respectively, for males and the C_{max} and $AUC_{0\text{-}672h}$ values were 597 ng/mL and 192,000 h•ng/mL, respectively, for females.

Animal study TX-200-2049 was conducted to determine the potential adverse effects of maternal LEN exposure from implantation to weaning on pregnancy, parturition, and lactation of the maternal (F_0) animals and on the growth, viability, and development of the F_1 neonates. A single SC dose of LEN was administered to assumed pregnant rats on Gestation Day 6 at dose levels of 30 and 300 mg/kg. Dams were exposed to LEN for the duration of gestation and to Lactation Day 10. No LEN-related systemic effects were noted at any dose level in the F_0 or F_1 generation; nonadverse local ISRs were observed in the F_0 LEN-dosed dams. Therefore, a dose level of 300 mg/kg, the highest level tested, was considered to be the no observed adverse effect level (NOAEL) for F_0 maternal systemic toxicity, and the NOAEL for F_1 developmental/neonatal, F_1 parental systemic, F_1 reproductive toxicity, and F_2 embryo intrauterine survival of LEN when administered SC as a single dose to Sprague-Dawley rats on Gestation Day 6. This dose level corresponds to F_0 maternal $AUC_{0–192h}$ and C_{max} values of 54,800 h•ng/mL and 412 ng/mL, respectively.

1.2.4.2. Lactation

In animal studies, it has been shown that TFV is secreted into milk.

1.2.5. Human Studies in Pregnancy

1.2.5.1. TDF Use During Pregnancy

The PK of TDF has been studied in pregnant women. In a retrospective population pharmacokinetic (PopPK) study of 46 pregnant women and 156 nonpregnant women who were receiving combination regimens that included TDF, pregnant women had a 39% higher apparent clearance of TFV compared with nonpregnant women {Benaboud 2012}. In the P1026s study of 37 pregnant women who received TDF-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum, the percentage of women with TFV AUC exceeding the target of 1.99 µg•hour/mL (the 10th percentile in nonpregnant adults) was lower in the third trimester than postpartum. Trough levels and AUCs were roughly 20% lower during the third trimester compared with postpartum. The median weight of the women below the target exposure (97.9 kg) was significantly higher than the median weight of the women who met the target exposure (74.2 kg) {Best 2015a}. In a study of women who did not have HIV and who were using TDF as part of PrEP, intracellular concentrations of tenofovir diphosphate (TFV-DP) in pregnant women were about 70% of those in nonpregnant women, even after adjusting for adherence {Pyra 2018}. These changes are not believed to be large enough to warrant dose adjustment of TDF during pregnancy.

Several studies have assessed outcomes in pregnant women receiving TDF or F/TDF for PrEP, demonstrating a favorable safety profile. In a study of 431 pregnancies that occurred during an HIV PrEP trial in which women who did not have HIV infection were randomized to receive placebo, TDF, or TDF plus FTC, there was no difference in risk of congenital anomalies between the TDF-containing arms and placebo arms {Mugo 2014}. A systematic review and meta-analysis evaluated the evidence for use of oral PrEP containing TDF as an additional HIV prevention strategy in populations at substantial risk for HIV. Eighteen studies were included, comprising data from 39 articles and 6 conference abstracts through April 2015. Across

populations and PrEP regimens, PrEP significantly reduced the risk of HIV acquisition compared with placebo. Additionally, oral PrEP containing TDF was not associated with increased pregnancy-related AEs or hormonal contraception effectiveness {Fonner 2016}.

TDF has been studied for HIV treatment during pregnancy and is currently included in first-line regimens for pregnant women in combination with FTC or lamivudine (3TC) in guidelines from the Republic of South Africa Department of National Health {Moorhouse 2018}, the World Health Organization (WHO) {Leslie 2004}, and the US National Institutes of Health (NIH) {AIDSinfo 2019}.

1.2.5.2. TAF Use During Pregnancy

See Appendix 7 for US-specific text.

1.2.5.3. FTC Use During Pregnancy

The PK data are available on the use of FTC during pregnancy. In the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s study, FTC exposure was modestly lower during the third trimester (geometric mean 8.0 µg•h/mL; 90% CI: 7.1–8.9) than during the postpartum period (9.7 µg•h/mL; 90% CI: 8.6–10.9). Fifty-eight percent of pregnant women (15 of 26 women) versus 95% of postpartum women (21 of 22 women) met the AUC target (≤ 30% reduction from typical exposure for nonpregnant historical controls). Trough FTC levels were also lower during pregnancy (C24 geometric mean trough [GMT] concentration 58 ng/mL; 90% CI: 37–63) than during the postpartum period (C24 GMT 85 ng/mL; 90% CI: 70-100) {Benaboud 2012}. Similar differences in PK parameters of FTC were found among women during pregnancy or after delivery in the PACTG 394 study and in a European study from the PANNA network {Best 2015a, Colbers 2013}. The increase in FTC clearance during pregnancy correlated with the normal pregnancy-related increase in GFR {Pyra 2018}. These changes are not believed to be large enough to warrant dose adjustment of FTC during pregnancy.

FTC has been studied for HIV treatment during pregnancy and it or the closely-related drug 3TC are currently included in first-line regimens for pregnant women in guidelines from the Republic of South Africa Department of National Health {Moorhouse 2018}, the Republic of Uganda Ministry of Health {Ministry of Health (MOH) 2016}, the WHO {Leslie 2004}, and the US NIH {AIDSinfo 2019}.

1.2.5.4. Lenacapavir Use During Pregnancy

There are no human studies of LEN in pregnancy. The partner study, GS-US-412-5624, evaluating the safety and efficacy of LEN in cisgender adolescent girls and young women, will evaluate LEN in pregnancy, including collection of pregnancy outcomes.

1.2.6. Human Studies in Lactation

1.2.6.1. TDF Use While Lactating

In a study of 50 lactating women without HIV infection who received F/TDF for PrEP (under directly observed therapy for 10 days), median peak and trough time-averaged TFV breast milk concentrations were similar at 3.2 ng/mL (interquartile range [IQR] 2.3–4.7) and 3.3 ng/mL (IQR 2.3–4.4), respectively. The infant plasma TFV concentration was unquantifiable (< 0.31 ng/mL) in 94% of infants (46 of 49 infants); in the 3 infants with detectable TFV, the level was 0.9 ng/mL in 2 infants and 17.4 ng/mL in 1 infant. Based on this study's results, the median TFV dose ingested through breast milk was estimated to be 0.47 µg/kg, or < 0.01% of the proposed daily 6 mg/kg pediatric TDF dose {Mugwanya 2016}. In a study of 59 breastfeeding women who received TDF/3TC/EFV in Uganda and Nigeria, no infant had detectable TFV in plasma {Waitt 2018}.

The inclusion of women who are lactating is consistent with the WHO guidelines concerning the benefits of breastfeeding and the recommendation that there does not appear to be a safety-related rationale for disallowing or discontinuing F/TDF for PrEP during lactation for HIV-negative women who are at continuing risk of HIV acquisition {World Health Organisation (WHO) Department of HIV/AIDS 2017}. This rationale is again further supported by the 2018 Southern African HIV Clinicians' Society (SAHCS) guidelines {Moorhouse 2018}. The WHO guidelines {World Health Organisation (WHO) Department of HIV/AIDS 2017} conclude that in settings with high risk of HIV acquisition and accompanying increased risk of mother-to-child transmission (MTCT), the advantages of using F/TDF for PrEP outweigh any potential risks, including any risks of fetal and infant exposure to TDF in PrEP regimens. This opinion is further supported by the 2018 SAHCS guidelines {Moorhouse 2018}. In these guidelines, SAHCS, in alignment with the WHO recommendations, advises that woman be maintained on F/TDF for PrEP throughout pregnancy and that the benefits of continuing F/TDF for PrEP throughout pregnancy in order to avoid seroconversion in the pregnant woman, with consequent significant risk of MTCT, are considered to far outweigh any potential risk of TFV or FTC exposure to the fetus.

1.2.6.2. TAF Use While Lactating

See Appendix 7 for US-specific text.

1.2.6.3. FTC Use While Lactating

Samples of breast milk obtained from 5 women living with HIV-1 show that FTC is secreted in human milk at estimated neonatal concentrations 3- to 12-times higher than the FTC half-maximal inhibitory concentration, but 3- to 12-times lower than the C_{min} achieved from oral administration of FTC. Breastfeeding infants whose mothers are being treated with FTC may be at risk for developing viral resistance to FTC in the setting of HIV infection {Benaboud 2011}. Other FTC-associated risks in infants breastfed by mothers being treated with FTC are unknown.

1.2.6.4. Lenacapavir Use While Lactating

It is not known if LEN is secreted in human breast milk.

1.2.7. Drug-Interaction Potential for F/TDF and LEN with Hormones

1.2.7.1. F/TDF and F/TAF

Emtricitabine (FTC) is primarily eliminated via renal excretion as unchanged drug and is not subject to enzyme or transporter-based DDIs. The primary metabolic route of TDF is hydrolase cleavage, a low-affinity and high-capacity system that is not likely to be impacted by commonly administered drugs. TDF, but not its major metabolite tenofovir (TFV), is a substrate for intestinal efflux transporters P-gp and BCRP {DESCOVY 2020, Tong 2007, TRUVADA 2020}. In clinical studies, F/TDF was not identified as a victim or perpetrator of clinically relevant enzyme or transporter-mediated DDIs {TRUVADA 2020}.

In agreement with these data, a dedicated Phase 1 evaluation between F/TDF and ethinylestradiol (EE)/norgestimate (a representative combination oral contraceptives [COC]) showed lack of clinically relevant changes in PK of either agent or pharmacodynamic markers of efficacy (luteinizing hormone, follicle-stimulating hormone, and progestin); thereby supporting the use of F/TDF with estrogen and progestin containing hormonal contraceptives. No meaningful differences in intracellular TFV-diphosphate or FTC-triphosphate were observed in TGW taking high-dose hormone therapy in the DISCOVER trial, suggesting that F/TDF is a safe and effective option for PrEP in TGW on gender-affirming hormone therapy (GAHT). A study with daily observed therapy of F/TDF in both TGW and TGM confirmed that there was no impact of GAHT on TFV-diphosphate in dried blood spots (DBS), nor was there any impact of F/TDF on estradiol or testosterone levels in either TGW or TGM {Grant 2020}.

See Appendix 7 for US-specific text.

1.2.7.2. LEN

The potential of LEN as a perpetrator of DDIs has been comprehensively evaluated in vitro and in the Phase 1 clinical program. LEN was identified as a moderate inhibitor of CYP3A and a weak inhibitor of P-gp using sensitive probe substrates MDZ and TAF, respectively, whereas in vitro data indicate it is not an inhibitor of UGT1A1. Based on these data, administration of CYP3A, UGT1A1, and P-gp substrates was permitted in LEN clinical development program. In vivo, P-gp plays a role limiting LEN oral absorption. LEN metabolism is primarily mediated by glucuronidation via UGT1A1 with CYP3A playing a minor role.

The general approach to GAHT therapy entails a combination of an estrogen (eg 17β-estradiol [E2]) with an androgen blocker (eg spironolactone, finasteride or dutasteride) and in some cases a progestogen {Deutsch 2016, Hembree 2017, Khan 2019, Unger 2016}. While a dedicated Phase 1 evaluation between LEN and GAHT has not been performed, Gilead has conducted a thorough literature review of inhibitory CYP3A-mediated drug interactions using the University of Washington Drug Interaction Solutions (UWDIS) database and other sources {Zhang 2018}.

The search revealed that the vast majority of hormone DDI studies have been performed with COC rather than GAHT. However, because of the overlap in the disposition pathways of EE and E2 (intestinal sulfation, hepatic CYP3A-mediated hydroxylation and conjugation with glucuronic acid), data from these studies can be extrapolated to E2.

Collectively, these studies showed that moderate CYP3A inhibitors (eg, isavuconazole, netupitant, fluconazole or grapefruit juice) caused only small (approximately 10% to < 40%) increases in the exposure (expressed as AUC) of EE, {Calcagnile 2013, DIFLUCAN 2020, Townsend 2017, Weber 1996} which did not warrant dose adjustment, and the use of COC has been allowed in LEN treatment studies. Similar or smaller increases were observed for oral E2 administered with the moderate CYP3A inhibitors erythromycin (E2 valerate) and grapefruit juice {Blode 2012, Schubert 1994}. While clinical DDI data for parenterally administered hormones in combination with CYP3A inhibitors are scarce, considering lack of intestinal contribution, no or only small changes in hormone levels are expected {Winkler 2015}. As perpetrators of DDIs, the effect of hormonal contraceptives is generally minor, with a few exceptions that involve drugs that undergo metabolism via CYP1A2 and UGT1A4 enzymes {Sun 2020}. Based on the totality of these data, a clinically relevant alteration in the PK of contraceptive hormones or LEN upon coadministration is not expected.

Similar to the estrogen hormones, anti-androgens and progestogens are extensively metabolized in the liver with CYP3A playing a role in the metabolism of dutasteride, finasteride and progestogens. While no to minimal clinical DDI data are available in the public domain, administration of these agents with moderate and strong CYP3A inhibitors is allowed regardless of potentially increased exposures per their respective prescribing information {AVODART 2020, PROSCAR 2013, PROVERA 2007}. Taken together, LEN can be safely coadministered with estrogen-based GAHT and androgen blockers in TGW on GAHT.

For TGM, exogenous testosterone is the mainstay of GAHT {Deutsch 2016, Unger 2016}. Long-acting injectable ester prodrugs of testosterone are typically used, in addition to topical formulations. Testosterone is metabolized to various 17-keto steroids through 2 different pathways {AndroGel 2020, Delatestryl 2016, Depo -Testosterone 2018}. The major active metabolites of testosterone are E2 and dihydrotestosterone, and about 90% of the dose is excreted renally as glucuronides and sulfates. Although testosterone is a CYP3A substrate, a search for clinical DDI studies in the UWDIS database did not return any results, neither for testosterone itself nor its marketed esters. The respective prescribing information does not contain restrictions with regard to coadministration of CYP inhibitors {AndroGel 2020, Delatestryl 2016, Depo -Testosterone 2018} and no interactions with LEN are anticipated. LEN can be safely coadministered with testosterone-based GAHT.

During this study, all participants on GAHT should be monitored according to clinical practice guidelines, including the evaluation of hormone levels as indicated.

1.3. Rationale for This Study

Both daily oral F/TDF and F/TAF have been shown to be highly effective for PrEP, and F/TDF is recommended per World Health Organization (WHO) guidelines as part of HIV prevention standard of care for individuals at risk for HIV {Center for Disease Control and Prevention 2019, World Health Organization (WHO) 2015}. However, the requirement of high adherence to a daily regimen has limited the potential population-level impact on reducing HIV incidence. The efficacy of PrEP is highly dependent on adherence. In studies that failed to demonstrate efficacy, lower adherence was clearly implicated {Marrazzo 2015, Van Damme 2012}.

According to Gilead estimates, there were approximately 140,000 individuals on TVD for PrEP and 95,000 on DVY for PrEP in the US as of July 2020, with an estimated 400,000 individuals who have initiated and discontinued use. This uptake of PrEP represents a small fraction of the 1.1 million people estimated by the US Centers for Disease Control and Prevention (CDC) to have an indication for PrEP {Sullivan 2018}. With a novel mechanism of action and a PK profile that can support every 6-month administration, LEN can address this significant unmet medical need to prevent HIV infection without relying on adherence to a daily oral regimen and by reducing stigma and concerns regarding disclosure, which limit uptake of PrEP. The availability of a long-acting SC option could significantly increase the number of people on PrEP and increase persistence and continued engagement on PrEP.

Long-acting PrEP options are expected to be a desired alternative to daily oral F/TDF or F/TAF for current PrEP users who self-identify as wanting less frequent dosing. In addition, long-acting PrEP will be an important option for a sizable population at high risk of HIV infection who have stopped taking or have never taken daily oral PrEP because of the requirement for daily pill taking. Most importantly, long-acting PrEP may increase the uptake of PrEP in the proportion of individuals who are at risk for HIV but who have never considered PrEP, which is particularly important for those disproportionately affected by HIV incidence. Developing long-acting PrEP options will be critical in both improving quality of life of PrEP users as well as providing protection against HIV infection in a broader set of individuals who could benefit from PrEP and has the potential to accelerate reduction in new HIV infections at a population level. This may be particularly important where use of daily oral PrEP options poses a challenge for a key portion of populations at disproportionate risk such as Black and Hispanic/LatinX individuals, TGW, particular Black and Hispanic/LatinX TGW, adolescents and young people, others belonging to socially marginalized groups in developed countries and in more general populations in the developing world {Coelho 2019}.

This study will aim to demonstrate the efficacy of LEN, particularly in these populations that are disproportionately affected by HIV incidence and with low uptake of current PrEP options, and who have been historically underrepresented in HIV clinical trials. Specifically, the study has set overall goals for the enrollment of 50% Black MSM in the US and 20% TGW study wide, to ensure the meaningful enrollment of historically underrepresented, disproportionately affected populations.

Early clinical data from the LEN for treatment program show that LEN demonstrates potent antiviral activity in PWH and sustained exposure supporting twice-yearly dosing. Data from the low-dose NHP rectal challenge model demonstrate that animals are protected from HIV-1 infection after a single dose of GS-CA1, a long-acting capsid inhibitor followed by multiple SHIV exposures. Taken together, these data suggest that LEN has the potential to provide substantial improvement over currently available PrEP therapies and to meet a high unmet need for alternative PrEP options by eliminating the need for daily adherence.

1.4. Rationale for Dose Selection of Study Drugs

F/TDF fixed dose combination (FDC) (200 mg FTC/300 mg TDF) will be dispensed to the randomized participants with instructions to administer 1 tablet orally by mouth once daily for PrEP. This dose of F/TDF was the dose evaluated in PrEP clinical trials and approved for PrEP.

See Appendix 7 for US-specific text.

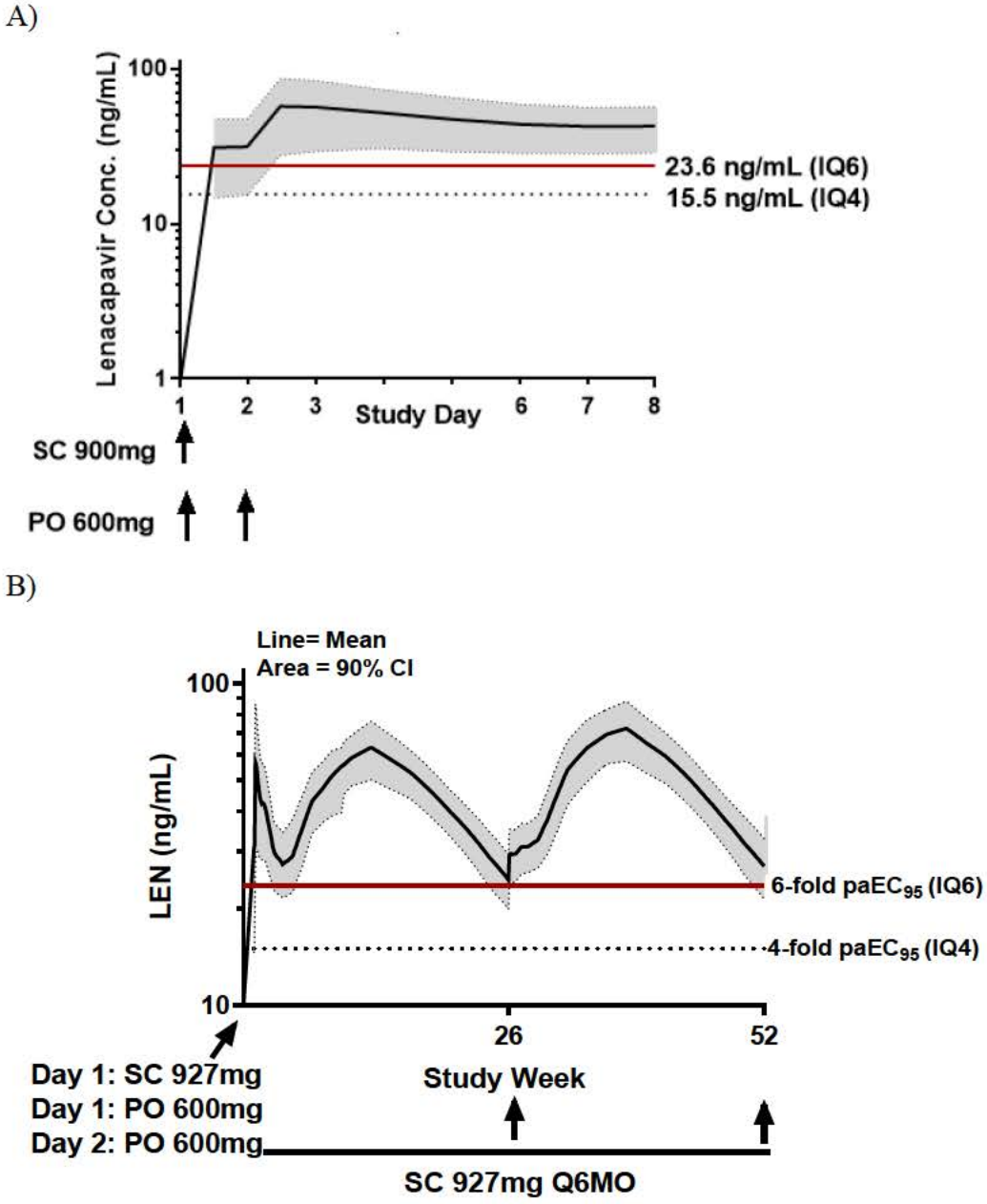
The rationale for dose selection for LEN in this study is supported by antiviral activity, PK and safety data from the ongoing Phase 1b POC study (GS-US-200-4072) in TN and treatment-experienced (but capsid inhibitor-naive) PWH, as well as PK and safety data from the two Phase 1 studies in healthy volunteers (Study GS-US-200-4538 and Study GS-US-200-4071). In the Phase 1b POC study (GS-US-200-4072), potent antiviral activity of LEN has been demonstrated; the mean maximum HIV-1 RNA decline over 10-day monotherapy after single SC doses of 50 to 450 mg was 1.8 to 2.2 $\log_{10}$ copies/mL. All treated participants achieved at least 1 $\log_{10}$ copies/mL decline in their HIV-1 RNA at Day 10. Antiviral activity on Day 10 was comparable across a dose range of single doses of 50 to 450 mg. At these doses, mean (%CV) LEN concentrations on Day 10 were 1.1- to 9.9-fold higher (eg, IQ 1.1 – 9.9) than the $paEC_{95}$ for wild type HIV-1 ($paEC_{95}$ = 3.87 ng/mL in MT-4 cells).

The LEN formulations and doses to be evaluated in this PrEP study are informed by PK and/or safety data from Phase 1 Studies GS-US-200-4071, GS-US-200-4538, and GS-US-200-5709 in healthy volunteers, as well as available safety data from the ongoing clinical studies in HTE and TN PWH (GS-US-200-4625 and GS-US-200-4334). In the absence of an established efficacy benchmark in the prevention setting, the current study will target systemic LEN exposures consistent with those of HIV-1 treatment, as per the recommendations of the US Food and Drug Administration (FDA) Guidance for Developing Systemic Drug Products for Pre-Exposure Prophylaxis {U. S. Department of Health & Human Services (DHHS) 2019}. To that end, the target LEN concentrations in the PrEP study are aligned with those of the ongoing Phase 2 and 3 clinical studies in PWH (GS-US-200-4625 and GS-US-200-4334). As with the ongoing Phase 2 and 3 studies in PWH, the proposed regimen targets an exposure whereby the lower bound of the 90% CI of mean LEN concentration is 4-fold higher than the $paEC_{95}$ (ie, IQ4) within a few days of dosing initiation through the end of the SC dosing interval (once every 6 months).

Currently, a SC LEN regimen (927 mg or 2 × 1.5 mL at 309 mg/mL, administered every 26 weeks) preceded by a 14-day oral lead-in is being evaluated in ongoing clinical studies in HTE and TN PWH (GS-US-200-4625 and GS-US-200-4334). As clinical data of LEN to date do not raise concern for acute safety issues, where an oral lead-in would be beneficial, a simplified LEN regimen is being proposed for this study: 927 mg SC LEN injection, 309 mg/mL

(2 × 1.5 mL) administered on Day 1 along with oral tablet doses of LEN 600 mg (2 × 300 mg) administered on Day 1 and Day 2. This will be followed by SC doses of LEN 927 mg administered every 26 weeks. The proposed simplified regimen is predicted to achieve target concentrations within a few days of dosing initiation with exposures maintained throughout the duration of the 6-month dosing interval (Figure 9). This is supported by preliminary PK data available through 26 weeks postdose from Study GS-US-200-5709 (Cohort 2; see Section 1.2.3.4.3) where the proposed simplified regimen demonstrates good agreement between the observed and predicted/simulated data.

Figure 9. **Simulated Plasma Profile of LEN Following the Proposed SC LEN Regimen Administered Every 26 Weeks With an Oral PK Load on Days 1 and 2**



CI = confidence interval; IQ4 = inhibitory quotient of 4; IQ6 = inhibitory quotient of 6; LEN = lenacapavir; $paEC_{95}$ = protein-adjusted 95% effective concentration from MT-4 cells (3.87 ng/mL); PO = oral; Q6MO = every 6 months; SC = subcutaneous

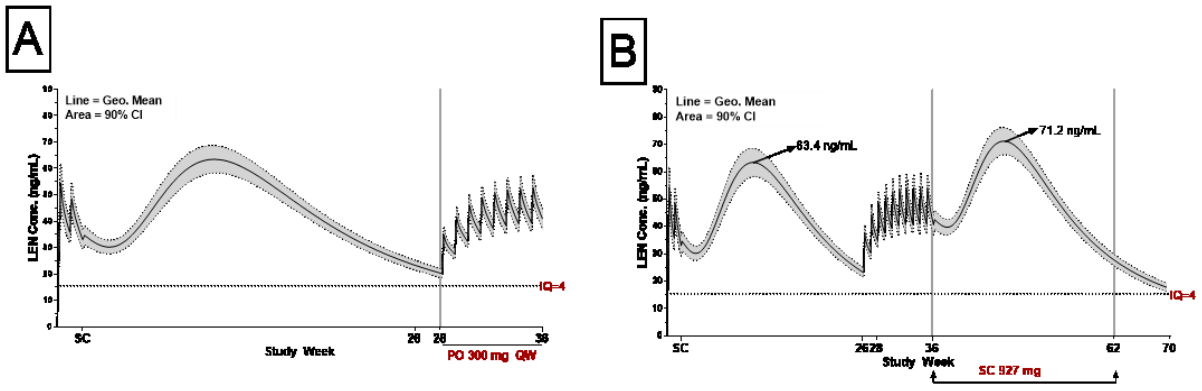
1.5. Rationale for Oral Weekly Bridging of Lenacapavir for Missed SC Injection

Oral bridging of LEN is supported by antiviral activity, PK, and safety data from a Phase 1b proof-of-concept study (GS-US-200-4072) and 2 ongoing Phase 2 and 2/3 studies (GS-US-200-4334 and GS-US-200-4625), as well as PK and safety data from 2 Phase 1 studies in healthy volunteers (GS-US-200-4071 and GS-US-200-4333). Phenotypic analyses and PK/PD modeling indicate that a LEN plasma concentration of ≥ 15.5 ng/mL, corresponding to IQ4 or higher, would provide near maximal antiviral activity (GS-US-200-4072).

The oral bridging dose of LEN is 300 mg administered once weekly starting 26 to 28 weeks after the last LEN SC injection. This oral weekly LEN bridging dose, even when started as late as 28 weeks after the last LEN SC injection, is predicted to immediately maintain the lower bound of the 90% CI of arithmetic mean for LEN C_{trough} above IQ4 (ie, even before reaching steady state) (Figure 10A). As long as the oral weekly LEN bridging is initiated between 26 to 28 weeks after the last SC LEN injection, the PK profile upon resuming SC injection is predicted to be comparable with that of the prior SC dose and within the target range regardless of when SC injection is resumed (Figure 10B).

LEN has been administered orally at doses up to 1800 mg (Study GS-US-200-4071). Safety data from all completed and ongoing clinical studies indicate that LEN is generally safe and well tolerated at the intended exposures.

Figure 10. Simulated Pharmacokinetic Profile of Oral Weekly Bridging of LEN (300 mg) (A) Prior to and (B) After Resuming SC Injection



EC_{95} = 95% effective concentration; IQ = inhibitory quotient; LEN = lenacapavir; PO = oral; SC = subcutaneous; QW = once weekly
The solid line and the shaded region correspond to the geometric mean and 90% CI, respectively. Inhibitory quotient is calculated as trough concentration/in vitro protein-adjusted EC_{95} ($paEC_{95}$) against wild-type virus. Horizontal dashed lines correspond to target IQ values of 4 based on phenotypic analyses and pharmacokinetic/pharmacodynamic modeling.

Preliminary Oral Bridging PK Data Available From Phase 2/3 Studies GS-US-200-4625 and GS-US-200-4334

Bridging with oral LEN was used in HIV treatment Studies GS-US-200-4625 and GS-US-200-4334 during a period of time when injection LEN was unavailable due to a clinical hold implemented as a result of container vial incompatibility.

In Study GS-US-200-4625, of 72 participants who were enrolled and received SC LEN, 57 participants received oral bridging during the clinical hold and were included in the Oral Bridging Analysis Set. All 57 participants completed the Week 26 visit (ie, 26 weeks after the first dose of SC LEN) before initiating oral bridging. A total of 13, 29, and 15 participants started oral bridging after Week 26 SC, Week 52 SC, and Week 78 SC, respectively. Three participants discontinued the study drug during oral bridging (1 due to death and 2 due to participant decision). A total of 54 participants resumed SC LEN after the Oral Bridging Period and are continuing the study drug at the date of the data cut.

Mean LEN concentration and the lower bound of the 90% CI were maintained above the efficacy target of IQ4 (15.5 ng/mL) from the first oral LEN bridging visit through the SC LEN resumption visit.

For the Oral Bridging Period, mean (%CV) predose concentration and the lower bound 90% CI at oral bridging Day 1 (46.1 ng/mL [56.3%]; lower 90% CI = 40.3 ng/mL), at oral bridging Week 10 (76.2 ng/mL [59.6%]; lower 90% CI = 66.1 ng/mL), at oral bridging Week 20 (74.8 ng/mL [116.1%]; lower 90% CI = 50.4 ng/mL), at oral bridging Week 30 (41.7 ng/mL [45.7%]; lower 90% CI = 29.9 ng/mL) exceeded IQ4. At the SC resumption visit, mean (%CV) predose concentration and the lower bound 90% CI (74.4 ng/mL [105.1%]; lower 90% CI = 56.2 ng/mL) also exceeded IQ4.

In Study GS-US-200-4334, 121 participants received oral bridging (SC LEN total group: 82 participants) or continued oral therapy (oral LEN group: 39 participants), 4 participants (3.3%; SC LEN total group: 2 participants; oral LEN group: 2 participants) prematurely discontinued study drug during the Oral Bridging Period (all due to participant decision). As of the oral bridging analysis data cutoff date, 117 participants (96.7%) were continuing study drug with SC LEN resumed (SC LEN total group: 80 [97.6%] participants) or continued oral therapy (oral LEN group: 37 [94.9%] participants).

In Study GS-US-200-4334, for Treatment Group 1 (SC LEN + [F/TAF → TAF]), mean (%CV) concentrations on Day 1 (28.8 ng/mL [47.7%]; lower bound 90% CI: 25.2 ng/mL), Week 10 (50.9 ng/mL [67.0%]; lower bound 90% CI: 41.1 ng/mL), and Week 20 (53.1 ng/mL [84.5%]; lower bound 90% CI: 39.6 ng/mL) exceeded IQ4. At Week 30, the mean (%CV) concentration was 43.7 ng/mL (74.7%), but a lower bound 90% CI was not reported due to a sample size of < 5. At the SC LEN resumption visit, the mean (%CV) concentration was 49.4 ng/mL (84.6%), with a lower bound 90% CI of 38.6 ng/mL.

For Treatment Group 2 (SC LEN + [F/TAF → BIC]), mean (%CV) concentrations on Day 1 (26.7 ng/mL [47.3%]; lower bound 90% CI: 23.0 ng/mL), Week 10 (59.3 ng/mL [73.6%]; lower bound 90% CI: 46.4 ng/mL), and Week 20 (51.9 ng/mL [70.2%]; lower bound 90% CI: 40.2 ng/mL) exceeded IQ4. At Week 30, the mean (%CV) concentration was 56.5 ng/mL (62.5%), but a lower bound 90% CI was not reported due to a sample size of < 5. At the SC LEN resumption visit, the mean (%CV) concentration was 52.2 ng/mL (66.6%), with a lower bound 90% CI of 42.7 ng/mL.

For Treatment Groups 1 and 2 combined (SC LEN total), mean (%CV) concentrations on Day 1 (27.8 ng/mL [47.4%]; lower bound 90% CI: 25.3 ng/mL), Week 10 (54.9 ng/mL [70.8%]; lower bound 90% CI: 47.1 ng/mL), Week 20 (52.5 ng/mL [77.7%]; lower bound 90% CI: 43.7 ng/mL), and Week 30 (50.1 ng/mL [62.3%]; lower bound 90% CI: 24.4 ng/mL) exceeded IQ4. At the SC LEN resumption visit, the mean (%CV) concentration was 50.7 ng/mL (75.7%), with a lower bound 90% CI of 43.6 ng/mL.

1.6. Risk/Benefit Assessment for the Study

F/TDF PrEP has previously been demonstrated to have high efficacy and favorable tolerability in cisgender men (CGM) and TGW in large randomized controlled trials, and thus F/TDF is expected to have good efficacy and safety in adherent participants in this study. While LEN has not been studied for PrEP in CGM, TGW, TGM, or GNB people, HIV treatment studies have demonstrated high antiviral potency and a favorable safety profile.

See Appendix 7 for US-specific text.

A Phase 2 study of the efficacy of LEN for PrEP has not been conducted because such a study could not be adequately powered to assess efficacy. However, data from studies of LEN for HIV treatment and from nonhuman primate studies indicate a sufficient probability of efficacy to justify a Phase 3 study. Studies of GS-CA1, a close analog of LEN with activity against HIV and SIV, has shown good protective efficacy against SHIV transmission from both rectal and vaginal challenge routes (see Section 1.2.3.3). Among human studies, the Phase 1b study GS-US-200-4072 assessed the ARV potency of LEN monotherapy in ART-naïve PWH. Participants in GS-US-200-4072 who received a single SC LEN dose of 450 mg or 750 mg had mean reductions in HIV-1 RNA greater than 2 $\log_{10}$ copies/mL by Day 10, demonstrating potent ARV activity of LEN (see Section 1.2.3.4.5). In the Phase 2 study GS-US-200-4334, ART-naïve PWH received LEN as part of a complete HIV-1 treatment regimen. Greater than 90% of participants receiving LEN had HIV-1 RNA < 50 copies/mL at Week 28, demonstrating the efficacy of LEN in the treatment of HIV (see Section 1.2.3.4.7 and {Gupta 2021}). Similarly, the Phase 2/3 study GS-US-200-4625 demonstrated good ARV efficacy of LEN in participants who were HTE and had multidrug resistance (see Section 1.2.3.4.6 and {Molina 2021}. Together, these preclinical and clinical data establish a sufficient likelihood of preventative efficacy to justify this Phase 3 study of the safety and efficacy of LEN for PrEP in CGM, TGW, TGM, and GNB.

1.6.1. Pandemic Risk and Mitigation

An infectious disease pandemic or other force majeure events may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is to evaluate the efficacy of LEN in preventing the risk of HIV-1 infection relative to the background HIV-1 incidence rate. Participants are CGM, TGW, TGM, and GNB.

2.1. Incidence Phase Objectives

The primary objective for the Incidence Phase of this study is to estimate the HIV-1 background incidence rate.

2.2. Randomized Blinded Phase Objectives

The primary objective for the Randomized Blinded Phase of this study is as follows:

- To evaluate the efficacy of LEN for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection

The secondary objectives for the Randomized Blinded Phase of this study are as follows:

- To compare the efficacy of LEN with F/TDF for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection
- To evaluate the efficacy of LEN for HIV-1 PrEP in participants at risk of HIV-1 infection in participants adherent to LEN
- To evaluate the safety and tolerability of LEN and F/TDF for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection
- To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥ 16 to < 18 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection


CCI

3. STUDY DESIGN

3.1. Incidence Phase Endpoints

The primary endpoint for the Incidence Phase of this study is the diagnosis of recent HIV-1 infection.

The background HIV-1 incidence per 100 person-years (PY) will be computed based on the recency assay algorithm.

3.2. Randomized Blinded Phase Endpoints

The primary endpoint for the Randomized Blinded Phase of this study is as follows:

- Diagnosis of HIV-1 infection

The secondary endpoints for the Randomized Blinded Phase of this study are as follows:

- Diagnosis of HIV-1 among participants while adherent to study drug (as defined by medium and high TFV-DP concentrations in DBS at the time of HIV-1 diagnosis for the F/TDF study drug group, and by LEN on time administration in the past 26 weeks for the LEN study drug group)
- Occurrence of treatment-emergent AEs (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP

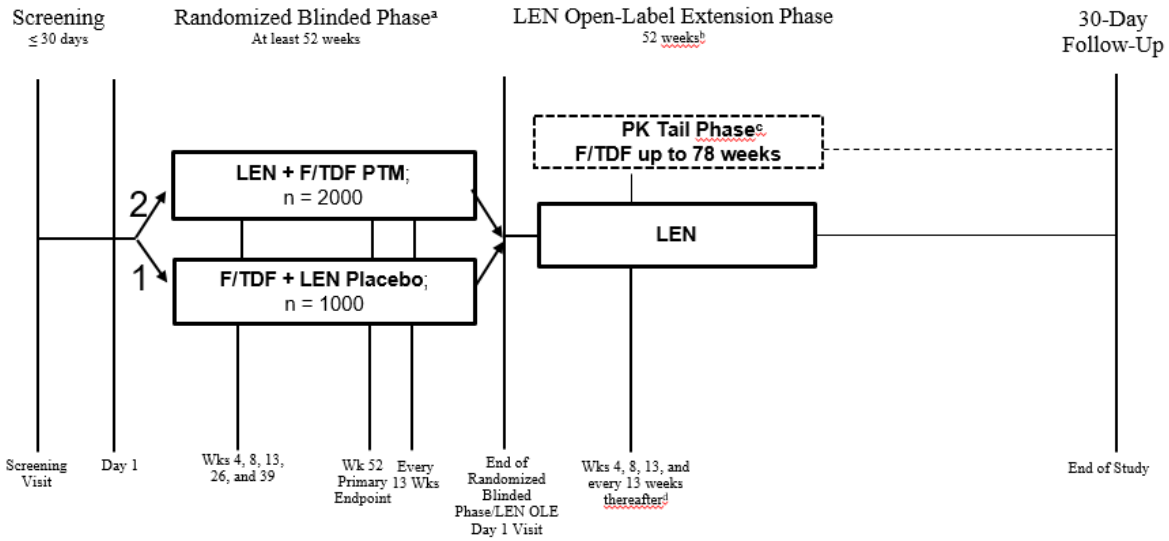
3.3. Study Design

This is a Phase 3, double-blind, multi-site, randomized study to compare HIV-1 incidence in the LEN study drug group with the nonrandomized control of background HIV-1 incidence, defined as the estimated HIV-1 incidence without PrEP in the population studied. F/TDF will serve as the internal active control. This includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-label Extension (OLE) Phase, and a PK Tail Phase. Participants eligible for the Randomized Blinded Phase will be randomized in a 2:1 ratio to receive LEN or F/TDF, respectively.

Enrollment of adolescents (participants 16 and 17 years of age) 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.

An overview of the study design is described below and shown in Figure 11.

Figure 11. Study Schema



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. If the Randomized Blinded Phase is stopped early for an efficacy outcome, some participants may have < 52 weeks of follow-up.

b In the OLE Phase, LEN will be administered every 26 weeks until either SC LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first. For participants on LEN in the Randomized Blinded Phase, the timing of the first OLE LEN injection will be dependent on the last LEN injection in the Randomized Blinded Phase. For participants on F/TDF in the Randomized Blinded Phase, the first OLE LEN injection will be on LEN OLE Day 1.

c Participants who prematurely discontinue study drug during the Randomized Blinded 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. In PK Tail Phase, US participants to receive F/TDF or F/TAF up to 78 weeks. See Appendix 7 for US-specific text.

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

3.3.1. Incidence Phase

The Incidence Phase will include initial assessments that will provide an estimate of the concurrent background HIV-1 incidence rate (the counterfactual rate), using a recency assay algorithm.

3.3.2. Randomized Blinded Phase

All eligible participants will receive study drug and be followed for approximately 52 weeks. On Day 1/Injection 1, SC LEN 927 mg or placebo will be administered at the study site with a PK loading dose of oral LEN 600 mg (2 × 300 mg tablets) or placebo-to-match (PTM) oral LEN (2 tablets). Participants should be observed for approximately 30 minutes after each SC injection dose. In addition, 2 oral LEN tablets or PTM LEN tablets will be provided to participants to self-administer on Day 2. If a participant misses the Day 2 dose, the dose should be administered immediately upon realizing the dose was missed. Subsequently, SC LEN or placebo SC LEN will be administered every 26 weeks (± 7 days). Participants will also receive oral F/TDF (200/300 mg), or PTM F/TDF to self-administer daily starting on Day 1/Injection 1. The site staff will contact the participant 1 week (± 2 days) after injection to assess for any ISRs and to confirm the participant has administered the Day 2 dose. Participants will attend study visits at Day 1/Injection 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days) thereafter until all enrolled participants have completed at least 52 weeks of follow-up in the study and Gilead completes the primary analysis. This will indicate the end of the Randomized Blinded Phase.

Participants randomized to LEN who decline to participate in the LEN OLE Phase will transition to the PK Tail Phase at this visit (ie, End of Randomized Blinded Phase visit will coincide with PK Tail Day 1 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 (Section 6.7.2).

Participants who prematurely discontinue blinded study drug during the Randomized Blinded 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.

3.3.3. Lenacapavir Open-Label Extension Phase

Following the completion of the primary analysis, if LEN demonstrates acceptable safety and efficacy in the Randomized Blinded Phase, the study will proceed to the LEN OLE Phase. 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 Randomized Blinded Phase visit will have the option to transition to the LEN OLE Phase at this visit (ie, End of Randomized Blinded Phase visit will coincide with LEN OLE Day 1 visit).

Participants will receive SC LEN injections every 26 weeks (± 7 days), until either LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first.

LEN OLE Day 1 will coincide with the end of the Randomized Blinded Phase. Participants randomized to LEN in the Randomized Blinded Phase who choose to participate in the LEN OLE Phase will receive SC LEN every 26 weeks (± 7 days) and have study visits every 13 weeks (± 7 days). The SC LEN injection visits in the LEN OLE Phase will be determined by the previous LEN injection (ie, participants whose last LEN injection was 13 weeks before LEN OLE Day 1 will receive their first open-label LEN injections at the LEN OLE Week 13 visit; participants whose last LEN injection was 26 weeks before LEN OLE Day 1 will receive their first open-label LEN injections at the LEN OLE Day 1 visit).

Participants randomized to F/TDF in the Randomized Blinded Phase will switch to SC LEN and have study visits at LEN OLE Day 1, Weeks 4 and 8 (± 2 days), Week 13 (± 7 days), and every 13 weeks (± 7 days) thereafter. Subcutaneous LEN will be administered at the LEN OLE Day 1, Week 26, and every 26 weeks thereafter. These participants will also receive a loading dose of oral LEN on LEN OLE Days 1 and 2, as described in the Randomized Blinded Phase. If a participant misses the Day 2 dose, the dose should be administered immediately upon realizing the dose was missed. Participants should be observed for approximately 30 minutes after each SC injection dose. The study site staff will contact the participant 1 week (± 2 days) after injection to assess for any ISRs and to confirm the participant has administered the Day 2 dose. Participants will complete the LEN OLE Phase once LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first.

Upon completion of the LEN OLE Phase or discontinuation of the study, participants will transition to locally available PrEP, which may include lenacapavir or other available PrEP modalities as clinically indicated. If a participant chooses to end participation in the LEN OLE Phase prior to conclusion, then the participant will complete an ESDD visit, be referred to locally available PrEP services as clinically indicated, and will complete a 30-day follow-up visit.

3.3.4. Pharmacokinetic Tail Phase

Participants who prematurely discontinue study drug in the RBP will receive OL oral F/TDF once daily for up to 78 weeks to cover the PK Tail Phase and complete study visits every 13 weeks (± 7 days).

These participants will complete the PK Tail Day 1 visit 26 weeks (± 7 days) after their last SC LEN injection. Upon completion of the PK Tail Week 78 visit, participants will be transitioned to local HIV prevention services, and return for a 30-day follow-up visit; at this point, participation in the study ends.

Upon unblinding, participants who were randomized to LEN in the Randomized Blinded Phase who decline to participate in the LEN OLE Phase will transition to the PK Tail Phase.

Upon unblinding, participants who were randomized to F/TDF in the Randomized Blinded Phase who decline to participate in the LEN OLE Phase will complete the ESDD visit, transition to local HIV prevention services, and return for a 30-day follow-up visit.

Participants can also transition to the PK Tail Phase if study drug is prematurely discontinued in the Randomized Blinded Phase. Upon unblinding, participants from the Randomized Blinded

Phase who were randomized to LEN will continue the PK Tail Phase for 78 weeks. Upon unblinding, participants from the Randomized Blinded Phase who were randomized to F/TDF will complete the ESDD visit, transition to local HIV prevention services, and return for a 30-day follow-up visit.

Participants who permanently discontinue study drug during the PK Tail Phase will complete an ESDD visit (Section 6.7.1) and a 30-day follow-up visit.

Participants who began receiving OL F/TDF due to unavailability of SC LEN/placebo may rejoin the RBP of the study if approved by the medical monitor. In these cases, as soon as SC LEN/placebo is available, the participant should be contacted and notified to return to the site and complete the injection visit that was missed due to SC LEN/placebo unavailability. For instance, if a participant could not receive SC LEN/placebo at Week 26 and began OL F/TDF, the participant would return to the site as soon as SC LEN/placebo administration is feasible and resume the study at the Week 26/Injection 2 visit.

See Appendix 7 for US-specific text.

3.3.5. Discontinuation Criteria

If a participant discontinues study drug for any reason other than acquiring HIV, every attempt should be made to keep the participant in the study. Participants who prematurely discontinue study drug in the Randomized Blinded Phase will transition to the PK Tail Phase. If a participant chooses not to enter the PK Tail Phase (after discussion of benefits/risks with the investigator), the participant will complete an ESDD visit (Section 6.7.1) and a 30-day follow-up visit (Section 6.7.2) and be withdrawn from the study. The ESDD 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.

A participant who is diagnosed with HIV during the study will discontinue study drug and will be required to return to the study site for follow-up at 30 days (± 14 days) and 90 days (± 14 days) after confirmation of HIV infection (Section 6.7.3). 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 is < 50 copies/mL at which point their participation will conclude. Participants will be followed up for a maximum of 1 year from the date they were diagnosed with HIV infection. The procedures performed at the 90-day post-HIV follow-up visit should be carried forward for these visits thereafter.

Study drug will be discontinued as applicable in the following instances:

- HIV infection is diagnosed
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest

- Participant request to discontinue for any reason
- Study drug may be discontinued as applicable in the following instances:

A) Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the participant may resume study dosing at the discretion of the investigator (see Section 6.8.1 for criteria for restarting study drug after an interruption)

B) Participant nonadherence to study drug or injection visits

- At the discretion of the investigator
- Discontinuation of the study at the request of Gilead, a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC).

3.4. Study Drugs

Approximately 3000 participants who meet all eligibility criteria will be randomized in a 2:1 ratio into 1 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)

3.5. Duration of Study Drug Administration

Participants enrolled in the Randomized Blinded Phase will receive study drug for approximately 52 weeks as described in Section 3.3.2.

Participants transitioning to the LEN OLE Phase will receive SC LEN injections every 26 weeks until either LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first as described in Section 3.3.3.

Participants eligible for the PK Tail Phase will receive oral F/TDF once daily for up to 78 weeks as described in Section 3.3.4.

See Appendix 7 for US-specific text.

3.6. End of Study

End of study is defined as the last participant's last observation (last visit).

3.7. Poststudy Care

Participants randomized in the study who have completed or terminated participation in the study will be transitioned to local HIV prevention services.

Participants who are diagnosed with HIV during the study will be referred to locally available HIV treatment and care services upon confirmation of HIV infection and be encouraged to immediately begin an HIV-1 treatment regimen (Section 6.13).

3.8. Source Data

The source data for this study will be obtained from electronic data capture (EDC), interactive web response system (IWRS), central laboratory, local laboratory, specialty laboratory, and questionnaires.

3.9. Biomarker Testing

4. PARTICIPANT POPULATION

Inclusion of participants disproportionally affected by HIV and historically underrepresented in HIV clinical studies, particularly Black and Hispanic/LatinX MSM and transgender people, is an important goal of this study. Furthermore, the novel counterfactual background HIV incidence design of this study necessitates recruitment and enrollment of participants in populations with high background HIV incidence (eg, at least 3 per 100 PY). In order to ensure the study achieves the goals of recruiting priority populations disproportionately affected by HIV and historically underrepresented in HIV clinical studies, specific enrollment goals have been established. In the US, where Black MSM are disproportionally affected by HIV, the study will strive to enroll at least 50% Black MSM, consistent with normative guidance for the goals of enrollment of Black MSM {Watson 2014}. Globally, the study will strive to enroll 20% TGW study wide. The study team will collaborate with individual sites to develop site-specific recruitment plans to ensure the inclusion of priority populations. During the enrollment period, the study team will monitor the race, ethnicity, and gender of participants and provide ongoing guidance, feedback, and support to ensure that individual sites and the study overall achieves its goals for the recruitment of priority populations.

4.1. Number of Participants and Participant Selection

The study includes a cross-sectional study (Incidence Phase), Randomized Blinded Phase, LEN OLE Phase, and PK Tail Phase.

The Incidence Phase of the study will remain open until the background HIV-1 incidence rate has been determined. Approximately 3000 participants will be randomized in the Randomized Blinded Phase to receive study drug. Participants must meet all eligibility criteria to be eligible for participation in the Incidence Phase and the Randomized Blinded Phase. The collection of race, ethnicity, gender, and age data allows for the analysis and reporting of safety and efficacy data by demographic subgroups as required by certain health authorities.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Eligibility Criteria for the Incidence Phase

4.2.1. Inclusion Criteria for the Incidence Phase

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

2) 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.

3) Age ≥ 16 years at screening. Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first DMC review of the unblinded safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents.

4) HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months

5) Sexually active with ≥ 1 partner assigned male at birth (condomless receptive anal sex) in the last 12 months and 1 of the following:

   a) Condomless receptive anal sex with ≥ 2 partners in the last 12 weeks

   b) History of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks

   c) Self-reported use of stimulants with sex in the last 12 weeks

6) Willing and able to comply with study procedures

4.2.2. Exclusion Criteria for the Incidence Phase

1) Prior use of HIV PrEP (including F/TDF or F/TAF) or HIV postexposure prophylaxis (PEP) in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir)

2) 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).

4.3. Eligibility Criteria for the Randomized Blinded Phase

4.3.1. Inclusion Criteria for the Randomized Blinded Phase

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

1) Negative local rapid fourth generation HIV-1/2 Ab/Ag, central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative nucleic acid amplification testing (NAAT) (Appendix 5)

2) Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min at screening according to the Cockcroft-Gault formula for creatinine clearance (CLcr) {Cockcroft 1976}:

$$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times [0.85 \text{ if female}] = CL_{cr} \text{ (mL/min)}$$

3) Body weight ≥ 35 kg

4) 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 as described in Appendix 6.

4.3.2. Exclusion Criteria for the Randomized Blinded Phase

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

1) 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, which is allowed and does not require medical monitor approval.

2) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

3) Acute viral hepatitis A, B, or C or evidence of chronic hepatitis B or C infection

   a) If a participant has a negative hepatitis B surface antigen (HBsAg), negative hepatitis B surface antibody (HBsAb), and positive hepatitis B core antibody (HBcAb), hepatitis B virus (HBV) DNA testing will be completed. If the HBV DNA result is positive, the participant is a screen failure. Participants found to be susceptible to HBV infection will be offered HBV vaccination.

   b) If the hepatitis C virus (HCV) Ab result is positive, then HCV RNA will be evaluated. Participants found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.

4) Severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, variceal bleeding)

5) Have a suspected or known active, serious infection(s) (eg, active tuberculosis, etc)

6) Need for continued use of any contraindicated concomitant medications

7) Have a history of osteoporosis or bone fragility fractures

8) Current alcohol or substance abuse judged by the investigator to be problematic such that it potentially interferes with participant study adherence

9) Grade 3 or Grade 4 proteinuria or glycosuria at screening that is unexplained or not clinically manageable

10) Participants assigned female at birth of childbearing potential who are pregnant or lactating at screening or on Day 1. Participants must have a negative pregnancy test at screening and on Day 1 (see "Definition of Childbearing Potential" in Appendix 6).

11) Any other clinical condition, laboratory abnormalities, or psychosocial condition or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

Participants will be assigned a screening number using IWRS on the day of the Incidence Phase screening visit. Participants who consent and are eligible for the Randomized Blinded Phase will keep their screening number assigned from the Incidence Phase. Upon confirmation that all screening procedures have been completed and eligibility criteria have been met, the investigator or designee will enroll and randomize the participant into the study using IWRS to receive study drug (Randomized Blinded Phase only). Once a participant number has been assigned, it will not be reassigned to another participant.

Randomization in IWRS may occur approximately 3 days prior to the Day 1/Injection 1 visit.

5.1.1. Randomization

Participants who meet all Randomized Blinded Phase eligibility criteria will be randomized in a 2:1 ratio to either active LEN or once daily oral F/TDF starting on Day 1/Injection 1 using IWRS. There is no stratification for randomization. The randomization list will be generated by the IWRS provider.

5.1.2. Blinding

During the Randomized Blinded Phase, participants and all personnel directly involved in the conduct of the study will be blinded to study drug assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the unblinded study pharmacist, or designee, in a blinded fashion to the participants. The PK File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management who facilitates the data transfer of PK files between Gilead and vendors will remain unblinded. Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS for purposes of study drug inventory management will remain unblinded. Individuals in Patient Safety (PS) responsible for safety signal detection, investigational new drug (IND) safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group-level summaries. Individuals in Clinical Pharmacology may be unblinded for the purpose of PopPK/pharmacodynamic analysis. External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded to produce outputs supporting data review by an independent DMC or IND safety reporting. External dried blood spot and pharmacology bioanalytical vendors may be unblinded for the purposes of identifying participants for whom study drug concentrations are to be analyzed. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or regulatory agency inspections. If the DMC recommends early study termination, including stopping enrollment for efficacy, an Oversight Committee may be unblinded for a thorough evaluation of the recommendation. None of the unblinded staff at the investigational site, vendors or Gilead will be involved in daily activities related to capturing and processing clinical data.

During the Randomized Blinded Phase, the site pharmacist, investigational site staff preparing and administering the study drugs, and study monitors responsible for study drug accountability will be unblinded while Gilead staff, any other investigational site personnel, and study participants will remain blinded. A limited number of Gilead or CRO Clinical Operations personnel may potentially receive unblinding information as part of a sponsor oversight role. To mitigate the risks of inadvertently releasing the treatment information, Gilead staff will only be provided with the unblinded information when there is a need to access such information. Should Gilead staff receive unblinding information, they will maintain the confidentiality of the unblinded information and will not communicate the information to blinded sites or participants as specified in Gilead standard operating procedures (SOPs).

Detailed instructions and additional procedures for maintaining the blinding of SC LEN and placebo SC LEN are outlined in the study Pharmacy Manual, which will be provided to each site.

5.1.3. Planned Interim Unblinding

Additionally, to assess the safety and/or efficacy of LEN for planning and development of this compound, a Gilead unblinded internal DMC, independent of the blinded study team, may be assembled. This committee, if assembled, will consist of at least 1 representative from Clinical Research, Biostatistics, and PS, and may include other personnel as necessary. The Gilead medical monitor, other Clinical Research, Biostatistics or PS staff directly interacting with the study sites or data processing or analysis will not be participating in the internal monitoring committee and will not be unblinded to the participant study drug assignment.

The scope of responsibilities, access to data as well as level of unblinding, membership, conduct, and meeting schedule of the internal unblinded team will be documented in the planned unblinding committee charter as specified in Gilead SOPs.

5.1.4. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain study drug assignment directly from the IWRS for that participant. In case of technology failure, the principal investigator (PI) will contact the support line of the IWRS provider directly. After proper identification of user credentials, the support personnel will provide the treatment assignment to the PI and the participant will discontinue study drug but may continue participation in the study. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Study drug assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation along with the date on which the study drug assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any study drug unblinding.

Blinding of study drug is critical to the integrity of this clinical study. Therefore, if a participant's study drug assignment is disclosed to the investigator, the participant will have blinded study drug discontinued and proceed to the PK Tail Phase. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

5.2. Description and Handling of Study Drugs

5.2.1. Formulation

5.2.1.1. Lenacapavir

LEN injection, 309 mg/mL, is a clear, yellow to brown solution for SC injection. In addition to the active ingredient, LEN injection, 309 mg/mL, contains the following inactive ingredients: PEG 300 and water for injection.

Placebo for LEN injection is a clear, colorless solution for SC injection. Placebo for LEN injection contains the following inactive ingredient: PEG 400.

LEN tablets, 300 mg, are capsule-shaped, film-coated beige tablets, debossed with "GSI" on one side of the tablet and "62L" on the other side of the tablet. Each tablet core contains the equivalent of 300 mg LEN in the form of LEN sodium. In addition to the active ingredient, LEN tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, mannitol, poloxamer 407, copovidone, croscarmellose sodium, magnesium stearate, PEG, polyvinyl alcohol, talc, titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow.

PTM LEN tablets, 300 mg, are capsule-shaped, film-coated beige tablets, debossed with "GSI" on one side of the tablet and "62L" on the other side of the tablet. PTM LEN tablets, 300 mg, contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, PEG, polyvinyl alcohol, talc and titanium dioxide, iron oxide red, iron oxide black, and iron oxide yellow.

5.2.1.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

F/TDF 200/300 mg tablets are blue, capsule-shaped, film-coated tablets debossed with "GILEAD" on one side of the tablets and "701" on the other side of the tablet. Each tablet core contains 200 mg of FTC and 300 mg of TDF. In addition to the active ingredients, the F/TDF tablets contain the following inactive ingredients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, lactose monohydrate, magnesium stearate, hypromellose, titanium dioxide, triacetin, and FD&C blue #2/indigo carmine aluminum lake.

PTM F/TDF tablets are blue, capsule-shaped, film-coated tablets debossed with "GILEAD" on one side of the tablets and "701" on the other side of the tablet. PTM F/TDF tablets contain the following inactive ingredients: denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, triacetin, and FD&C blue #2/indigo carmine aluminum lake.

5.2.1.3. Emtricitabine/Tenofovir Alafenamide (F/TAF)

See Appendix 7 for US-specific text.

5.2.2. Packaging and Labeling

5.2.2.1. Lenacapavir

LEN injection, 309 mg/mL, and placebo for LEN injection are supplied as a sterile solution packaged in a single-use, clear vial fitted with a rubber stopper and an aluminum flip-off seal.

LEN tablets, 300 mg, and PTM LEN tablets, 300 mg, are packaged in white, high-density polyethylene (HDPE) bottles. Each bottle contains 4 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, and aluminum-faced liner.

Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.2.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

F/TDF tablets and PTM F/TDF tablets are packaged in a white HDPE bottle. Each bottle contains 30 tablets and silica gel desiccant. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Study drugs to be distributed to centers in the US, and other participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.2.3. Emtricitabine/Tenofovir Alafenamide (F/TAF)

See Appendix 7 for US-specific text.

5.2.3. Storage and Handling

Until dispensed to the participants, all study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.2.3.1. Lenacapavir

LEN injection, 309 mg/mL and placebo for LEN injection should be stored below 30°C (86°F), protected from light. Storage conditions are specified on the label.

LEN tablets, 300 mg, and PTM LEN tablets, 300 mg, should be stored below 30°C (86°F). Storage conditions are specified on the label.

5.2.3.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

F/TDF tablets and PTM F/TDF tablets must be stored at a controlled room temperature below 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

5.2.3.3. Emtricitabine/Tenofovir Alafenamide (F/TAF)

See Appendix 7 for US-specific text.

5.3. Dosage and Administration of Study Drugs

5.3.1. Lenacapavir

5.3.1.1. Dosage and Administration of Subcutaneous Lenacapavir

LEN will be administered without regard to food during the Randomized Blinded Phase and the LEN OLE Phase as follows:

- Randomized Blinded Phase
  - SC LEN 927 mg (2 × 1.5 mL injections) or placebo SC LEN (2 × 1.5 mL injections) every 26 weeks starting on Day 1/Injection 1
  - Loading dose: oral LEN 600 mg (2 × 300 mg tablets) or PTM oral LEN (2 tablets) once daily on Day 1/Injection 1 and Day 2
- LEN OLE Phase
  - SC LEN 927 mg (2 × 1.5 mL injections) every 26 weeks
  - Loading dose for participants randomized to F/TDF: oral LEN 600 mg (2 × 300 mg tablets) once daily on Days 1 and 2

See Section 5.3.1.2 if SC LEN/placebo cannot be administered within the injection visit window.

5.3.1.2. Dosage and Administration of Oral Weekly Bridging of Lenacapavir

If SC LEN/placebo cannot be administered within the injection visit window due to extenuating circumstances and the investigator deems it clinically appropriate to continue LEN/placebo, bridging with oral LEN/placebo may be permitted with medical monitor approval. Information on assessments during oral weekly LEN/placebo bridging is found in Section 6.8.3.

Dosing for bridging with oral LEN/placebo will differ depending on the time elapsed since the last SC LEN/placebo injection. See Table 20 for details.

- If 25 to 28 weeks have elapsed since the last SC LEN/placebo injection, LEN/placebo reloading is not required prior to starting oral weekly LEN/placebo bridging.
- If > 28 weeks have elapsed since the last SC LEN/placebo injection, LEN/placebo reloading will be required prior to starting oral weekly LEN/placebo bridging.

Table 20. Oral LEN/Placebo Bridging and SC LEN/Placebo Restart Dosing Schedule

Day of Oral Bridging	No Reloading 25 to 28 Weeks Since Last Injection	Reloading > 28 Weeks Since Last Injection
Day 1	Oral LEN 300 mg (1 × 300 mg tablet) or PTM oral LEN (1 tablet)	Oral LEN 600 mg (2 × 300 mg tablets) or PTM oral LEN (2 tablets)
Day 2	NA	Oral LEN 600 mg (2 × 300 mg tablets) or PTM oral LEN (2 tablets)
Day 8 and weekly until SC LEN/placebo resumed	Oral LEN 300 mg (1 × 300 mg tablet) or PTM oral LEN (1 tablet)	Oral LEN 300 mg (1 × 300 mg tablet) or PTM oral LEN (1 tablet)

LEN = lenacapavir; NA = not applicable; PTM = placebo-to-match; SC = subcutaneous

If a participant misses an oral LEN/placebo dose during weekly bridging, recommendations for restarting are summarized in Table 21.

Table 21. Missed Oral LEN/Placebo Dose Recommendations During Oral LEN/Placebo Weekly Bridging

Number of Days Since Missed Weekly Oral 300 mg LEN/Placebo Dose	Recommendation
1 to 6 days (1 missed weekly dose)	Take 300 mg (1 tablet) LEN/placebo orally as soon as possible. Then resume weekly dosing by taking 300 mg (1 tablet) LEN/placebo orally on the next scheduled weekly dosing day and weekly thereafter.
7 to 14 days (1-2 missed weekly doses)	Take 600 mg (2 tablets) LEN/placebo orally as soon as possible. Then resume weekly dosing by taking 300 mg (1 tablet) LEN/placebo orally on the next scheduled weekly dosing day and weekly thereafter. If participant remembers on the scheduled weekly dosing day, take a total of 600 mg (2 tablets) LEN/placebo (never take greater than 600 mg on a single day).
More than 14 days (3 or more missed weekly doses)	Consult with medical monitor

LEN = lenacapavir

5.3.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

F/TDF (200/300 mg) tablets and PTM F/TDF tablets will be provided by Gilead. Study drug will be dispensed to participants at the Day 1/Injection 1 visit. Participants will be instructed to take their first dose of study drug following completion of the study procedures at the Day 1/Injection 1 visit. If study drug was not taken in the clinic following the completion of Day 1/Injection 1 study procedures, initiation of the study drug must take place within 24 hours after the Day 1/Injection 1 visit and after the investigator has confirmed eligibility with the participant.

Participants will continue to take their daily dose of F/TDF or PTM F/TDF each day.

5.3.3. Emtricitabine/Tenofovir Alafenamide (F/TAF)

See Appendix 7 for US-specific text.

5.4. Prior and Concomitant Medications

Medications and use of herbal/natural supplements listed in Table 22 are excluded or should be used with caution while participants are taking study drug on the study due to potential DDIs with LEN or F/TDF. Antiretroviral medications with potential drug-drug interactions with LEN are listed in Table 23.

See Appendix 7 for US-specific text.

Bidirectional adverse interactions with GAHT with exogenous hormones are not expected (see Section 1.2.7).

Table 22. Prior and Concomitant Medications that are Prohibited or To Be Used with Caution due to the Potential for Drug-Drug Interaction with Study Drugs

	Use Discouraged and To Be Used with Caution		Prohibited Medications	
Medication Class	**Medication(s)**	**Drug-Drug Interaction Potential**	**Medication(s)**	**Drug-Drug Interaction Potential**
Antiarrhythmics	Amiodarone, quinidine: May increase concentration of TAF and/or TFV	F/TDF[a]	-	-
Anticoagulants	Dabigatran etexilate: monitoring and/or dose reduction may be needed for certain populations per prescribing information	LEN	-	-
Anticonvulsants	-	-	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	LEN
Antimycobacterials	Clarithromycin: may increase concentration of TAF and/or TFV	F/TDF	Rifampin, rifabutin, rifapentine	LEN
Antifungals	Systemic itraconazole, ketoconazole, voriconazole: may increase concentration of TAF and/or TFV	F/TDF	-	-
Calcium channel blockers	Diltiazem, felodipine, verapamil: may increase concentration of TAF and/or TFV	F/TDF	-	-
Digoxin	Concomitant use may result in an increased or decreased digoxin concentration; use with caution and with appropriate monitoring of serum digoxin concentrations	F/TDF; LEN	-	-
Ergot derivatives	-	-	Ergotamine, ergonovine, dihydroergotamine, methylergonovine, ergometrine	LEN
Herbal/Natural Supplements	-	-	St. John's Wort, Echinacea, Milk thistle (eg, silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)	F/TDF; LEN
Hepatitis C therapies	Ledipasvir/sofosbuvir: has been shown to increase TFV exposure	F/TDF	Boceprevir, telaprevir	F/TDF

	Use Discouraged and To Be Used with Caution		Prohibited Medications	
Medication Class	**Medication(s)**	**Drug-Drug Interaction Potential**	**Medication(s)**	**Drug-Drug Interaction Potential**
HMG-CoA Reductase Inhibitors	Concentrations of statins may increase with LEN. Start with the lowest dose and titrate to clinical response. For each of the following statins, the maximum allowed dose is: Simvastatin: 10 mg Lovastatin: 20 mg Atorvastatin: 40 mg Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis	LEN	-	-
Nephrotoxic medications	High-dose or multiple nonsteroidal anti-inflammatory drug (NSAIDs)	F/TDF	Systemic chemotherapeutic agents, systemic aminoglycoside antibiotics, amphotericin B, systemic cidofovir, cisplatin, foscarnet, IV pentamidine, or, other agents with significant nephrotoxic potential	F/TDF
Other	-	-	probenecid	F/TDF
Phosphodiesterase-5 Inhibitors	Concentrations of PDE-5 inhibitors may increase with LEN. Sildenafil, vardenafil, tadalafil: It is recommended that a single dose of sildenafil no more than 25 mg in 48 hours, vardenafil no more than 2.5 mg in 72 hours, or tadalafil no more than 10 mg in 72 hours be coadministered.	LEN	-	-
Sedatives/Hypnotics	midazolam, triazolam concentrations may increase with LEN	LEN	-	-
Systemic Corticosteroids	Concomitant use may increase corticosteroid exposure. Limit use to 7 days or less. Concomitant use of dexamethasone may decrease LEN exposures, particularly with long-term use.	LEN	Use of all agents for greater than 7 days	LEN

F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); F/TDF = emtricitabine/tenofovir disoproxil fumarate; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LEN= Lenacapavir; PK = pharmacokinetic(s); TAF = tenofovir alafenamide; TFV = tenofovir; US = United States

a F/TAF may be used in the US during PK Tail Phase. See Appendix 7 for US-specific text.

Should participants have a need to initiate treatment with any prohibited concomitant medication, the Gilead medical monitor must be consulted, and approval granted prior to initiation of the new medication. In instances where a prohibited medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

Table 23. Antiretroviral Medications With Potential Drug-Drug Interactions With LEN

Drug	Interaction Potential	Use for HIV Treatment[a]	Use for PEP[a]
INSTI (BIC, CAB, DTG, EVG, RAL)	No clinically relevant interactions with LEN	Acceptable	Acceptable
NRTI (3TC, FTC, TAF, TDF)	No clinically relevant interactions with LEN	Acceptable	Acceptable
NNRTI (DOR, EFV, ETV, NVP, RPV)	EFV, ETV, and NVP may reduce LEN levels	Acceptable[b]	Do not use
ATV with RTV or cobicistat	ATV significantly increases LEN levels	Do not use	Do not use
LPV with RTV or cobicistat	No clinically relevant interactions with LEN	Acceptable[b]	Acceptable
DRV with RTV	No clinically relevant interactions with LEN	Acceptable[b]	Acceptable
DRV with cobicistat	No clinically relevant interactions with LEN	Acceptable	Acceptable

3TC = lamivudine; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; ETV = etravirine; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = postexposure prophylaxis; PI = protease inhibitor; RAL = raltegravir, RPV = rilpivirine; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide

a Refer to applicable guidelines for information on suitable regimens for HIV treatment and PEP.

b Reduction in LEN levels are acceptable because LEN is not considered an active agent for HIV treatment regimens in this study.

If a participant is nonadherent to oral study drug or nonadherent with injection site visits, and experiences an event requiring PEP with ARV medications, then the ARVs which reduce LEN concentrations (EFV, ETV, NVP, LPV with cobicistat, and DRV with ritonavir) are not recommended if the participant plans to continue in the study on study drug after the 28-day course of PEP (Section 6.13.1). If a person acquires HIV in the study, it is not recommended that the participant initiate an ART regimen containing ATV/cobicistat (or ATV/ritonavir) as coadministration could significantly elevate LEN levels.

5.5. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug kits. This includes acknowledgment of receipt of each shipment of study drug kits (quantity and condition). All used and unused study drug kits dispensed to participants must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits
- The date, participant number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug kits returned, along with the initials of the person recording the information

5.5.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during a monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 3 and described in the text that follows.

During emergency circumstances, such as an infectious disease pandemic and other force majeure events, refer to Appendix 2 for further details on the risks and risk mitigation strategy.

In exceptional circumstances (ie, if a participant is not able to come to the study site for an unavoidable reason), the investigator can conduct an off-site visit for non-injection visits only, after written approval from Gilead. The investigator must document any deviation from the protocol procedures and notify Gilead or the CRO.

From the time of obtaining informed consent through the first administration of study drug in the Randomized Blinded Phase, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AE electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. See Section 7, Adverse Events and Toxicity Management, for additional details.

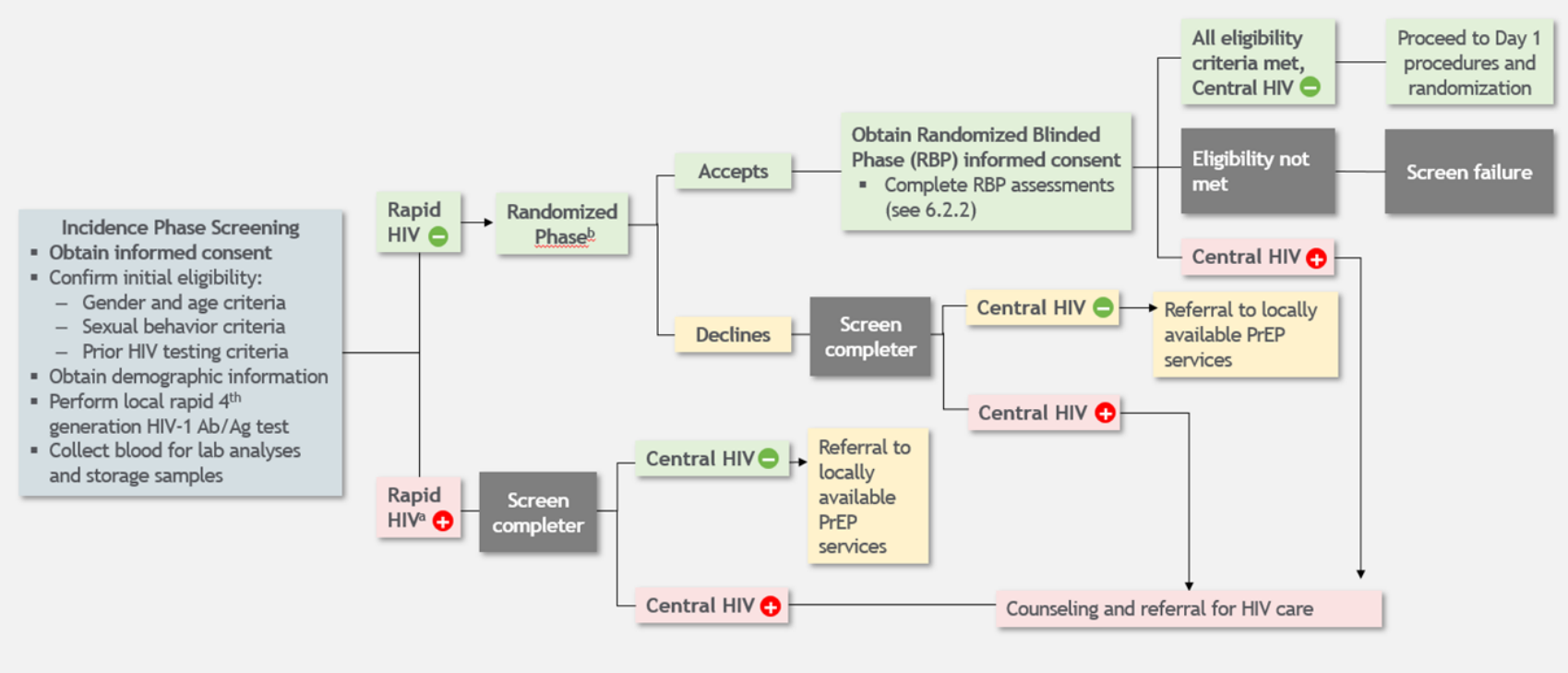
6.1. Participant Enrollment and Study Drug Assignment

Entry into screening does not guarantee enrollment of the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.2. Screening Assessments

Assessments to determine eligibility to enroll into the study and be randomized for study drug are depicted in Figure 12 and described in Sections 6.2.1 and 6.2.2. Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first DMC review of the unblinded safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents.

Figure 12. Assessments to Determine Enrollment and Randomization Eligibility



Ab = antibody; AG = antigen, PrEP = pre-exposure prophylaxis, RBP = Randomized Blinded Phase
a Local HIV confirmation may be performed in addition to central laboratory confirmation at the investigator's discretion.
b A participant with a negative rapid HIV-1/2 Ab/Ag test who is not offered the randomization due to investigator's discretion will be recorded as a screen completer. Participants with a positive rapid HIV-1/2 Ab/Ag test and a negative central HIV-1/2 Ab/Ag test will not be randomized into the study.

6.2.1. Incidence Phase Screening

Participants will be screened within 30 days of Day 1/Injection 1 to determine eligibility for participation in the study. Rescreening will not be allowed. In the event of a laboratory specimen technical failure requiring recollection, an extension of up to 7 days may be granted after medical monitor approval. Screening window extensions may be allowed with medical monitor approval in cases of study drug unavailability, as noted in Section 6.2.2. Exclusionary screening laboratory assessments will not be repeated for eligibility determination purposes unless assay failure is suspected. The following will be performed and documented at screening:

- Obtain written informed consent (and assent for participants < 18 years of age, in accordance with local laws and regulations) for the Incidence Phase assessments. A parent/guardian may provide informed consent for adolescents (in accordance with local laws and regulations). The investigator or person designated by the investigator will provide ample time to the participant to review the informed consent form (ICF) and allow the participant the opportunity to ask questions about the study.
- Obtain screening number from IWRS
- Obtain demographic information and medical history
- Query on sexual activity with partners assigned male at birth, including receptive anal sex
- Collect date and result (documented, if available) from the last HIV-1 test performed prior to the screening visit
- Query prior receipt of a long-acting PrEP medication or HIV vaccine
- Obtain history regarding prior PrEP use
- HIV risk reduction counseling including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site immediately for evaluation and HIV-1 testing if they develop such symptoms.
- Participation in any prior or concurrent HIV vaccine or other PrEP study
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the ICF
- Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6) (if positive, participants will not be eligible to enter the Randomized Blinded Phase)

- Blood collection (see Section 6.9.2) for:
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test if positive, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5).
  - HIV-1 RNA quantitative NAAT
  - Recency assay (run as indicated based on HIV test results)
  - DBS storage sample
  - Plasma storage samples for virology, safety, and/or PK testing
  - CD4 cell count (only if local rapid HIV-1/2 test is positive)

If the local rapid fourth generation HIV-1/2 Ab/Ag test is positive, participants will undergo confirmatory testing and counseling as appropriate (refer to Section 6.13), and study participation will conclude. If the local rapid fourth generation HIV-1/2 Ab/Ag test is negative, participants will proceed to complete Randomized Blinded Phase screening assessments if additional consent is obtained. At the investigator's discretion, a positive local rapid fourth generation HIV-1/2 Ab/Ag test may be separately confirmed by following local testing guidelines in order to facilitate rapid ART initiation.

After completion of Incidence Phase screening procedures, participants may be started on nonstudy oral PrEP at the investigator's discretion. If nonstudy oral PrEP is initiated during the screening window, the last dose should be taken the day prior to Day 1/Injection 1.

6.2.2. Randomized Blinded Phase Screening

If a participant's local rapid fourth generation HIV-1/2 Ab/Ag test is negative, pregnancy test is negative (in participants assigned female at birth who are of childbearing potential), and the Incidence Phase criteria are met, participants can be screened for the Randomized Blinded Phase if additional consent is obtained. The following will be performed:

- Offer the Randomized Blinded Phase ICF. If participant accepts, obtain written informed consent (and assent for participants < 18 years of age, in accordance with local laws and regulations) pertaining to Randomized Blinded Phase assessments. A parent/guardian may provide informed consent for adolescents (in accordance with local laws and regulations). The investigator or person designated by the investigator will provide ample time to the participant to review the ICF and allow the participant the opportunity to ask questions about the study.

- Urine collection (see Section 6.9.1) for:
  - Routine asymptomatic sexually transmitted infection (STI) testing for Neisseria gonorrhoeae (GC) and Chlamydia trachomatis (CT); for participants assigned female at birth, central laboratory urine Trichomonas vaginalis (TV) testing may be performed at the investigator's discretion
  - Urinalysis, urine proteins, urine chemistry
- Blood collection (see Section 6.9.2) for:
  - Chemistry and hematology profile
  - eGFR calculation
  - HBV testing
  - HCV testing
  - Serum pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
  - Local laboratory asymptomatic syphilis testing
- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator.
- Obtain medical history and prior medications used by the participant in the 30 days prior to the screening visit
- Complete physical examination including, vital signs (blood pressure, pulse, respiration rate, and temperature), weight, height, and waist circumference
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the ICF
- HIV risk reduction counseling and provision of both external (penile) and internal (vaginal) condoms and lubricant (only if Incidence Phase screening occurs on a separate day)
- Screening for intimate partner violence and appropriate referral when applicable
- Integrated sexual behaviors and alcohol and substance use (see Appendix 7 for US-specific text)

Participants who completed the Incidence Phase assessments and were unable to complete the screening process due to unavailability of study drug or related materials may undergo Randomized Blinded Phase screening assessments with medical monitor approval. In the event that some or all Randomized Blinded Phase screening assessments were previously completed

and the participant remained eligible after those completed assessments, all Randomized Blinded Phase screening assessments will be repeated, except for questionnaires. Additionally, a local rapid fourth generation HIV-1/2 Ab/Ag test, a central fourth generation HIV-1/2 Ab/Ag test, and an HIV-1 RNA quantitative NAAT must be repeated and resulted as negative prior to randomization. In this scenario, participants must be randomized within 30 days of the initiation of repeated Randomized Blinded Phase screening assessments if confirmed to be eligible.

6.3. Randomized Blinded Phase Assessments

6.3.1. Day 1/Injection 1

The following assessments are to be completed at the Day 1/Injection 1 visit (Appendix 3). The investigator must have confirmed eligibility in the Randomized Blinded Phase before proceeding with the Day 1/Injection 1 visit. Participants must complete all study procedures before being administered study drug, including having a negative local rapid fourth generation HIV-1/2 Ab/Ag test and a negative screen for signs and symptoms of acute HIV infection.

- Urine collection (see Section 6.9.1) for:
  - Routine asymptomatic STI testing for GC and CT; for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion
  - Urinalysis, urine proteins, urine chemistry
  - Urine storage sample
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
- Blood collection (see Section 6.9.2) for:
  - Chemistry, hematology, and metabolic assessments
  - eGFR calculation
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)
  - HIV-1 RNA quantitative NAAT
  - Recency assay (run as indicated based on HIV test results)

- CD4 cell count (only if local HIV-1/2 test is positive)
- DBS storage sample
- Plasma storage sample for virology, safety, and/or PK testing
- Serum storage sample for virology, safety, and/or PK testing
- Serum pregnancy testing (in the event of a positive urine pregnancy test)
- Local laboratory asymptomatic syphilis testing

Note: For participants diagnosed with HIV after receiving study drug, refer to Section 6.13

- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator.
  - Participants will be treated for STIs per local guidelines
- Review and record AEs per Sections 7.3 and 7.3.2, including screening for any signs or symptoms of acute HIV infection or STIs
- Review and record changes in concomitant medications
- Targeted (symptom directed) physical examination
- Vital signs, and height, weight and waist circumference (if the Day 1/Injection 1 visit is > 7 days after the screening visit)
  - Height is to be measured once on Day 1/Injection 1 if the participant is ≥ 20 years of age and annually if < 20 years of age until the age of 20 years.
- Questionnaires
  - Integrated sexual behaviors and alcohol and substance use (see Appendix 7 for US-specific text)
  - PrEP Impacts and Administration Preference Questionnaire - Day 1
  - Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection)
- Enrollment into the Randomized Blinded Phase and randomization in IWRS

- Drug dispensation
  - SC LEN/placebo administration and observed first administration of oral LEN/placebo 300 mg tablets (2) Day 1/Injection 1 and observed first dose administration of oral F/TDF (or placebo)
  - Participants should be observed for approximately 30 minutes after each SC injection dose
- One week (± 2 days) after each injection visit, participants will be contacted for a postinjection follow-up assessment and to confirm the participant has taken the Day 2 dose
- Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and study retention
- HIV risk reduction counseling including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site immediately for evaluation and HIV-1 testing if they develop such symptoms.
- Screening for intimate partner violence and appropriate referral when applicable

6.3.2. Weeks 4 and 8 (± 2 days) and Weeks 13, 26/Injection 2, 39, 52, and Every 13 Weeks (± 7 days) Until the End of Randomized Blinded Phase Visit

The following assessments will occur at Randomized Blinded Phase visits (Appendix 3).

Participants who are diagnosed with HIV during the Randomized Blinded Phase will discontinue study drug prior to the End of Randomized Blinded Phase visit and have samples collected (Section 6.13), and will be required to return to the study site for a post-HIV-infection follow-up visit (Section 6.7.3).

All study visits are to be scheduled relative to the previous injection visit date, except in instances of oral LEN/placebo bridging (Section 6.8.3).

- Targeted (symptom directed) physical examination if clinically indicated
- Vital signs, weight, height, and waist circumference
  - Height is to be measured annually if participant is < 20 years of age
- Review and record AEs per Sections 7.3 and 7.3.2, including screening for any signs and symptoms of acute HIV infection or STIs
- Review and record changes in concomitant medications

- Urine sample collection for the following laboratory analyses will be performed at every visit unless otherwise specified (see Section 6.9.1) for:
- Routine asymptomatic STI testing for GC and CT; for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion (Week 13 and every 13 weeks thereafter)
  - Urinalysis, urine proteins, urine chemistry
  - Urine storage sample
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
- Blood sample collection for the following laboratory analyses will be performed at every visit unless specified (see Section 6.9.2):
  - Chemistry and hematology profile
  - Metabolic assessments (Week 26/Injection 2, Week 52, and every 26 weeks thereafter)
  - eGFR calculation
  - HBV and HCV testing (Week 26/Injection 2, Week 52, and every 26 weeks thereafter)
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)
  - HIV-1 RNA quantitative NAAT storage sample
  - DBS storage sample
  - Anytime plasma PK sample
  - Plasma storage sample for virology, safety, and/or PK testing
  - Serum storage sample for virology, safety, and/or PK testing
  - Serum pregnancy testing (in the event of a positive urine pregnancy test)
  - Local laboratory asymptomatic syphilis testing (Week 13, and every 13 weeks thereafter)

Note: For participants diagnosed with HIV after receiving study drug, refer to Section 6.13

- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing (Week 13 and every 13 weeks thereafter). Swabs may be self-collected by the participant at the discretion of the investigator.
  - Participants will be treated for STIs per local guidelines
- Questionnaires:
  - Adherence to Oral Study Product Questionnaire: Weeks 4, 8, and 13, and every 13 weeks thereafter
  - Integrated sexual behaviors and alcohol and substance use: Week 13 and every 13 weeks thereafter (see Appendix 7 for US-specific text)
  - Administration and Dosing Questionnaire for PrEP Medication: Weeks 13, 39, and 13 weeks after each injection visit thereafter
  - PrEP Impacts and Administration Preference Questionnaire: Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits
  - Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection): Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits
- HIV risk reduction counseling, including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection, and will be instructed to call and/or present to the site for evaluation and HIV-1 testing, if they develop such symptoms
- Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and study retention
- Collect and review used and unused study drug for accountability and calculate adherence
- Study drug dispensation
  - LEN/placebo administration at Week 26/Injection 2, Week 52, and every 26 weeks (± 7 days) thereafter. All SC injections will be administered 26 weeks (± 7 days) from the last SC injection.
  - Participants should be observed for approximately 30 minutes after each LEN injection
- One week (± 2 days) after each injection, participants will be contacted for a postinjection follow-up assessment
- Screening for intimate partner violence and appropriate referral when applicable

6.4. LEN Open-Label Extension Phase Assessments Day 1, Weeks 4 and 8 (± 2 days), and Weeks 13, 26, 39, 52, and every 13 weeks thereafter

The following assessments will occur at LEN OLE Phase study visits unless otherwise specified (Appendix 3).

All study visits are to be scheduled relative to the previous injection visit date, except in instances of oral LEN/placebo bridging (Section 6.8.3).

Note: the End of Randomized Blinded Phase visit coincides with LEN OLE Day 1. Refer to Section 3.3.3 for further details.

- Targeted (symptom directed) physical examination, if clinically indicated
- Vital signs and weight
  - Height is to be measured annually if participant is < 20 years of age
- Review and record AEs as per Sections 7.3 and 7.3.2, including any signs and symptoms of acute HIV infection or STIs
- Review and record changes in concomitant medications
- Urine sample collection for the following laboratory analyses will be performed at every visit unless otherwise specified (see Section 6.9.1):
  - Routine asymptomatic STI testing for GC and CT; for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 13 weeks thereafter)
  - Urinalysis
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6**)**
- Blood sample collection for the following laboratory analyses will be performed at every visit unless otherwise specified (see Section 6.9.2):
  - Chemistry and hematology profile (End of Randomized Blinded Phase visit/LEN OLE Day 1, and every 26 weeks thereafter)
  - Metabolic assessments (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 52 weeks thereafter)
  - eGFR calculation (End of Randomized Blinded Phase visit/LEN OLE Day 1, and every 26 weeks thereafter)

- HBV and HCV testing (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 52 weeks thereafter)
- Local rapid fourth generation HIV-1/2 Ab/Ag test
- Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)
- HIV-1 RNA quantitative NAAT storage sample
- DBS storage sample (End of Randomized Blinded Phase visit/LEN OLE Day 1 only)
- Anytime plasma PK sample
- Plasma storage sample for virology, safety, and/or PK testing
- Serum storage sample for virology, safety, and/or PK testing
- Serum pregnancy testing (in the event of a positive urine pregnancy test)
- Local laboratory asymptomatic syphilis testing (End of Randomized Blinded Phase visit/LEN OLE Day 1 and every 13 weeks thereafter)

Note: For participants diagnosed with HIV after receiving study drug, refer to Section 6.13).

- Questionnaires (until and including LEN OLE Week 52):
  - Integrated sexual behaviors and alcohol and substance use: End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter (see Appendix 7 for US-specific text)
  - Administration and Dosing Questionnaire for PrEP Medication questionnaire: 13 weeks after each injection visit
  - Experienced Preference for PrEP Medication Questionnaire: every injection visit
  - Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection): every injection visit
  - Adherence to Oral Study Product Questionnaire: End of Randomized Blinded Phase visit/LEN OLE Day 1 only

- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing (End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter). Swabs may be self-collected by the participant at the discretion of the investigator.

  — Participants will be treated for STIs per local guidelines

- Collect and review used and unused study drug for accountability and calculate adherence (End of Randomized Blinded Phase/LEN OLE Day 1 only and Week 4 for participants randomized to F/TDF)

- Drug dispensation

  — LEN administration if participant agrees to take part in the LEN OLE Phase. Participants who were randomized to F/TDF will receive their first LEN injection at End of Randomized Blinded Phase/LEN OLE Day 1 and every 26 weeks (± 7 days) thereafter until LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first. Participants who were randomized to LEN will receive their first OLE injection 26 weeks (± 7 days) after their last injection in the Randomized Blinded Phase. All SC injections will be administered 26 weeks (± 7 days) from the last SC injection.

  — Participants should be observed for approximately 30 minutes after each SC injection dose.

  — Dispensation of oral LEN and adherence counseling (only for participants randomized to F/TDF to receive loading dose of oral LEN) should be completed.

- One week (± 2 days) after each injection participants will be contacted for a postinjection follow-up assessment

- HIV risk reduction counseling, including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing, if they develop such symptoms.

- Counseling to encourage the importance of attending study visits in a timely fashion, adherence to study drug injections, and study retention

- Screening for intimate partner violence and appropriate referral when applicable

6.5. Pharmacokinetic Tail Phase Assessments Day 1 and Weeks 13, 26, 39, 52, 65, and 78 (± 7 days)

The following assessments will occur at PK Tail Phase visits unless otherwise specified (Appendix 3). Refer to Section 3.3.4 for further detail. All study visits are to be scheduled relative to PK Tail Day 1:

- Targeted (symptom directed) physical examination, if clinically indicated.
- Vital signs and weight
  - Height is to be measured annually if participant is < 20 years of age
- Review and record AEs per Sections 7.3 and 7.3.2, including screening for any signs and symptoms of acute HIV infections or STIs, and changes in concomitant medications
- Urine sample collection for the following laboratory analyses will be performed at every visit unless otherwise specified (see Section 6.9.1)
  - Routine asymptomatic STI testing for GC and CT; for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion
  - Urinalysis, urine proteins, urine chemistry
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
- Blood sample collection for the following laboratory analyses will be performed at every visit unless otherwise specified (see Section 6.9.2):
  - Chemistry and hematology profile (PK Tail Day 1 and every 26 weeks thereafter)
  - Metabolic assessments (PK Tail Day 1 and every 52 weeks thereafter)
  - eGFR calculation (PK Tail Day 1 and every 26 weeks thereafter).
  - HBV and HCV testing (PK Tail Day 1 and every 52 weeks thereafter)
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)

  - HIV-1 RNA quantitative NAAT storage sample
  - DBS storage sample (PK Tail Day 1 for participants who prematurely discontinue study drug during the Randomized Blinded Phase, Week 13, and every 13 weeks thereafter)
    - If PK Tail Day 1 local rapid is positive, collect DBS

Anytime plasma PK sample

  - Plasma storage sample for virology, safety, and/or PK testing
  - Serum storage sample for virology, safety, and/or PK testing
  - Serum pregnancy testing (in the event of a positive urine pregnancy test)
  - Local laboratory asymptomatic syphilis testing (PK Tail Day 1 and every 13 weeks thereafter).

Note: For participants diagnosed with HIV after receiving study drug, refer to Section 6.13)

- Questionnaires:
  - Integrated sexual behaviors and alcohol and substance use: PK Tail Day 1, Week 13, and every 13 weeks thereafter (see Appendix 7 for US-specific text)
  - PrEP Impacts and Administration Preference Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase
  - Administration and Dosing Questionnaire for PrEP Medication: PK Tail Day 1
  - Adherence to Oral Study Product Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase, Week 13, and every 13 weeks thereafter
- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator.
- Participants will be treated for STIs per local guidelines
- Collect and review used and unused study drug for accountability and calculate adherence
- Study drug dispensation
- Observed first-dose administration of oral OL F/TDF (see Appendix 7 for US-specific text)

- HIV risk reduction counseling, including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing, if they develop such symptoms

- Adherence counseling to encourage the importance of attending study visits in a timely fashion, daily adherence to study drug, and study retention

- Screening for intimate partner violence and appropriate referral when applicable

6.6. Unscheduled Visits

Additional unscheduled assessments may be performed at the discretion of the investigator (eg, for evaluation of AEs and/or laboratory abnormalities, including any signs and symptoms for STIs). Participants who have HIV testing performed during an unscheduled visit will have a local rapid fourth generation HIV-1/2 Ab/Ag test and DBS performed. If the HIV-1/2 Ab/Ag test is positive, participants will be followed as described in Section 6.13.

6.7. Post-Study Drug Assessments

6.7.1. Early Study Drug Discontinuation Visit

This study has multiple phases and study drug refers to any and all drugs provided to the participant while participating in the study. An early study drug discontinuation visit will occur 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. Participants will be asked to return to the clinic for an ESDD visit within 72 hours of stopping study drug in the Randomized Blinded Phase or PK Tail Phase, or within 72 hours of informing the investigator they no longer wish to receive SC LEN injections in the LEN OLE Phase.

At the ESDD visit, any assessment showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drug, will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The following assessments occur at the ESDD visit:

- Targeted (symptom directed) physical examination, if clinically indicated; vital signs, weight, and waist circumference (only for Randomized Blinded Phase)

  — Height if participant is < 20 years of age

- Review and record AEs as per Sections 7.3 and 7.3.2, including screening for any signs and symptoms of acute HIV infection or STIs, and changes in concomitant medications

- Urine sample collection (see Section 6.9.1)
  - Urinalysis, urine proteins, urine chemistry
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
- Blood sample collection (see Section 6.9.2) for:
  - Chemistry and hematology profile
  - eGFR calculation
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing including a fourth generation HIV-1/2 Ab/Ag test if positive, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)
  - HIV-1 RNA quantitative NAAT storage sample
  - DBS storage sample (only for Randomized Blinded Phase and PK Tail Phase)
  - Anytime plasma PK sample
  - Plasma storage sample for virology, safety, and/or PK testing
  - Serum storage sample for virology, safety, and/or PK testing
  - Serum pregnancy testing (in the event of a positive urine pregnancy test)

Note: For participants diagnosed with HIV after receiving study drug, refer to Section 6.13)

- Questionnaires:
  - Adherence to Oral Study Product Questionnaire (if ESDD occurs during the Randomized Blinded Phase or PK Tail Phase)
  - PrEP Impacts and Administration Preference Questionnaire (if ESDD occurs during the Randomized Blinded Phase)
  - Experienced Preference for PrEP Medication Questionnaire (if ESDD occurs during the LEN OLE Phase)
  - Integrated sexual behaviors and alcohol and substance use (at ESDD during any phase) (see Appendix 7 for US-specific text)

- Collect and review used and unused study drug for accountability and calculate adherence according to Appendix 3

- For participants not discontinuing due to HIV infection, provide HIV risk reduction counseling, including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms

- Screening for intimate partner violence and appropriate referral when applicable

If participant is unwilling to return to the clinic for an ESDD visit, every effort will be made by the site staff to contact the participant to assess the current risk behavior, provide guidance and counseling, and understand the reason for discontinuing study drug.

6.7.2. 30-Day Follow-Up Visit

Participants who have received at least one dose of study drug may 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

- Completing the PK Tail Phase

If the participant does not wish to proceed to the PK Tail Phase during the Randomized Blinded Phase or LEN OLE Phase, the participant will be required to return to the study site for the 30-day follow-up visit.

At the 30-day follow-up visit, any assessment showing abnormal results that the investigator determines to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

The following assessments are to be completed at the 30-day follow-up visit:

- Targeted (symptom directed) physical examination if clinically indicated; vital signs, weight, height and waist circumference (only for Randomized Blinded Phase)

  — Height if the participant is < 20 years of age

- Review and record AEs as per Sections 7.3 and 7.3.2, including screening for any signs and symptoms of acute HIV infection or STIs, and changes in concomitant medications

- Urine sample collection (see Section 6.9.1) for:
  - Routine asymptomatic STI testing for GC and CT; for participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion
  - Urinalysis, urine proteins, urine chemistry
  - Urine pregnancy test for participants assigned female at birth who are of childbearing potential (see Appendix 6)
- Blood sample collection (see Section 6.9.2) for:
  - Chemistry and hematology profile
  - eGFR calculation
  - Local rapid fourth generation HIV-1/2 Ab/Ag test
  - Central HIV-1/2 testing including a fourth generation HIV-1/2 Ab/Ag test if positive, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (refer to Appendix 5)
  - Local laboratory asymptomatic syphilis testing
  - HIV-1 RNA quantitative NAAT storage sample
  - DBS storage sample (only for Randomized Blinded Phase and PK Tail Phase)
  - Anytime plasma PK sample
  - Plasma storage sample for virology, safety, and/or PK testing
  - Serum storage sample for virology, safety, and/or PK testing
  - Serum pregnancy testing (in the event of a positive urine pregnancy test)
  - CD4 cell count, HIV-1 RNA quantitative NAAT, and HIV resistance genotype (for participants diagnosed with HIV after receiving study drug, refer to Section 6.13)
- Pharyngeal and rectal swab collection for asymptomatic GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator.
- Participants will be treated for STIs per local guidelines

- For participants not discontinuing due to HIV infection, provide HIV risk reduction counseling, including provision of both external (penile) and internal (vaginal) condoms and lubricant. Participants will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms.

- Screening for intimate partner violence and appropriate referral when applicable

6.7.3. Post-HIV-Infection Follow-Up

All participants diagnosed with HIV after receiving study drug will be required to complete a follow-up assessment 30 days (± 14 days) and 90 days (± 14 days) after confirmed HIV infection.

6.7.3.1. 30-Day Post-HIV-Infection Follow-Up

The following assessments are to be completed at the 30-day post-HIV-infection follow-up visit:

- Assessments in Section 6.7.2, except for the fourth generation HIV-1/2 Ab/Ag test, HIV-1 RNA quantitative NAAT storage sample and DBS

- CD4 cell count

- HIV resistance genotype (run only if genotype was not already collected at time of infection)

- HIV-1 by HIV-1 RNA quantitative NAAT

- Review and record AEs per Sections 7.3 and 7.3.2, including screening for any signs and symptoms of STIs, and changes in concomitant medications

- Status of HIV counseling and support received

6.7.3.2. 90-Day Post-HIV-Infection Follow-Up

The site staff will contact the participant to obtain the following information at 90 days (± 14 days) after confirmed HIV infection:

- CD4 cell count

- HIV-1 by HIV-1 RNA quantitative NAAT

- Concomitant medications (including HIV treatments) and relevant information

If the participant does not have the above information, the site staff will ask the participant for permission to contact the participant's doctor for the information. If CD4 cell counts and HIV-1 VL data are not available, the participant will be requested to attend a site visit for laboratory and data collection.

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 is < 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. The procedures performed at the 90-day post-HIV follow-up visit should be carried forward for these visits thereafter.

6.8. Assessments for Study Drug Interruptions

If a participant discontinues study drug dosing (see Section 6.7.1) for any reason other than acquiring HIV, every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures. The participant will be requested to return for an ESDD visit. If it is not possible or acceptable to the participant, (after discussion of benefits/risks with the investigator) to keep the participant in the study, the participant will be withdrawn from the study and be required to return to the study site for a 30-day follow-up visit (Section 6.7.2).

6.8.1. Criteria for Restarting F/TDF or F/TDF Placebo After an Interruption

If a participant interrupts F/TDF or F/TDF placebo dosing for more than 7 consecutive days, the participant should have samples collected for the following HIV tests prior to restarting study dosing:

- Local rapid fourth generation HIV-1/2 Ab/Ag
  - If the result for the rapid testing is positive, diagnosis should be confirmed per Appendix 5 and participant should be referred to local HIV care (Section 6.13)
  - Upon testing negative for the rapid HIV-1/2 test, the participant may restart study drug dosing while pending the central laboratory HIV-1/2 tests, at the investigator's discretion (Appendix 5).
- Blood sample collection for the following central laboratory analyses:
  - Central HIV-1/2 testing (Appendix 5)
  - HIV-1 RNA quantitative NAAT and sample collection for possible genotypic resistance testing

6.8.2. Criteria for Administering SC LEN Outside of the Target Visit Window (26 weeks ± 7 days)

Each study visit, including the injection visit, should be conducted within the target visit window. In the event this is not possible, visits outside of the target dates may be completed with the guidance below. Study drug injections must not be given before the target visit window.

- CCI [redacted]
- If the participant is past the target visit window (26 weeks + 7 days) and > 28 weeks have elapsed since the last study drug injection, administration of injection study drug is allowed at the investigator's discretion. Prior to resuming treatment, the following procedures should be followed:
  - Local rapid fourth generation HIV-1/2 Ab/Ag
    - If the result for the rapid testing is positive, diagnosis should be confirmed per Appendix 5 and participant should be referred to local HIV care (Section 6.13).
  - Blood sample collection for the following central laboratory analyses:
    - Central HIV-1/2 testing (Appendix 5)
    - HIV-1 RNA quantitative NAAT and sample collection for possible genotypic resistance testing
  - If rapid fourth generation HIV-1/2 Ab/Ag testing is negative, the participant may reinitiate study drug by administration of oral LEN/placebo (reloading dose) and injection LEN/placebo as described for Day 1 procedures (Sections 5.3.1 and 6.3.1), while central HIV-1/2 testing is pending, at the investigator's discretion.

6.8.3. Bridging With Oral LEN/Placebo

If SC LEN/placebo cannot be administered within the injection visit window due to extenuating circumstances and the investigator deems it clinically appropriate to continue LEN/placebo, bridging with oral LEN/placebo may be permitted with medical monitor approval.

If oral LEN/placebo bridging is initiated during the Randomized Blinded Phase, the participant will receive blinded oral LEN or PTM oral LEN aligned with their original study drug assignment, taken once weekly. Participants will continue to take daily oral F/TDF or PTM F/TDF during LEN/placebo bridging (ie, participants will receive active study drug and placebo).

If oral LEN bridging is initiated during the LEN OLE Phase, the participant will receive open-label oral LEN to be taken once weekly.

The procedures for initiating oral LEN/placebo bridging and resuming SC LEN/placebo injections are listed below:

- The site will obtain permission from the medical monitor prior to initiating LEN/placebo bridging.
- The participant will return to the site 26 weeks ± 7 days from the last SC LEN/placebo administration. Participants who are > 28 weeks from the last SC LEN/placebo injection require additional oral doses for loading as described in Section 5.3.1.2 and Table 20.

- The scheduled visit assessments (see Sections 6.3.2 or 6.4) will be performed, with the exception of SC LEN/placebo administration and 1-week post-injection follow-up. No questionnaires will be required for the bridging initiation visit.

- Only the number of bottles needed for the LEN/placebo bridging period will be dispensed to participants. Up to 4 bottles (16 tablets) of LEN/placebo may be dispensed to bridge to the next scheduled every-13-week visit.

- If the participant requires LEN/placebo bridging beyond 12 doses, the site will contact the medical monitor to approve continued bridging. The participant will then return to the site for the scheduled every-13-week visit and complete all associated assessments, except for the questionnaires. The site should schedule this visit to occur before or on the day that the participant is due for their 13th oral LEN/placebo dose. At this visit, the site may dispense up to an additional 3 bottles (12 tablets) of LEN/placebo.

- The participant will take the first dose of oral LEN/placebo at the site (bridging Day 1) and continue taking LEN/placebo 300 mg (1 tablet) orally once per week (eg, bridging Days 8, 15, 22, etc). See Section 5.3.1.2 for dosing details including additional loading doses for participants who are > 28 weeks from the last SC LEN/placebo injection (Table 20) and for guidance on missed oral LEN/placebo bridging doses (Table 21).

- During oral LEN/placebo bridging, the site will contact the participant weekly to confirm dosing of oral LEN/placebo (by telehealth, phone, and if required on-site visit, off-site visit, or other means).

- The participant will resume SC LEN/placebo injections as soon as possible; this does not need to occur on a scheduled visit date. Once it becomes possible to administer SC LEN/placebo, the participant will return to the site and complete the injection visit that was originally missed. For instance, if a participant began oral LEN/placebo bridging because they could not receive SC LEN/placebo injection at Week 26, the participant would return to the site as soon as SC LEN/placebo administration is feasible and resume the study at the Week 26/Injection 2 visit.

- When resuming SC LEN/placebo, the SC LEN/placebo injection can be given any time within 7 days of the last oral LEN/placebo dose.

6.9. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below and in Appendix 3.

6.9.1. Urine Samples

- Urine sample for urinalysis, urine proteins, and urine chemistry (uric acid, phosphate, and creatinine)
  - Participants who test positive for Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable will be withdrawn from the study
- Urine storage sample (samples collected at RBP)
- Urine collection for GC and CT testing
- For participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion
- Urine pregnancy test for participants assigned female at birth who are of childbearing potential (See Appendix 6)

6.9.2. Blood Samples

- Central HIV-1/2 testing, including a fourth generation HIV-1/2 Ab/Ag test, reflexively confirmed by HIV-1/2 differentiation assay and HIV-1/2 RNA qualitative NAAT, if the fourth generation test and differentiation assay results are discrepant (Appendix 5)
- Local rapid fourth generation rapid HIV-1/2 Ab/Ag test
  - If the result for rapid testing is positive, refer to Section 6.13.
- HIV-1 RNA quantitative NAAT at Incidence Phase screening and on Day 1/Injection 1 of the Randomized Blinded Phase (Appendix 5)
  - If a participant is confirmed to have acquired HIV, refer to Section 6.13.
- Hematology profile: complete blood count (CBC) with differential and platelet count
- Chemistry profile: alkaline phosphatase, AST, ALT, gamma-glutamyl transferase (GGT), total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase (LDH), bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, lipase, and creatinine phosphokinase (only at RBP).
- Blood sample for syphilis analysis per local testing protocol

- Metabolic assessments: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) lipid panel (total cholesterol, high-density lipoprotein [HDL], direct LDL, and triglycerides) and hemoglobin A_{1c} (HbA_{1c}). Glucose (part of the chemistry profile) will be collected in a fasting state on visits when metabolic assessments are performed. If the participant has not fasted prior to the visit, the visit may proceed but the participant should return within 72 hours in a fasted state to draw blood for the metabolic assessments.

- Estimated GFR according to the Cockcroft-Gault formula for CL_{cr}

- Hepatitis B testing (HBsAg, HBsAb, HBcAb):

  — If a participant has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed. If the HBV DNA result is positive, the participant is a screen failure.

  — Participants found to be susceptible to HBV infection will be offered HBV vaccination.

- Hepatitis C testing

  — If the HCV Ab result is positive at screening, then HCV RNA will be completed. For other visits aside from screening, HCV RNA will not be performed if HCV Ab is positive and HCV RNA is negative at screening.

- Blood sample for DBS storage

- CD4 cell count

- HIV resistance genotype

- HIV-1 recency assay

- Blood storage sample for HIV-1 RNA quantitative NAAT

- Anytime plasma PK sample for LEN

- Plasma storage sample for virology, safety, and/or PK testing

- Serum storage sample

- Serum pregnancy test if urine pregnancy test is positive

6.10. End of Study

End of study is defined the last participant's last observation (last visit).

6.11. Poststudy Care

Participants randomized in the study who have completed or terminated participation in the study will be transitioned to local HIV prevention services.

Participants who are diagnosed with HIV during the study will be referred to locally available HIV treatment and care services upon confirmation of HIV infection (Section 6.13).

6.12. STI Testing

Scheduled asymptomatic screening for STIs will occur regularly throughout the study for participants enrolled in the Randomized Blinded, LEN OLE, and PK Tail Phases, and will include:

- Asymptomatic urine sample, pharyngeal and rectal swab collection for GC and CT testing per central laboratory testing. Swabs may be self-collected by the participant at the discretion of the investigator.
- For participants assigned female at birth, central laboratory asymptomatic urine TV testing may be performed at the investigator's discretion
- Asymptomatic blood syphilis analysis as per local testing protocol

In addition to scheduled asymptomatic screening for STIs, if participants report any sign or symptom of an STI, they should be managed (diagnosed and treated) according to local clinical guidelines and practice.

6.13. Diagnosis of HIV-1 Infection

HIV Diagnoses Identified at Screening

At screening, participants will have HIV-1/2 testing samples collected as specified in Section 6.2.1, and eligibility will be determined as noted in Figure 12 and in the HIV testing algorithm (Appendix 5, part a). Procedures for specific situations are noted below:

- Participants with any positive HIV-1/2 test at screening (local rapid fourth generation HIV-1/2 Ab/Ag, central laboratory fourth generation HIV-1/2 Ab/Ag, or HIV-1 RNA quantitative NAAT) are not eligible for randomization.
- If the local rapid fourth generation HIV-1/2 Ab/Ag test is positive at screening, the participant will not proceed with Randomized Blinded Phase screening procedures, and the central laboratory will reflexively run confirmatory testing (per the central HIV-1/2 testing algorithm in Appendix 5, part a). A CD4 cell count will be run reflexively while central confirmatory testing is underway.
- HIV recency assay will be performed as indicated based on the participant's HIV testing results.

- Any participant with a confirmed diagnosis of HIV will be counseled and referred for local HIV-related care as appropriate, and study participation will conclude.

- Any participant with a positive HIV test who is subsequently determined to be HIV negative (ie, false positives) will be ineligible for randomization. Participants will be counseled on the meaning of their test results and will be referred to locally available HIV prevention services

HIV Diagnoses Identified at Day 1/Injection 1

At Day 1/Injection 1, all participants will have HIV-1/2 testing samples collected as specified in Section 6.3.1, and results will be managed as outlined in Appendix 5, part b. Procedures for specific situations are noted below:

- If the local rapid fourth generation HIV-1/2 Ab/Ag test is negative and all other eligibility criteria are satisfied, the participant may proceed to randomization and receipt of study drug.

- If the local rapid fourth generation HIV-1/2 Ab/Ag test is positive, the participant will not proceed to randomization or receive study drug, and the central laboratory will reflexively run confirmatory testing and a CD4 cell count.

- HIV recency assay will be performed as indicated based on the participant's HIV testing results.

- Participants with a positive local rapid fourth generation HIV-1/2 Ab/Ag test on Day 1/Injection 1 who test negative by the central HIV-1/2 testing algorithm (ie, false positive rapid test) remain ineligible for randomization. Participants will be counseled on the meaning of their test results and will be referred to locally available HIV prevention services.

- Participants with a negative local rapid fourth generation HIV-1/2 Ab/Ag test on Day 1/Injection 1 who test positive by the central HIV-1/2 testing algorithm (ie, false negative rapid test) will return to the site as soon as possible to have samples collected for a CD4 cell count and HIV resistance genotype.

- Participants with a positive HIV-1 RNA quantitative NAAT who test negative by local rapid fourth generation HIV-1/2 Ab/Ag test and central HIV-1/2 testing algorithm will undergo repeat testing (local rapid HIV-1/2 Ab/Ag, central HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT). If repeat testing is completely negative, the participant may continue study drug and study procedures after approval by the medical monitor.

- Any participant with a confirmed diagnosis of HIV will be counseled and referred for local HIV-related care as appropriate.

HIV Diagnoses Identified Beyond Day 1/Injection 1

For the Randomized Blinded Phase, LEN OLE Phase, and PK Tail Phase, participants will have HIV-1/2 testing samples collected as specified in the Sections 6.3.2, 6.4, and 6.5, respectively, and results will be managed as outlined in Appendix 5, part c. Procedures for specific situations are noted below:

- Participants with a positive local rapid fourth generation HIV-1/2 Ab/Ag test will undergo reflexive confirmatory testing by the central HIV-1/2 testing algorithm (Appendix 5). If HIV diagnosis is confirmed by the central HIV-1/2 testing algorithm, the participant will return to the site as soon as possible to have samples collected for CD4 cell count, and HIV resistance genotype. At the investigator's discretion, CD4 cell count, and resistance genotype may be sent at the same visit where the positive local rapid fourth generation HIV-1/2 Ab/Ag test occurs, while central laboratory confirmation is pending. Injection study drug will not be administered to participants with a positive local rapid fourth generation HIV-1/2 Ab/Ag test unless central HIV-1/2 testing confirms HIV-negative status (see below).

- Participants with a positive local rapid fourth generation HIV-1/2 Ab/Ag test who test negative by the central HIV-1/2 testing algorithm including HIV-1 RNA quantitative NAAT (ie, false positive rapid test) may continue study drug, receive study drug injections if due, and continue study procedures after confirmation from the medical monitor.

- Participants with a negative local rapid HIV-1/2 Ab/Ag who test positive by the central HIV-1/2 testing algorithm (ie, false negative rapid test) will return to the site as soon as possible to have samples collected for CD4 cell count and HIV resistance genotype.

- Any participant with confirmed diagnosis of HIV will be counseled and referred for local HIV-related care as appropriate.

Additional HIV Testing

At any point in the study, if the local rapid fourth generation HIV-1/2 Ab/Ag is positive, the investigator may, at their discretion, perform additional local testing in order to expedite diagnosis and initiation of ART. At any point in the study, if HIV testing results are inconclusive or discrepant, additional testing may be performed after discussion with the medical monitor. Additionally, retrospective testing of stored specimens may be conducted to confirm the date of HIV acquisition.

If the participant's HIV-1 VL at diagnosis is > 200 copies/mL at any time after the study drug dosing, a stored plasma sample will be sent for HIV resistance genotype testing.

HIV Follow-up and ART Initiation

Rapid ART initiation should be considered for any participant diagnosed with HIV. In cases where HIV diagnosis is not yet confirmed or HIV testing results are discrepant, decisions regarding discontinuation of oral study drug and initiation of ART will be made by the investigator in consultation with the medical monitor. Initiation of ART while awaiting confirmation of HIV-1 diagnosis is allowed, and in the event that a participant initiates ART and is ultimately determined to be HIV-negative, study drug may be resumed after approval by the medical monitor.

All participants diagnosed with HIV after receiving study drug will undergo additional study follow-up as described in Section 6.7.3.

Participants will be interviewed to understand the details of their seroconversion, including elicitation of signs and symptoms of acute HIV-1 infection, self-report of study drug adherence/injection visit adherence, and any other relevant clinical historical and/or behavioral information via the HIV infection/seroconversion interview. They will receive counseling (including the benefit of rapid start of an ARV treatment regimen) and be referred to receive local HIV-related care to initiate HIV-1 treatment as appropriate. Participants will be required to return to the study site for post-HIV-infection follow-up visits (Section 6.7.3).

6.13.1. Suspected Acute HIV-1 Infection/Postexposure Prophylaxis

Investigators may at their discretion provide PEP in accordance with local medical practice and/or guidelines when a participant is suspected of having an acute HIV-1 infection or high-risk exposure under the following circumstances:

- In the Randomized Blinded Phase: if a participant has been nonadherent to the oral study drug or has been nonadherent to per-protocol LEN injection administration and has had a high-risk exposure event, the investigator may discontinue the participant from the study drugs and provide a 3-drug regimen for PEP. Further details on recommendations for prior and concomitant medications with LEN are included in Section 5.4.

- In the LEN OLE Phase, if a participant has missed a scheduled LEN injection and subsequently had a high-risk exposure event, the investigator may provide a 3-drug regimen for PEP.

- In the PK Tail Phase, if the participant has been nonadherent to F/TDF and has had a high-risk exposure event, the investigator may restart the participant on F/TDF and add a third agent to comprise PEP treatment (see Appendix 7 for US-specific text).

- Guidance on PEP drugs suitable for coadministration with LEN can be found in Table 23.

Participants who undertake PEP treatment may resume with oral study drug after meeting the criteria for restarting study drug after interruption (Section 6.8.1) after 28 days of PEP.

6.14. HIV Risk Reduction Counseling

HIV risk reduction counseling will be provided at each study visit, in accordance with local standard of care, and will include messaging about consistent condom use. External (penile) and internal (vaginal) condoms and lubricant will be offered to all participants at each study visit consistent with local standards.

6.15. Adherence and Retention

The effectiveness of daily oral PrEP (F/TDF) is strictly correlated with adherence.

The study will provide adherence support/counseling to oral F/TDF or PTM at Day 1/Injection 1 and at all dispensing visits for all participants. Participants will also be counseled to adhere to the injection schedule for LEN or LEN placebo.

See Appendix 7 for US-specific text.

6.16. Participant-Reported Questionnaires

The questionnaires may include questions on the participant's sexual behavior, HIV risk perception, and participation in the study. The questions may also include questions on mental health, and alcohol and drug use.

Randomized Blinded Phase Questionnaires

- PrEP Impacts and Administration Preference Questionnaire: Day 1/Injection 1, Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits
- Administration and Dosing Questionnaire for PrEP Medication: Weeks 13, 39, and 13 weeks after each injection visit thereafter
- Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection) Day 1/Injection 1, Week 26/Injection 2, Week 52, and every 26 weeks thereafter at injection visits
- Integrated sexual behaviors and alcohol and substance use: Randomized Blinded Phase screening, Day 1/Injection 1, Week 13, and every 13 weeks thereafter (see Appendix 7 for US-specific text)
- Adherence to Oral Study Product Questionnaire: Weeks 4, 8, 13, and every 13 weeks thereafter

LEN OLE Phase Questionnaires (until and including LEN OLE Week 52)

- Experienced Preference for PrEP Medication Questionnaire: every injection visit
- Administration and Dosing Questionnaire for PrEP Medication: 13 weeks after each injection visit
- Numeric Pain Rating Scale – Injection Pain Questionnaire (must be completed postinjection): at every injection visit
- Integrated sexual behaviors and alcohol and substance use: End of Randomized Blinded Phase visit/LEN OLE Day 1, Week 13, and every 13 weeks thereafter (see Appendix 7 for US-specific text)
- Adherence to Oral Study Product Questionnaire: End of Randomized Blinded Phase visit/LEN OLE Day 1 only

PK Tail Phase Questionnaires

- PrEP Impacts and Administration Preference Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase
- Administration and Dosing Questionnaire for PrEP Medication: PK Tail Day 1
- Integrated sexual behaviors and alcohol and substance use: PK Tail Day 1, Week 13, and every 13 weeks thereafter (see Appendix 7 for US-specific text)
- Adherence to Oral Study Product Questionnaire: PK Tail Day 1 for participants who transition from the Randomized Blinded Phase, Week 13, and every 13 weeks thereafter

ESDD Visit Questionnaires

- PrEP Impacts and Administration Preference Questionnaire: Randomized Blinded Phase ESDD visit
- Experienced Preference for PrEP Medication Questionnaire: LEN OLE Phase ESDD visit
- Adherence to Oral Study Product Questionnaire: Randomized Blinded Phase or PK Tail Phase ESDD visit
- Integrated sexual behaviors and alcohol and substance use: ESDD visit for any phase (see Appendix 7 for US-specific text)

6.17. Pregnancy

Participants who were assigned female at birth and are of reproductive potential must have a negative pregnancy test at the Randomized Blinded Phase screening and Day 1/Injection 1 and agree to utilize protocol-specified method(s) of contraception as described in Appendix 6.

Participants assigned female at birth who are of childbearing potential are required to use effective contraception for the duration of the study. Any participant who becomes pregnant after randomization may remain in the study and continue to receive study drug after a reconsent process in which they will be informed of the benefits and risks of continuing receipt of study drug and the collection of birth outcomes for the child and lactation information (Section 9.1.4). Participants who are taking testosterone and become pregnant during the study must discontinue testosterone if continuing the pregnancy and wish to continue on study drug. Prenatal care will be at the investigator's discretion per local standard of care and will not be provided as part of the study. Pregnant participants who continue on study drug will also be informed that plasma PK samples that are being collected may be tested for LEN.

6.18. Social Harms Reporting

It is possible that participants' involvement in the study could become known to others, and that a social harm may result (ie, because participants could be perceived as having acquired HIV or at "high risk" for HIV infection). Social harms events are events that a participant reports as affecting them as a result of being involved in a research study, not the researcher's opinion of how they perceive an event has affected a participant. For example, participants might be treated unfairly if it is known that they are participating in the study. Participants may also have problems being accepted by their families and/or communities.

The site staff will discuss social harms with participants via an interview, and the social harms may be reported according to local regulations and requirements.

In the event a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant.

6.19. Sample Storage

CCI [redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.1.1. Protocol-Specific Adverse Event Reporting Exemptions

Incidence of HIV-1 infection is an outcome of this study and therefore should not be reported as an AE (Section 6.13 for reporting of HIV infection).

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Serious Adverse Event Definitions

In this study, vertical transmission in participants who become infected with HIV on study drug is to be considered medically important and therefore "serious." Vertical transmission of HIV infection can occur during gestation, delivery, or breastfeeding. Instructions for reporting SAEs are described in Section 7.4.1.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via chestfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

A "reasonable possibility" of a causal relationship means that there is evidence, fact and/or other rationale to suggest a causal relationship, rather than a relationship that cannot be ruled out.

It should be emphasized that lack of efficacy of study drug should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale.

The DAIDS scale is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and any AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship throughout the duration of the study, including the protocol-specified follow-up period, and report them on the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the protocol-defined follow-up period, must be reported on the applicable eCRFs and PS as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur within the protocol-defined follow-up period, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the protocol-defined follow-up period, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the protocol-defined follow-up period, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

Site personnel will record all initial or follow-up SAE data (including updates to the reported event term[s]) on the applicable eCRFs within 24 hours of the investigator's knowledge of the initial event/update in order for the SAE information to be transmitted timely to PS. Serious adverse event information must be reported from the time of the ICF signature throughout the duration of the study, including the protocol-required follow-up period.

If for any reason it is not possible to record and transmit the SAE information electronically, site personnel must record the SAE on the paper Initial or Follow-up SAE Report Form and transmit by emailing or faxing the report within 24 hours of the investigator´s knowledge of the initial event/update using the contact information below:

Gilead Patient Safety
Email: PPD
or
Fax: PPD

If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information to Gilead PS from study drug initiation throughout the duration of the study, including the protocol-defined follow-up period.

If for any reason it is not possible to record the SSR information electronically, record the SSR on the paper special situation reporting form and transmit to:

Gilead Patient Safety
Email: PPD
or
Fax: PPD

If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to PS.

See Section 7.4.2.2 for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper special situations report form to:

Gilead Patient Safety
Email: PPD
or
Fax: PPD

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report any pregnancies in study participants of reproductive potential that are identified after initiation of study drug and throughout the study, including the protocol-defined follow-up period, to Gilead PS using both the eCRF pregnancy form and the paper the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead Patient Safety
Email: PPD
or
Fax: PPD

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead PS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy should be reported to Gilead PS throughout the study, including the protocol-defined follow-up period, using both the eCRF pregnancy form and the paper pregnancy outcome report form. In addition, if the investigator learns of any pregnancy or pregnancy outcomes that occur after the protocol-defined follow-up period has concluded but within 700 days following the last dose of LEN or blinded LEN (if unblinding has not occurred), the investigator should promptly document and report the pregnancy outcome directly to Gilead PS using the paper pregnancy outcome form. Gilead PS contact information is as follows:

Gilead Patient Safety
Email: PPD
or
Fax: PPD

Refer to Appendix 6 for Randomized Blinded Phase Pregnancy Precautions, Definition Childbearing Potential for Participants Assigned Female at Birth, and Contraceptive Requirements

AEs/SAEs observed in a neonate at the time of delivery will be reported via the paper Pregnancy Outcome Report form and to Gilead PS via the paper Clinical Study Infant/Child Report form (except vertical transmission). Events of vertical transmission should be reported to Gilead PS via the electronic SAE reporting process described in section 7.4.1.1.

Subsequent to delivery if there are any identified AEs/SAEs observed they will be reported via the paper Clinical Study Infant/Child Report form to Gilead PS (except vertical transmission as stated above).

7.4.2.4. Reporting Lactation Exposure When a Participant Chestfeeds During the Study

If a lactation exposure occurs and the participant will continue to chestfeed while enrolled in the study, then an SSR should be submitted within 24 hours of awareness of the event. A follow-up "lactation exposure" SSR will need to be submitted to capture the end of exposure to study drug via milk.

If an AE/SAE occurs in the infant following lactation exposure, the electronic SSR should be utilized to report the event in addition to submitting the paper Clinical Study Infant/Child Report form (except for vertical transmission) to Gilead PS. Events of vertical transmission should be reported to Gilead PS via the electronic SAE reporting process described in 7.4.1.1.

Refer to Section 7.4.2 and the eCRF completion guidelines for instructions on submitting SSRs involving study drug.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line listings, serious adverse drug reactions, or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 as outlined below:

- All clinically significant Grade 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of investigational medicinal product for any Grade 3 and 4 laboratory abnormality that in the opinion of the investigator is clinically significant and may pose a risk to the participant's safety.
- Clinical events and clinically significant laboratory abnormalities will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (refer to Section 7.2.2).

Any questions regarding toxicity management should be directed to the medical monitor.

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

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

7.7.2. Grades 3 Laboratory Abnormality or Clinical Event

For Grade 3 clinically significant laboratory abnormality or clinical event, study drug may be continued if the event is considered to be unrelated to study drug.

For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to study drug, study drug should be withheld until the toxicity returns to ≤ Grade 2.

If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued, and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation.

7.7.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to study drug, study drug should be permanently discontinued, and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically nonsignificant Grade 3 or 4 laboratory abnormality (eg, CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a Grade 3 or 4 clinical event considered unrelated to study drug.

7.7.4. Management of Changes in Estimated Glomerular Filtration Rate

Estimated GFR, according to the Cockcroft-Gault formula, will be followed postbaseline during the study. All participants with eGFR < 60 mL/min must have serum creatinine and participant's weight measured again within 3 calendar days of receipt of results. If a participant has confirmed eGFR < 60 mL/min, the investigator should notify the medical monitor, evaluate potential causes, re-assess the potential risks and benefits of continued treatment in the study and consider consultation with a qualified nephrologist.

7.7.5. Management of Adverse Events of Injection Site Reactions of Grade 3 or Higher or Persisting for More Than 26 Weeks

In clinical studies of SC LEN, Grade 3 or higher AEs of ISRs were uncommon. Some participants experienced AEs of injection site nodule and induration, which decreased in size over 6 months or longer. Investigators will contact the medical monitor to discuss the evaluation and management of long-lasting or severe (Grade 3 or higher) ISRs if the ISR is determined to be of clinical concern by the investigator. Photographic documentation of ISRs that meet the above criteria is recommended but not mandatory. If obtained, documentation of ISR evaluation findings, including photographs, may be shared with the sponsor and study team.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is to evaluate the efficacy of LEN in preventing the risk of HIV-1 infection relative to the background HIV-1 incidence rate. Participants are CGM, TGW, TGM, and GNB.

8.1.1.1. Incidence Phase Objectives

The primary objective for the Incidence Phase of this study is to estimate the HIV-1 background incidence rate.

8.1.1.2. Randomized Blinded Phase Objectives

The primary objective for the Randomized Blinded Phase of this study is as follows:

- To evaluate the efficacy of LEN for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex partners assigned male at birth and are at risk for HIV-1 infection

The secondary objectives for the Randomized Blinded Phase of this study are as follows:

- To compare the efficacy of LEN with F/TDF for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection
- To evaluate the efficacy of LEN for HIV-1 PrEP in participants at risk of HIV-1 infection in participants adherent to LEN
- To evaluate the safety and tolerability of LEN and F/TDF for HIV-1 PrEP in participants ≥ 16 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection
- To evaluate the safety and tolerability of LEN for HIV-1 PrEP in adolescent participants ≥ 16 to < 18 years of age who have condomless receptive anal sex with partners assigned male at birth and are at risk for HIV-1 infection

8.1.2. Primary Endpoint

8.1.2.1. Incidence Phase Primary Endpoint

The primary endpoint for the Incidence Phase of this study is the diagnosis of recent HIV-1 infection.

The background HIV-1 incidence per 100 PY will be computed based on the recent infection testing algorithm using a recency assay.

8.1.2.2. Randomized Blinded Phase Primary Endpoint

The primary efficacy endpoint for the Randomized Blinded Phase will be the diagnosis of HIV-1 infection.

The HIV-1 incidence per 100 PY will be computed as the number of participants who acquired HIV-1 divided by the total of a) for participants not diagnosed with HIV-1, sum of all duration of follow-up time in years (where a year is 365.25 days) and b) for participants diagnosed with HIV-1, sum of all duration of time to confirmed HIV-1 diagnosis.

8.1.3. Secondary Endpoints

The secondary endpoints for the Randomized Blinded Phase of this study are as follows:

- Diagnosis of HIV-1 among participants while adherent to study drug
- Occurrence of TEAEs and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and F/TDF for HIV-1 PrEP

8.2. Planned Analyses

8.2.1. Interim Analyses

A DMC will periodically evaluate participants' safety and conduct one interim efficacy evaluation. The DMC will have access to treatment codes for all their reviews and evaluations (unblinded).

8.2.1.1. 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 16 and 17 years of age) will commence following the first DMC review of the safety data and recommendation to continue the study. DMC review meetings of safety data will occur approximately annually thereafter during the Randomized Blinded Phase of the study.

8.2.1.2. Interim Analyses of Efficacy Data

The DMC will formally evaluate efficacy data, only once for efficacy and futility, after 50% of participants enrolled have completed at least 52 weeks of follow-up in the study or prematurely discontinued from the study. The DMC may recommend stopping the study early if the prespecified evaluation criteria are met. If the Randomized Blinded Phase is stopped early due to an efficacy outcome, the interim analysis will serve as the primary analysis. The general approach for interim decisions and DMC recommendations are discussed in Section 8.7 (Adjustments for Multiplicity) and further details will be prespecified in the interim analysis plan and/or statistical analysis plan.

8.2.2. Primary Analysis

The primary analysis will be conducted when all enrolled participants have completed a minimum of 52 weeks (1 year) of follow-up in the study or prematurely discontinued from the study (whichever occurs first) after randomization.

8.2.3. Final Analysis

The final 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. The HIV-1 incidence rate during the LEN OLE Phase will be conducted in the final analysis.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis sets for efficacy analysis are the All Screened Set (Incidence Phase) and the FAS (Randomized Blinded Phase). The All Screened Set includes all participants who were screened for HIV-1 in the Incidence Phase and had nonmissing HIV-1 diagnosis based on HIV 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) should be included in the All Screened Set and considered as HIV-1 negative. The FAS will include all randomized participants who received at least 1 dose of study drug and have not been diagnosed with HIV-1 by Day 1. Participants will be grouped according to the randomly assigned study drug. Sensitivity analyses may be performed to assess the impact of those with no postbaseline HIV-1 test on the interpretation of the study results.

8.3.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set which will include all randomized participants who received at least one dose of study drug. Participants will be grouped according to the study drug they receive.

8.3.1.3. Pharmacokinetics

The DBS Analysis Set will include all participants who have at least 1 reported TFV-DP concentration. The LEN PK Analysis Set will include all participants who have at least 1 reported LEN concentration.

8.3.2. Data Handling Conventions

In general, age at first dose of study drug, relative to date of birth, will be considered for analysis. As only year of birth will be collected “01 July” will be used for calculations of age when age is not collected.

For calculation of HIV-1 incidence, HIV-1 negative participants ongoing in the study at the time of the primary analysis will be censored at the date of their last HIV test.

In general, analysis of safety measures will be based on observed data. Although last observation carried forward (LOCF) or other imputation for safety measures may be considered for sensitivity analyses, there are no preplanned imputations rules for analysis of safety data. Details on imputation of numerical values reported as beyond the limit of quantitation will be provided in the statistical analysis plan.

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include, but would not be limited to, race/ethnicity, age, sex at birth, sexual orientation, gender identification, alcohol and substance use.

Baseline characteristics data will include, but would not be limited to, a summary of body weight (kg), height (cm), body mass index (kg/m^2), and waist circumference (cm).

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint will be analyzed using a method appropriate for a single Poisson rate based on the FAS. The primary objective of the study will be achieved by showing that the HIV-1 incidence rate for the LEN study drug group is significantly lower than the background incidence rate estimated in the Incidence Phase with 1-sided alpha of 0.025.

Null hypothesis $H_{01}: \text{LEN/bHIV} \geq 1.0$ (superiority over background)

Here LEN and background HIV represent the HIV incidence rate of the LEN study drug group and the background, respectively.

Additionally, the primary success criteria for the US FDA regulatory review is defined as the HIV-1 incidence rate ratio of at least 20% lower in the LEN study drug group compared with the background incidence rate estimated in the Incidence Phase, formulated as the key alpha-controlled H_{02} in the next section (gated on rejection of H_{01} with overall 1-sided alpha of 0.025) with the point estimate of LEN/bHIV ≤ 0.5 and comparability of LEN to F/TDF, formulated as the key alpha-controlled H_{03} in the next section.

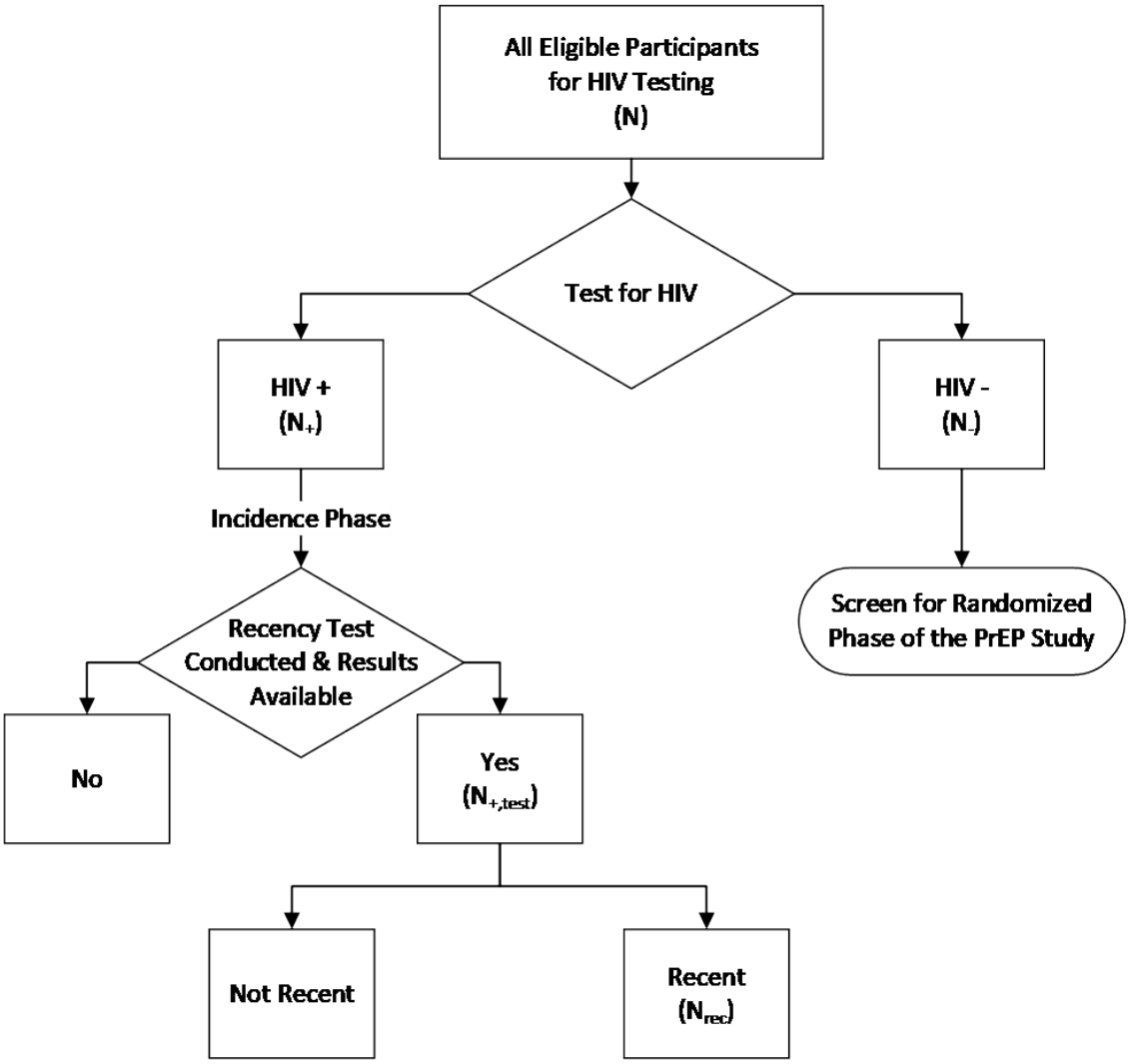
The background incidence will be estimated based on the HIV-1 recency assay results of those who were not on PrEP when screened in the Incidence Phase, using an HIV-1 incidence formula similar to {Kassanjee 2012}, adjusting for participants with HIV-1 who may not have recency assay results.

The incidence rate ratio of the LEN study drug group to the background, the associated 95% CI, and the p-value will be estimated using the delta method {Gao 2021} or a likelihood-based

method{Shao 2024} if the number of HIV-1 infections in the LEN group is zero. The incidence rate difference of LEN from F/TDF, the associated 95% CI and the P value will be calculated based on a hybrid approach{Li 2011}.

The primary analysis will be conducted when all enrolled participants have completed a minimum of 52 weeks (1 year) of follow-up in the study or prematurely discontinued from the study (whichever occurs first) after randomization.

Figure 13. A High-Level Screening Schema and Contribution of Participants to the Estimation of the Background HIV-1 Incidence Rate



HIV = human immunodeficiency virus; PrEP = pre-exposure prophylaxis
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 Recent Infection Testing Algorithm

Then the background incidence rate 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: Mean duration of recent infections (MDRI)
β: False recency rate (FRR)

The standard error of $\hat{\lambda}_0$ in the log scale $\hat{\sigma}_{\log(\lambda_0)}$ will be estimated by the delta method {Gao 2021}, considering the variance of Ω, β, and the observed counts of N_-, $N_{+,test}$, N_{rec}.

The HIV-1 incidence rate $\hat{\lambda}_1$ in the study will be estimated by the number of HIV-1 infections divided by the total follow-up time for each arm. The standard error of the incidence estimate $\hat{\lambda}_1$ in the log scale $\hat{\sigma}_{\log(\lambda_0)}$ will be the inverse of the number of infections, based on the Poisson assumptions. The difference in log scale will be estimated by $\log(\hat{\lambda}_1) - \log(\hat{\lambda}_0)$, with the standard error being $\sqrt{\hat{\sigma}^2_{\log(\lambda_0)} + \hat{\sigma}^2_{\log(\lambda_1)}}$. The confidence interval of the incidence ratio $\hat{\lambda}_1/\hat{\lambda}_0$ will be obtained by exponentiating the confidence interval of $\log(\lambda_1) - \log(\lambda_0)$.

8.5.2. Secondary Analyses

The key α-controlled secondary analyses in the study include the following tests of null hypotheses. In the equation below, F/TDF is being replaced with TVD for brevity and simplifying formulation of ratio in the listed null hypotheses:

1) HIV-1 incidence rate of the LEN study drug group to the background HIV-1 is at least 20% lower in the LEN study drug group compared with the background incidence rate estimated in the Incidence Phase and the point estimate of LEN/background HIV ≤ 0.5.

    - H_{02}:$LEN/bHIV \geq 0.8$ (at least 20% reduction over background HIV-1), which will be tested in a similar manner to the primary endpoint and the point estimate of LEN/background HIV ≤ 0.5.

2) HIV-1 incidence rate of the LEN study drug group is at most 0.8/100 PY higher than the F/TDF study drug group

    - H_{03}:$LEN - TVD \geq 0.8/100PY$ (comparable to F/TDF), which will be tested using a rate difference approach.

3) HIV-1 incidence rate of the LEN study drug group is significantly lower than the HIV-1 incidence rate of the F/TDF study drug group

- H_{04}:$LEN/TVD \geq 1.0$ (superiority over F/TDF), which will be tested using a rate ratio approach.

A secondary analysis of the primary endpoint will be the comparison of the HIV-1 incidence rate in the LEN study drug group with a predefined bound of 1.525 per 100 PY. This bound represents 50% of the lower 95% confidence bounds of the nonrandomized control of background HIV-1 incidence rate reported as 3.49 (3.05, 3.92) {Mera 2020}.

The background HIV-1 incidence rate may also be estimated using prerandomization methods such as recent epidemiologic data and/or the screening HIV-1 positivity rate, and postrandomization, such as correlation of rectal gonorrhea incidence rate with HIV-1 incidence rate in each study group or other methods as they become validated.

The rate ratio of HIV-1 incidence between LEN and F/TDF 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, or an exact conditional Poisson model if the number of infections is zero in any of the experimental groups. Proportional hazard models, comparing LEN vs F/TDF, may be used as sensitivity analyses for H_{04}.

8.6. Safety Analysis

All treatment-emergent safety data collected on or after the date that study drug was first dispensed up to the end of the statistical analysis plan-defined follow-up period will be summarized by study drug arm. Data for the prestudy drug initiation and poststudy drug initiation follow-up time will be included in data listings.

In general, and unless specified otherwise, for categorical safety data including incidence of AEs or categorical laboratory data, a Fishers exact test may be used to compare study drug arms. For continuous safety data including laboratory data, a t-test or analysis of variance (ANOVA) model may be used to compare study drug arms. Some details are noted below, and full details will be provided in the statistical analysis plan (to be finalized before database lock for the primary analysis).

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by study drug group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug exposure, inclusive, regardless of temporary interruptions in study drug administration. Dosing information for individual participants will be listed.

A participant is defined as adherent to F/TDF during an HIV-1 testing interval (time period between determining HIV-1 status through study testing) if TFV-DP in DBS is adequate ($\geq$ 350 fmol/punch for the F/TDF study drug group). A participant is defined as adherent to LEN if they have received a per-protocol administration of LEN within the last 26 weeks (± 14 days).

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the end of the statistical analysis plan-defined follow-up period.

Summaries (number and percentage of participants) of TEAEs (by SOC and PT) will be provided by study drug arm. Additional summaries will include summaries for AEs by grade, investigator's assessment of relationship to study drug, and effect on study drug dosing.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Appendix 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time postbaseline up to the end of the statistical analysis plan-defined follow-up period, will be summarized by study drug arm. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade observed for participants will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug or after the end of the statistical analysis plan-defined follow-up period will be included in a data listing.

8.6.4. Renal Safety

The change from baseline in serum creatinine at Week 52 will be summarized using descriptive statistics. The difference in change from baseline between 2 study drug arms will be tested using analysis of covariance (ANCOVA) model with study drug as fixed effect and baseline measure as a covariate.

8.6.5. Other Safety Evaluations

Weight (kg) and waist circumference (cm) will be summarized by visit and change (and/or percent change) from baseline in study drug arms may be compared using ANCOVA model with study drug as fixed effect and baseline measure as a covariate.

8.7. Adjustments for Multiplicity

One formal evaluation of interim efficacy is planned. The overall 1-sided Type I error rate of 0.025 for the primary and key α-controlled secondary endpoints at both the interim and primary analyses will be controlled using a Bonferroni type spending function accompanying a gatekeeping testing strategy. The overall alpha of 0.025 will be split between the interim analysis ($\alpha_1 = 0.0026$) and the primary analysis ($\alpha_2 = 0.0224$). At both the interim and primary analyses, the 1-sided Type I error rate will be controlled using a fixed-sequence gatekeeping testing strategy (ie, tested sequentially in the order given below).

1) H_{01}: LEN/bHIV $\geq$ 1.0 (superiority over background)
2) H_{02}: LEN/bHIV $\geq$ 0.8 (at least 20% reduction over background HIV-1)
3) H_{03}: LEN−TVD $\geq$ 0.8/100PY (comparable to F/TDF)
4) H_{04}: $LEN/TVD \geq 1.0$ (superiority over F/TDF)

In the above mathematical formulas, TVD stands for the incidence rate of the F/TDF arm.

The DMC may recommend to stop the randomized part of the study early:

1) For efficacy, if the hypothesis H_{02} is rejected at the level $\alpha 1 = 0.0026$ with the point estimate for the LEN/bHIV ≤ 0.5 and H_{04} is rejected at the level $\alpha 1 = 0.0026$.
2) For futility, if F/TDF is found to be superior to LEN at the level $\alpha 1 = 0.0026$.

The use of a recency assay to estimate the background HIV incidence in PrEP studies is a novel approach. The estimate of the background HIV is subject to many assay and operational issues. If the point estimate of the recency based counterfactual background HIV is less than 1.5/100 PY at the interim analysis, the estimate of background HIV incidence by the recency-assay based methodology will be deemed as not performing as expected. In this case, hypotheses H_{01} and H_{02} will be skipped at the interim analysis and recommendations to stop the randomized part of the study will be based on rejecting H_{04} at $\alpha_1 = 0.0026$.

8.8. Pharmacokinetic Analysis

LEN plasma concentrations will be summarized by timepoint for SC and oral LEN. Additionally, the PopPK analysis of LEN is planned.

8.9. Sample Size

A total sample size of 3000 is considered for the study in CGM, TGW, TGM, and GNB. 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 background incidence rate (powered for both H_{01} and H_{02}). In this sample size analysis, the following assumptions are made:

- Background HIV-1 incidence of 3.00/100 PY

- LEN incidence of 0.6/100 PY, with an 80% risk reduction in HIV-1 compared with the nonrandomized control of background HIV-1 incidence
- 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 background HIV-1 incidence rate assumption is a conservative estimate based on epidemiologic data {Mera 2019}. The LEN incidence rate corresponds to an 80% risk reduction and is consistent with the incidence rates 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 LAg assay {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 8.5.1. Under the assumption of T = 1 year, the power remains at > 95%. These assay parameters are still under investigation and may be fine-tuned further. The power calculation is based on the formula in Gao, et al (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 95% CI will be estimated to characterize the comparative evaluation.

8.10. Data Monitoring Committee

An external DMC will primarily evaluate the safety of LEN in this population. 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 beyond 600 participants before the safety review is conducted and, if determined by the DMC, the study is allowed to continue. Enrollment of adolescents (participants 16 and 17 years of age) will commence following the first DMC review of the safety data and recommendation to continue the study. Gilead will notify sites when they may begin enrollment of adolescents. DMC safety review meetings will occur approximately annually thereafter during the Randomized Blinded Phase of the study.

The DMC will formally evaluate efficacy data, only once for efficacy and futility, after 50% of participants enrolled have completed at least 52 weeks of follow-up in the study or prematurely discontinued from the study. The DMC may recommend stopping the study early if the prespecified evaluation criteria are met. The general approach for interim decisions and DMC recommendations are discussed in Section 8.7 (Adjustments for Multiplicity) and further details will be prespecified in the interim analysis plan and/or statistical analysis plan.

The external independent multidisciplinary DMC will review the progress of the study and provide recommendations to Gilead whether the nature, frequency, and severity of adverse effects associated with study drug warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications. Should there be a substantial difference in HIV-1 incidence between the 2 study arms emergent during study follow-up, the DMC is empowered to recommend changes to the study protocol or procedures, as such a difference may fall within their purview to make recommendations based on concerns related to participant safety. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, interim data cut, scope of responsibilities, and meeting schedule.

CCI [redacted]

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness if required by IRB or IEC or local requirements.

The ICF will inform participants about planned sample retention. CCI [redacted] The results of the tests done on the samples will not be given to the participant or the investigator. In addition to the study-specific ICF to be signed by each participant taking part in the study, participants assigned female at birth who are of reproductive potential who become pregnant after randomization may remain on the study after the reconsent process, as applicable according to local rules and regulation, where they will be informed of the benefits and risks of continuing receipt of study drug while pregnant and lactating and the collection of birth outcomes for the child. Participants who are taking testosterone and become pregnant during the study must discontinue testosterone due to teratogenic potential if continuing the pregnancy and wish to continue on study drug.

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, case report forms (CRFs)/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification
- Documentation that participant meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Electronic Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the case report form Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification (SDV). System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year (6 months for pediatric studies, in accordance with Regulation [EC] No. 1901/2006) after the global end of study (as defined in Section 3.6).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any participant records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority, IRBs, and IECs. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGMENT

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

GS-US-528-9023, Amendment 4, 21 October 2024

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)

[See appended electronic signature]

Signature

PPD

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During emergency circumstances, such as an ongoing infectious disease pandemic, and other force majeure events, potential risks associated with participants being unable to attend study visits have been identified for this study. For infectious disease pandemics, sites will utilize regional or local guidelines to manage the clinic and participants.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

   a) Participants may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any participant visits. Without study drug, the participant would not be able to stay on the study drug as planned per protocol.

      Mitigation plan: Oral study drug supplies at non-injection scheduled visits may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on study drug as determined by the principal investigator (PI) or qualified designee. However, study drug injections of lenacapavir (LEN)/placebo must occur at the study site. For any missed injection visits the site must remind the participant of the potential risks. A virtual study visit, via phone or video conferencing, must be performed prior to remote oral study drug resupply. Prior to the virtual visit, the PI or qualified designee should contact the participant to obtain verbal consent from the participant to ship and perform the home rapid HIV test or arrange for the participant to attend a local laboratory/facility for HIV testing. Participants should be given clear instructions on how to perform the HIV test. The date and time that consent was obtained must be documented in the participant's medical records. The PI or qualified designee will then perform the virtual visit, including review of the HIV test result, within the protocol target visit window dates whenever possible. The calls should be documented in the source documents at the site and relevant information entered in EDC. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study participants if permitted by local ethics committee (EC)/institutional review boards (IRB)/regulatory authority, as applicable and with sponsor's approval.

   b) Shipments of study drug and study drug supplies could be delayed because of transportation issues. Without study drug, participant would not be able to stay on the study drug as planned per protocol.

      Mitigation plan: The sites' study drug inventory and study drug supplies should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Participant's safety monitoring and follow-up:

a) Participants may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified designee will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations and follow-up on any unresolved AEs/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm participants' oral study drug supply is sufficient to last until the next planned visit date. If oral study drug resupply is needed it will be provided as described above in (1).

iv) If feasible, participant will be provided with adherence, retention, HIV risk assessment and reduction. Participant will be reminded to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: The following planned assessments during specified study visits will continue to be performed: HIV and DBS collection. Participants will be asked to conduct self-HIV assessments using home testing kits, if there is no option to perform these tests by study staff during a home/alternate location visit. Self-administered test results will be transmitted to site via photo or verbally. For visits which require a blood sample for DBS collection, study staff to arrange with participant to collect blood sample via home/alternate location visit. Local laboratories may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

   a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

      Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the electronic case report form (eCRF) and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

   b) Monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice (GCP) compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

      Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed. The study monitor is to reference the study monitoring plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of study drug(s) in study participant remains unchanged.

Appendix 3. Study Procedures Table

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	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	

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]				
Local Rapid 4th Generation HIV-1/2 Ab/Ag	X		X	X	X	X	X	X	X	Every 13 weeks	X	X	X		
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	

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]			
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				
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)					

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]				
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	
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[q]			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				

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]				
CD4 cell count (Screening if local rapid HIV-1/2 test is positive and for participants diagnosed with HIV after receiving study drug, refer to Section 6.13)	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, refer to Section 6.13)			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 Informed consent/assent are 2 separate ICFs specific to Incidence Phase and Randomized Blinded Phase. Reconsent is required if participant becomes pregnant.

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 Metabolic Assessments: 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 LEN OLE Phase

Study Procedure	LEN OLE Phase – Weeks (± 7 days; ± 2 days for Weeks 4 and 8)[u]											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)
	End of Randomized Blinded Phase Visit/LEN OLE Day 1	4[d]	8[d]	13	26	39	52[e]	Post Week 52			Oral Bridging Visit[f]				
								Q13	Q26	Q52					
Concomitant Medications	X	X	X	X	X	X	X	X			X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X			X	X	X	X	
Targeted Physical Exam	X	X	X	X	X	X	X	X			X	X	X	X	
Vital Signs, Weight, and Height[g]	X	X	X	X	X	X	X	X			X	X	X	X	
Asymptomatic STI Testing for GC, CT, TV, and Syphilis[h]	X			X	X	X	X	X			Every 13 weeks		X	X	
Local Rapid Fourth Generation HIV-1/2 Ab/Ag	X	X	X	X	X	X	X	X			X	X	X		
Central Fourth Generation HIV-1/2 Ab/Ag	X	X	X	X	X	X	X	X			X	X	X		
Hepatitis B Testing (HBsAg/HBsAb/ HBcAb)	X						X			X	Every 52 weeks				
Hepatitis C Testing (HCV Ab)	X						X			X	Every 52 weeks				
Blood Sample for Chemistry/Hematology	X				X		X		X		Every 26 weeks	X	X	X	
Blood Storage Sample for HIV-1 RNA by NAAT	X	X	X	X	X	X	X	X			X	X	X		

Study Procedure	LEN OLE Phase – Weeks (± 7 days; ± 2 days for Weeks 4 and 8)[u]														
	End of Randomized Blinded Phase Visit/LEN OLE Day 1	4[d]	8[d]	13	26	39	52[e]	Post Week 52			Oral Bridging Visit[f]	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)
								Q13	Q26	Q52					
Blood Sample for DBS	X														
Blood Sample for Metabolic Assessments[i]	X						X			X	Every 52 weeks				
Anytime Plasma PK Sample	X	X	X	X	X	X	X	X			X	X	X	X	
Plasma Storage Sample	X	X	X	X	X	X	X	X			X	X	X	X	
Serum Storage Sample	X	X	X	X	X	X	X	X			X	X	X	X	
Estimated GFR	X				X		X		X		Every 26 weeks	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X			X	X	X		
Urine Pregnancy Test[j]	X	X	X	X	X	X	X	X			X	X	X	X	
Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire	X			X	X	X	X					X			
Adherence to Oral Study Product Questionnaire	X														
Experienced Preference for PrEP Medication Questionnaire	Every injection visit											X			
Numeric Pain Rating Scale - Injection Pain (completed postinjection)	Every injection visit														

Study Procedure	LEN OLE Phase – Weeks (± 7 days; ± 2 days for Weeks 4 and 8)[u]											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)
	End of Randomized Blinded Phase Visit/LEN OLE Day 1	4[d]	8[d]	13	26	39	52[e]	Post Week 52			Oral Bridging Visit[f]				
								Q13	Q26	Q52					
Administration and Dosing Questionnaire for PrEP Medication	13 weeks after each injection visit[k]														
Participants contacted 1 week (± 2 days) after each injection visit for postinjection follow-up assessment[l]	Every injection visit								X						
Intimate partner violence screening	X	X	X	X	X	X	X	X			X	X	X	X	
HIV Risk Reduction Counseling	X	X	X	X	X	X	X	X			X	X	X		
F/TDF or PTM F/TDF Accountability[m]	X														
Oral LEN Dispensation and Accountability and Adherence Counseling	X[n,o]	X[p]									X				
CD4 cell count, HIV-1 RNA quantitative NAAT, and HIV resistance genotype (for participants diagnosed with HIV only, refer to Section 6.13 and Appendix 5)	X	X	X	X	X	X	X	X			X	X	X	X[q]	X[r]
LEN administration[s]	Every 26 weeks after the previous injection[t]								X						

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; LEN = lenacapavir; NAAT = nucleic acid amplification test; OLE = open-label extension; PK = pharmacokinetic(s); PrEP = pre-exposure prophylaxis; PTM = placebo-to-match; Q*N* = every N number of weeks; 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 within 72-hours of informing the investigator they no longer wish to receive SC LEN injections in the LEN OLE 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 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 they were diagnosed with HIV infection.

d Only participants randomized to oral F/TDF (in the Randomized Blinded Phase) who switch to SC LEN will have visits at LEN OLE Weeks 4 and 8.

e The first SC LEN administration in the LEN OLE Phase will be determined by the previous LEN injection and should be dosed within 26 weeks (± 7 days) of the last administered dose of SC LEN (ie, participants whose last LEN injection was 13 weeks before LEN OLE Day 1 will receive their first open-label LEN injections at the LEN OLE Week 13 and every 26 weeks thereafter; participants whose last LEN injection was 26 weeks before LEN OLE Day 1 will receive their first open-label LEN injections at the LEN OLE Day 1 and every 26 weeks thereafter).

f 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.

g For participants < 20 years old, height is to be measured annually until they reach 20 years of age.

h 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 as per local testing protocol. For participants assigned female at birth, central laboratory urine TV testing may be performed at the investigator's discretion.

i Metabolic panel: Participants should be instructed to fast (no food or drinks, except water), at least 8 hours prior to blood collection.

j 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.

k Participants will either have the questionnaire at Week 13 and Week 39 or at Week 26 and Week 52, depending on when they receive their SC LEN injections.

l For the LEN OLE Day 1 follow-up, the site staff will also confirm the participant has been administered the Day 2 dose.

m Drug accountability will be performed by pill count for adherence.

n Only for participants randomized to F/TDF; oral LEN is to be dosed on LEN OLE Days 1 and 2.

o Study drug dispensation only.

p No study drug will be dispensed. Drug accountability will be performed by pill count for adherence.

q HIV resistance genotype will be performed only if not already collected at time of infection.

r CD4 cell count and HIV-1 RNA quantitative NAAT only.

s LEN injections are to be given every 26 weeks (± 7 days) after the previous one until either LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first.

t End of Randomized Blinded Phase visit coincides with the LEN OLE Day 1 visit. Participants who were randomized to F/TDF and are entering into the LEN OLE Phase will receive their first LEN injection at this visit. Participants who were randomized to LEN and are continuing in the LEN OLE Phase will receive their first LEN OLE injection 26 weeks (± 7 days) after their last injection in the Randomized Blinded Phase.

u 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)[a]							
	Randomized Blinded Phase to PK Tail Day 1	13	26	Post Week 26 Every 13 or 26 Weeks to Week 78	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)
Concomitant Medications	X	X	X	Every 13 weeks	X	X	X	X
Adverse Events	X	X	X	Every 13 weeks	X	X	X	
Targeted Physical Examination	X	X	X	Every 13 weeks	X	X	X	
Vital Signs, Weight, and Height[e]	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	Every 13 weeks	X	X		
Central 4th Generation HIV-1/2 Ab/Ag	X	X	X	Every 13 weeks	X	X		
Hepatitis B Testing (HBsAg/HBsAb/ HBcAb)	X			Every 52 weeks				
Hepatitis C Testing (HCV Ab)	X			Every 52 weeks				
Blood Sample for Chemistry/Hematology	X		X	Every 26 weeks	X	X	X	
Blood storage sample for HIV-1 RNA NAAT	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			Every 52 weeks				
Anytime Plasma PK sample	X	X	X	Every 13 weeks	X	X	X	
Plasma Storage Sample	X	X	X	Every 13 weeks	X	X	X	
Serum Storage Sample	X	X	X	Every 13 weeks	X	X	X	
Estimated GFR	X		X	Every 26 weeks	X	X	X	
Urinalysis, Urine Protein, Urine Chemistry	X	X	X	Every 13 weeks	X	X	X	
Urine Pregnancy Test[i]	X	X	X	Every 13 weeks	X	X	X	
Integrated Sexual Behaviors and Alcohol and Substance Use Questionnaire	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							

Study Procedure	PK Tail Phase – Weeks (± 7 days)[a]							
	Randomized Blinded Phase to PK Tail Day 1	13	26	Post Week 26 Every 13 or 26 Weeks to Week 78	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)
Administration and Dosing Questionnaire for PrEP Medication	X							
Intimate partner violence screening, when applicable	X	X	X	Every 13 weeks	X	X	X	
HIV Risk Reduction Counseling	X	X	X	Every 13 weeks	X	X		
Adherence Counseling	X	X	X	Every 13 weeks				
F/TDF Dispensation and Accountability[j]	X	X	X	Every 13 weeks	X[k]			
CD4 cell count, HIV-1 RNA quantitative NAAT, and HIV resistance genotype (for participants diagnosed with HIV only, refer to Section 6.13 and Appendix 5)	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*; US = United States

a All PK tail visits should be scheduled from 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.

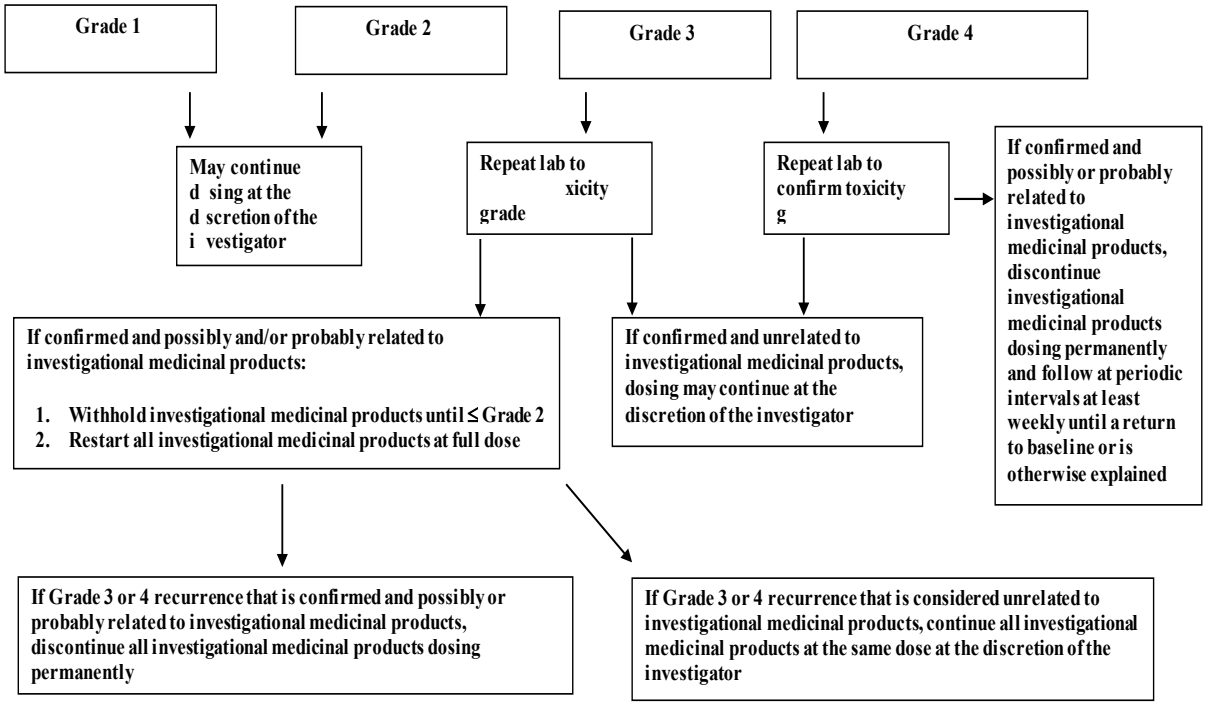
g Only collect if the participant prematurely discontinues from the Randomized Blinded Phase.

h Metabolic Assessment: 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.

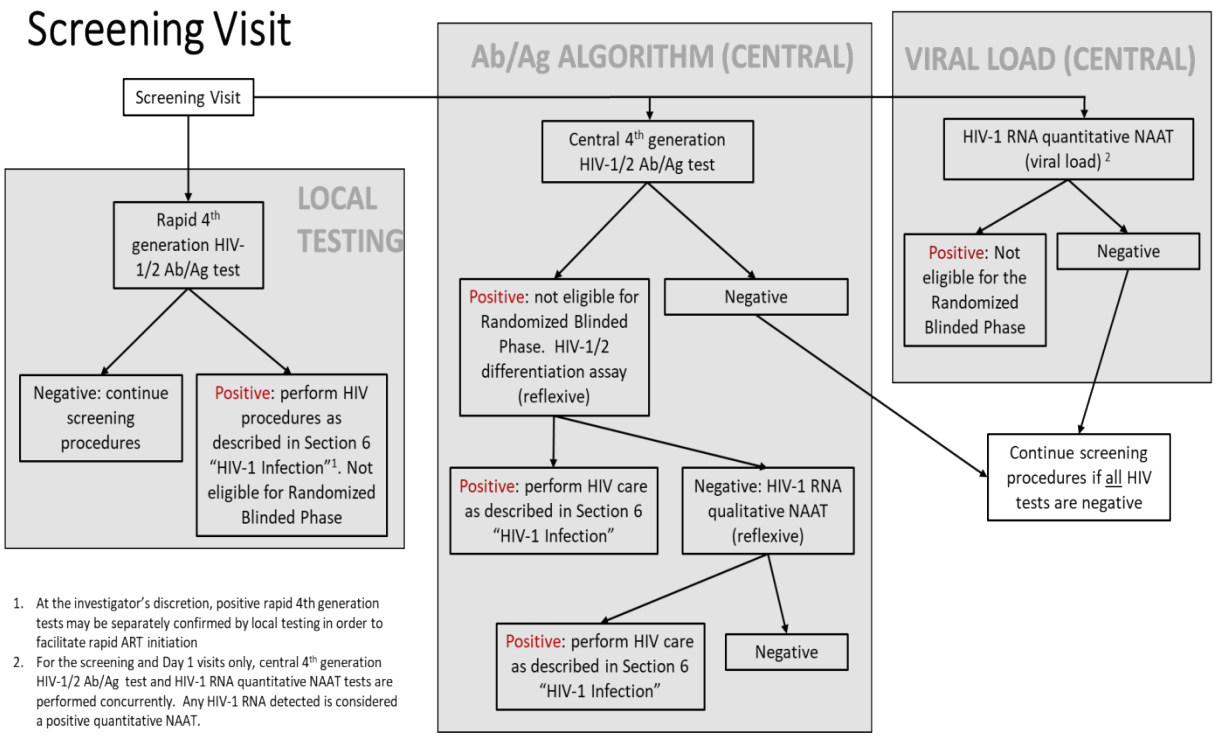
j Drug accountability will be performed by pill count for adherence. (See Appendix 7 for US-specific text.)
k No study drug will be dispensed.
l HIV resistance genotype will be performed only if not already collected at time of infection.
m CD4 cell count and HIV-1 RNA quantitative NAAT only.

Appendix 4. Management of Clinical and Laboratory Adverse Events



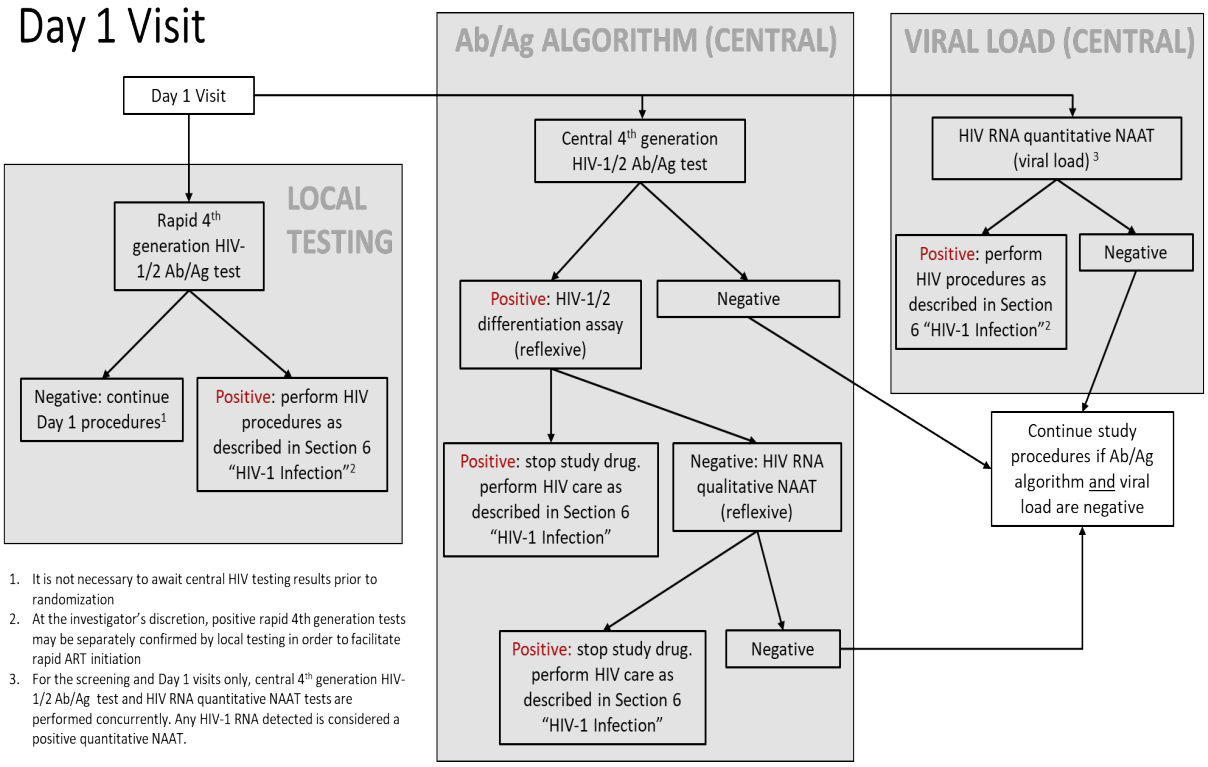
Appendix 5. HIV Testing Algorithms

5a Screening Visit



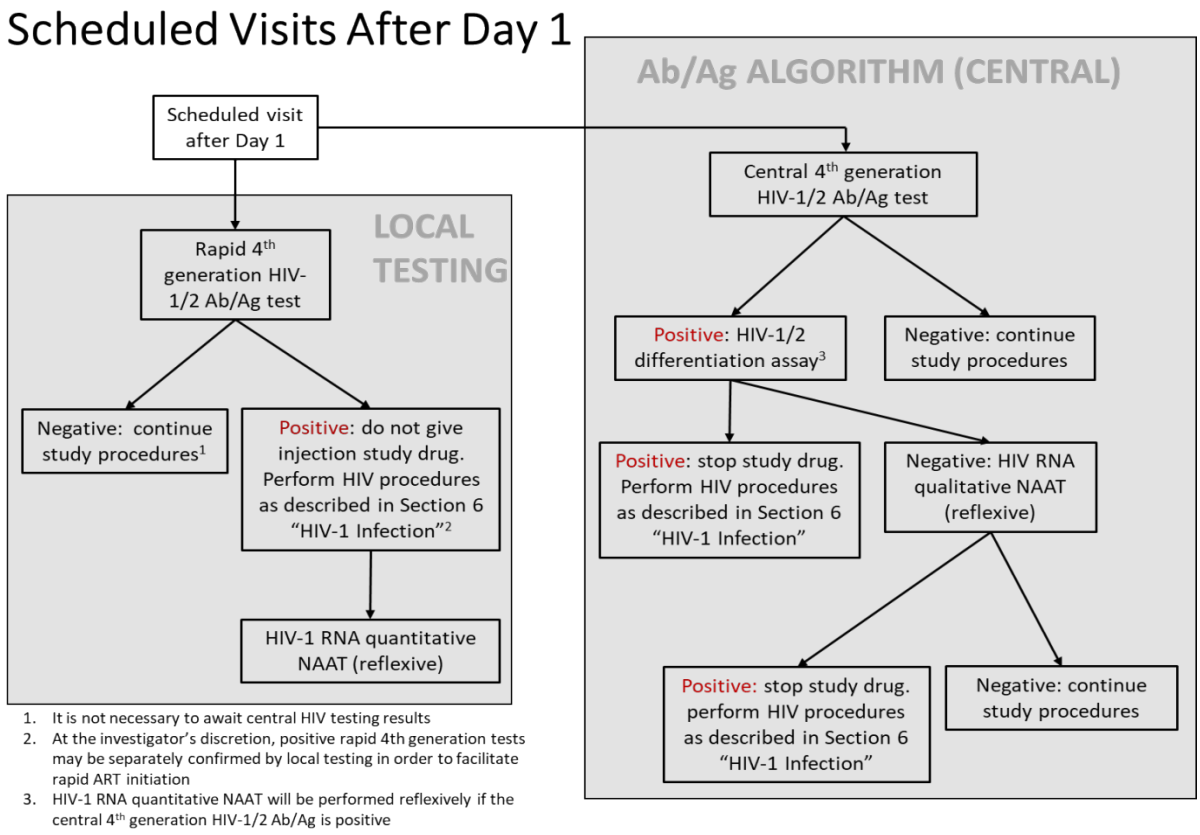
1. At the investigator's discretion, positive rapid 4th generation tests may be separately confirmed by local testing in order to facilitate rapid ART initiation
2. For the screening and Day 1 visits only, central 4th generation HIV-1/2 Ab/Ag test and HIV-1 RNA quantitative NAAT tests are performed concurrently. Any HIV-1 RNA detected is considered a positive quantitative NAAT.

5b Day 1/Injection 1 Visit



1. It is not necessary to await central HIV testing results prior to randomization
2. At the investigator's discretion, positive rapid 4th generation tests may be separately confirmed by local testing in order to facilitate rapid ART initiation
3. For the screening and Day 1 visits only, central 4th generation HIV-1/2 Ab/Ag test and HIV RNA quantitative NAAT tests are performed concurrently. Any HIV-1 RNA detected is considered a positive quantitative NAAT.

5c Scheduled Visits After Day 1/Injection 1



1. It is not necessary to await central HIV testing results
2. At the investigator's discretion, positive rapid 4th generation tests may be separately confirmed by local testing in order to facilitate rapid ART initiation
3. HIV-1 RNA quantitative NAAT will be performed reflexively if the central 4th generation HIV-1/2 Ab/Ag is positive

Appendix 6. Randomized Blinded Phase Pregnancy Precautions, Definition Childbearing Potential for Participants Assigned Female at Birth, and Contraceptive Requirements

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth, including transgender men, gender nonbinary people, and individuals taking testosterone and not experiencing regular menses are considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b) Definition of Fertility in Participants assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Participants Assigned Female at Birth

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical pharmacokinetic interaction studies of emtricitabine/tenofovir disoproxil fumarate (F/TDF) have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Based on in vitro and in vivo drug-drug interaction liability assessment, a clinically significant drug-drug interaction with lenacapavir (LEN) and hormonal contraceptives is not expected; an oral contraception drug-drug interaction study was not done (see Section 1.2.7).

Nonclinical toxicity studies of F/TDF and LEN have demonstrated no adverse effect on fertility or embryo-fetal development.

No safety concerns have been associated with F/TDF for pre-exposure prophylaxis (PrEP) in early pregnancy or their offspring. No safety concerns have been identified among infants exposed to F/TDF during lactation. The long-term safety of infants exposed to F/TDF in utero is not yet known.

There are no clinical studies of LEN in pregnancy (Section 1.2.5.4). It is not known whether LEN is secreted in human milk (Section 1.2.6.4).

Please refer to the latest version of the investigator's brochures, and Sections 1.2.5 and 1.2.6 for additional information.

b) Contraception Requirements for Participants Assigned Female at Birth of Childbearing Potential

The inclusion of participants assigned female at birth of childbearing potential requires using at least an acceptable effective contraceptive measure. Pregnancy tests will be performed as defined by the study procedures in Appendix 3. They must have a negative serum pregnancy test at Randomized Blinded Phase screening and a negative pregnancy test at the Day 1/Injection 1 Randomized Blinded Phase visit prior to the dose of study drug. At any time pregnancy is suspected, a pregnancy test must be performed to rule out pregnancy. This is also applicable for participants assigned female at birth of childbearing potential with infrequent or irregular periods.

Duration of contraception for participants assigned female at birth of childbearing potential enrolled in this clinical trial should start from the screening visit until 700 days after the last dose of LEN.

Participants assigned female at birth of childbearing potential must agree to one of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal and nonhormonal intrauterine device
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

Or

Participants assigned female at birth of childbearing potential who initiate use of a hormonal contraceptive > 7 days after onset of menses as one of their birth control methods should use additional back-up contraception or avoid sexual intercourse for 7 days. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods
  - External (penile) condom (with or without spermicide)
  - Internal (vaginal) condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Participants assigned female at birth must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Participants Assigned Male at Birth

No contraception measures are needed.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. An internal (vaginal) condom and an external (penile) condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study until 700 days from last dose of LEN. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3. See also Section 9.1.4 regarding reconsent and remaining in the study.

See Appendix 7 for US-specific text.

Appendix 7. Country-Specific Requirements

1) Additional Country-Specific Requirements for the US

Country-specific Requirements	Affected Sections
Included a background subsection for emtricitabine/tenofovir alafenamide (F/TAF; Descovy). F/TAF is approved for pre-exposure prophylaxis (PrEP) in the United States (US), Canada, Australia, and Taiwan. For further information on F/TAF, including findings of nonclinical studies of F/TAF for PrEP, refer to the current investigator's brochure (IB) for F/TAF.	Section 1.2.2
Included summary of nonclinical studies in pregnancy for tenofovir alafenamide (TAF) stating that animal studies do not indicate direct or indirect harmful effects of TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. Tenofovir alafenamide is not considered to be genotoxic. In offspring from rat and rabbit dams treated with TAF during pregnancy, there were no toxicologically significant effects on developmental endpoints (DESCOVY IB).	Section 1.2.4.1
Included summary of TAF use during human pregnancy stating that the pharmacokinetics (PK) of TAF has been studied in pregnant women. Pharmacokinetics in pregnant women was reported in 31 women taking TAF 25 mg without any pharmacoenhancer and in 27 women taking TAF 10 mg boosted with cobicistat 150 mg {Best 2015a, Best 2015b, Chinula 2020}. This study evaluated plasma TAF exposures with and without boosting in pregnant and postpartum women relative to those in nonpregnant adults. No significant differences in PK were seen between pregnant and postpartum women taking boosted TAF. Among women taking unboosted TAF, exposures were lower during pregnancy than postpartum, but this was driven by higher exposures postpartum. Despite the differences observed, exposures in both regimens were within the range of those typically observed in nonpregnant adults {Momper 2018}. Tenofovir alafenamide levels were below the limit of quantification in all 15 cord blood samples tested. Tenofovir alafenamide was safe and well tolerated by mothers and babies in this small sample. Recent results from the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) 2010 study have added to the available pregnancy data for TAF. IMPAACT investigators randomized 643 women with HIV to begin HIV treatment 14 to 28 weeks into their pregnancies with efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF; Atripla®), dolutegravir (DTG) + F/TAF, or DTG+F/TDF. Participants taking TAF-containing therapy had superior composite pregnancy outcomes: 24% of women taking DTG+F/TAF had an adverse pregnancy outcome compared with 33% of women taking DTG+F/TDF or EFV/FTC/TDF {Chinula 2020}. Furthermore, advantages of TAF over TDF demonstrated in HIV-1 treatment studies include less impact on bone mineral density (BMD). It has been shown that growing children treated for HIV-1 infection with a TAF-based regimen have minimal changes in BMD height-age Z-scores which offers advantage over TDF-based regimens {Gaur 2016}. The expectation is that this could be extrapolated to the fetus in utero, thus conferring this advantage for safe use of F/TAF for PrEP during pregnancy. Also, as loss of BMD in newborns exposed to TDF in utero during maternal antiretroviral therapy (ART) has been shown {Siberry 2015}, it is expected that this would be less likely to be the case for TAF-exposed newborns during pregnancy based on the evidence for the bone safety benefit of TAF versus TDF in growing children. The antiretroviral pregnancy registry (APR) is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral (ARV) products. The APR collects provider-reported birth outcomes of women taking ART and compares the prevalence of birth defects with birth defects rates reported by 2 large registries, the US Centers for	Section 1.2.5.2

Country-specific Requirements	Affected Sections
Disease Control and Prevention's (CDC's) birth defects surveillance system (Metropolitan Atlanta Congenital Defects Program [MACDP]) and the Texas Birth Defects Registry (TBDR). The 31 July 2021 APR report included 606 pregnancies with TAF exposure, with a birth defect rate that was not statistically different from the MACDP or the TBDR. While current guidelines do not recommend routine initiation of TAF during pregnancy due to limited data {Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission 2020}, the currently available data on TAF use in pregnancy have not revealed safety concerns and support its continued study in clinical studies.	
Included summary of TAF use while lactating stating that there are little data on the secretion of TAF into breast milk, although the 90% lower circulating levels of TFV associated with TAF 25 mg administration compared with TDF 300 mg administration make it likely that breast milk and fetal exposures would be significantly lower than those observed with TDF administration. This is supported by data from a study of TAF and TDF used for hepatitis B treatment in pregnant women. In this study, 26 pregnant women received TAF for hepatitis B virus (HBV), and TAF concentrations were below the limit of quantification (0.5 ng/mL) in cord blood or breast milk samples from all women {Bojun 2020}.	Section 1.2.6.2
Included summary of drug-interaction potential for F/TAF with hormones stating that TAF along with TDF, but not their major metabolite TFV, are substrates for intestinal efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) {DESCOVY 2020, Tong 2007, TRUVADA 2020}. However, the results of Phase 1 drug-drug interactions (DDI) evaluations revealed that a clinically relevant alteration in systemic exposure of TAF is limited to strong induction of intestinal P-gp by rifampin {Custodio 2017}. As such, the use of strong P-gp inducers with F/TAF is not recommended. While in vitro, TAF, but not TDF or TFV, weakly inhibited cytochrome P450 enzyme (CYP)3A, the results of the dedicated Phase 1 evaluation demonstrated lack of TAF effect on CYP3A activity using midazolam, a sensitive CYP3A probe {DESCOVY 2020}. These data confirm that F/TAF and F/TDF may be administered with CYP3A substrates. Collectively, these studies demonstrated that F/TAF and F/TDF have a low propensity to act as victims or perpetrators of clinically significant drug interactions, including with estrogens, testosterone, and nonhormonal gender-affirming hormone therapy (GAHT). In agreement with these data, dedicated Phase 1 evaluations between TDF, F/TAF, and estrogen containing contraceptives showed no clinically relevant changes in PK parameters of either ARV agent or estradiol, thereby supporting the use of F/TDF and F/TAF with estrogen containing medications. No meaningful differences in intracellular TFV diphosphate or FTC-triphosphate were observed in transgender women (TGW) taking high-dose hormone therapy concomitantly with F/TDF and F/TAF in the DISCOVER trial, suggesting that F/TDF and F/TAF are safe and effective options for PrEP in TGW on GAHT. A study with daily observed therapy of F/TDF in both TGW and transgender men (TGM) confirmed that there was no impact of GAHT on TFV-diphosphate in dried blood spots (DBS), nor was there any impact of F/TDF on estradiol or testosterone levels in either TGW or TGM {Grant 2020}. The metabolic profiles of F/TDF and F/TAF also make clinically significant interactions with testosterone or nonhormonal gender-affirming therapy unlikely (Section 1.2.7.2). In summary, the available data suggest that estrogen-containing contraceptives, estrogen-containing GAHT, testosterone, and nonhormonal gender-affirming therapy can be used concomitantly with F/TDF and F/TAF.	Section 1.2.7.1

Country-specific Requirements	Affected Sections
Included rationale for dose selection F/TAF FDC (200 mg FTC/25 mg TAF) stating it will be dispensed to participants in the PK Tail Phase, as applicable, with instructions to administer 1 tablet orally by mouth once daily for PrEP. This dose was evaluated in the DISCOVER study and approved for PrEP in men who have sex with men (MSM) and TGW in the US.	Section 1.4
Risk/Benefit assessment data were updated to state that F/TAF has been demonstrated to have high efficacy and a favorable safety profile for PrEP in MSM and TGW.	Section 1.6
Included that participants in the US can receive either F/TDF or F/TAF in the PK tail phase for up to 78 weeks. Participants may switch between F/TDF and F/TAF during the PK Tail Phase if determined to be necessary by the investigator. Furthermore, participants who began receiving open-label (OL) F/TDF or F/TAF due to unavailability of SC LEN/placebo may rejoin the Randomized Blinded Phase of the study if approved by the medical monitor. In these cases, as soon as SC LEN/placebo is available, the participant should be contacted and notified to return to the site and complete the injection visit that was missed due to SC LEN/placebo unavailability. For instance, if a participant could not receive SC LEN/placebo at Week 26 and began OL F/TDF or F/TAF, the participant would return to the site as soon as SC LEN/placebo administration is feasible and resume the study at the Week 26/Injection 2 visit.	Figure 11, Sections 3.3, 3.3.4, 3.5, 6.5, Appendix 3
Included information pertaining to F/TAF formulation, packaging and labeling, storage and handling, and dosage and administration as below. F/TAF 200/25 mg tablets are blue, rectangular-shaped, film-coated tablets, debossed with “GSI” on one side of the tablets and “225” on the other side of the tablet. Each tablet core contains 200 mg of FTC and 25 mg of TAF. In addition to the active ingredients, the F/TAF tablets contain the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2/indigo carmine aluminum lake. F/TAF tablets are packaged in a white high-density polyethylene bottle. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum faced liner. Study drugs to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration, International Council for Harmonisation (ICH), and/or other local regulations. F/TAF tablets must be stored at a controlled room temperature below 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. F/TAF (200/25 mg) tablets will be provided by Gilead. The decision to administer F/TAF during the PK Tail Phase is at the discretion of the investigator. Study drug will be dispensed to participants on PK Tail Day 1. Participants will be instructed to take their first dose of study drug following completion of the study procedures at the PK Tail Day 1 visit. If study drug was not taken in the clinic following the completion of PK Tail Day 1 study procedures, initiation of the study drug must take place within 24 hours after the PK Tail Day 1 visit and after the investigator has confirmed eligibility with the participant. Participants will continue to take their daily dose of F/TAF each day.	Sections 5.2.1.3, 5.2.2.3, 5.2.3.3, 5.3.3
Prior and concomitant medications were updated to clarify that medications and use of herbal/natural supplements listed in Table 22 that are excluded or should be used with caution while participants are taking study drug on the study due to potential DDIs with F/TDF also apply F/TAF.	Section 5.4, Table 22

Country-specific Requirements	Affected Sections
Clarified that if in the PK Tail Phase the participant has been nonadherent to F/TDF or F/TAF and has had a high risk exposure event, the investigator may restart the participant on F/TDF or F/TAF and add a third agent to comprise postexposure prophylaxis treatment.	Section 6.13.1
Included clarification that oral PrEP can include F/TDF or F/TAF.	Section 6.15
Text was updated to include F/TAF information with respect to the effects of study drug on pregnancy and hormonal contraception to state that data from clinical PK interaction studies of F/TAF have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Based on in vitro and in vivo drug-drug interaction liability assessment, a clinically significant drug-drug interaction with LEN and hormonal contraceptives is not expected; an oral contraception drug-drug interaction study was not done. That nonclinical toxicity studies of F/TAF have demonstrated no adverse effect on fertility or embryo-fetal development. F/TAF for PrEP has not been studied in pregnant women; however, a randomized controlled study of F/TAF plus DTG for HIV treatment in pregnant women identified no safety concerns. Safety of lactation while taking F/TAF has not been studied; however, a PK study reported that breast milk TAF levels were below the limit of quantification in all women studied. The long-term safety of infants exposed to F/TAF in utero is not yet known.	Appendix 6

Appendix 8. Amendment History

A high-level summary of amendment history is provided in tabular form in the subsection below. Minor changes such as the correction of typographic errors, grammar, or formatting are not detailed.

Separate summary of change documents for earlier amendments are available upon request.

A separate tracked change (red-lined) document comparing the previous version of the protocol to this amendment will be made available upon the publication of this protocol.

1) Amendment 4 (21 October 2024)

Rationale for Key Changes Included in Amendment 4	Affected Sections
Clarified that duration of Randomized Blinded Phase (RBP) will be approximately 52 weeks. This revision acknowledges that RBP would be shorter than 2 weeks if RBP is stopped early by the study's independent Data Monitoring Committee (DMC).	Synopsis, Sections 3.3.2 and 3.5
Revised LEN OLE Phase language to extend SC LEN treatment every 26 weeks until LEN becomes available in their location or the sponsor elects to discontinue the study, whichever occurs first. This revision was made following the finding of superior efficacy of LEN over emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®; TVD) at the study's primary analysis. This extension of the OLE will allow study participants to continue receiving the superior intervention (LEN) until it becomes available in their country. While unlikely to occur, the sponsor retains the right to stop the study if circumstances require.	Synopsis, Figure 11, Sections 3.3.3, and 6.4 Appendix 3
Dosing time point for first dose of SC LEN updated.	Synopsis, Figure 11, Section 3.3, Appendix 3
The study schema and footnotes were updated to align with the changes in the LEN OLE Phase and PK Tail Phase.	Figure 11
Updated language related to use of LEN during pregnancy.	Section 1.2.54
Revised PK Tail Phase language to clarify that participants who prematurely discontinue study drug in the RBP will transition to the PK Tail Phase and that participants who complete the LEN OLE Phase or discontinue from the study will be transitioned to local HIV prevention services.	Synopsis, Figure 11, Sections 3.3.4 and 3.3.5, Appendix 3
Clarified that participants eligible for the PK Tail Phase will receive oral F/TDF once daily for up to 78 weeks.	Section 3.3.4
Updated language pertaining to participant randomized to F/TDF in the RBP and switched to LEN.	Section 3.3.3, Figure 11
Removed drug-drug interaction (DDI) potential between F/TDF and anticonvulsants as well as antimycobacterials from list of Prohibited Medications. Added that "concomitant use of dexamethasone may decrease LEN exposures, particularly with long-term use."	Table 22

Rationale for Key Changes Included in Amendment 4	Affected Sections
The DDI language regarding F/TDF was erroneous in the prior version and corrected here. The language regarding dexamethasone reflects the currently available data on this DDI, as described in the Investigator's Brochure.	
Revised frequency language for sexually-transmitted infection (STI) assessments and questionnaires.	Synopsis, Sections , 6.4 and 6.5, Appendix 3
Reduced frequency of assessments for chemistry and hematology profile, metabolic assessments, estimated glomerular filtration rate (eGFR), and hepatitis B and hepatitis C virus testing for the LEN OLE Phase and PK Tail Phase. A reduced frequency is appropriate since no safety signals with LEN were identified in the RBP and the updated schedule of assessments will reduce burden on participants.	Synopsis, Sections 6.4 and 6.5, Appendix 3
Removed urine protein and urine chemistry for all LEN OLE Phase visits. Additional urine assessments are not needed in the LEN OLE Phase since participants are not receiving tenofovir-containing PrEP. Removed urine storage sample for all LEN OLE Phase visits and PK Tail Phase visits.	Synopsis, Sections 6.4, 6.5, 6.7.1, and 6.9.1, Appendix 3
Clarified that waist circumference will only be collected at RBP. Adequate waist circumference data were collected in the RBP, making additional data collection unnecessary in the LEN OLE Phase and PK Tail Phase.	Synopsis, Sections 6.4, 6.5, 6.7.1 and 6.7.2, Appendix 3
Added text for creatinine phosphokinase collected only at RBP. No safety signals were detected in the Randomized Blinded Phase for creatine phosphokinase and reduced specimen collection is appropriate for OLE in order to reduce burden on participants.	Section 6.9.2
Updated eGFR assessment to be conducted every 2 weeks to match blood chemistry for the LEN OLE Phase and PK Tail Phase. Monitoring of eGFR every 13 weeks is unnecessary in the LEN OLE Phase as participants are not receiving tenofovir-containing PrEP.	Synopsis, Sections 6.4 and 6.5, Appendix 3
Updated text pertaining to HIV-1 infection questionnaire eCRF.	Section 6.13
Updated participant-reported questionnaires for the LEN OLE Phase (Experienced Preference for PrEP Medication, Administration and Dosing Questionnaire for PrEP Medication, Numeric Pain Rating Scale, Integrated Sexual Risk and Behaviors and Alcohol and Substance Use, Adherence to Oral Study Product Questionnaire) to be stopped at 52 weeks and eliminated the administration of the Experienced Preference for PrEP Medication questionnaire from the PK Tail Phase. Adequate data on these topics will have been collected by Week 52 of the LEN OLE Phase, making additional collection unnecessary. This will reduce the burden on sites and participants in the later stages of the LEN OLE Phase. Footnote k was added to the procedures for the LEN OLE Phase Table to provide additional guidance to sites as to when the Administration and Dosing Questionnaire for PrEP Medication should be administered.	Synopsis, Sections 6.4, 6.5 and 6.16, Appendix 3
Added language regarding adverse events/serious adverse events (AEs/SAEs) reporting for neonates/infants for at the time of delivery, following delivery, and following lactation exposure. This change was made to provide clearer reporting guidance to sites and ensure timely and accurate reporting of any adverse events in neonates and infants.	Sections 7.4.2

Rationale for Key Changes Included in Amendment 4	Affected Sections
Revised LEN OLE Phase adherence counseling language to clarify that since all participants will receive LEN injections in the OLE phase, therefore daily adherence to an oral study drug is not required.	Synopsis, Section 6.4
Removed text stating that the End of LEN OLE Phase visit coincided with PK Tail Day 1 as the LEN OLE Phase was extended until LEN becomes available or the sponsor elects to discontinue the study and eligibility requirements for the PK Tail Phase were updated.	Section 6.5
Guidance for administering LEN injections when > 28 weeks have elapsed since the last injection was updated to remove the requirement that medical monitor approval is required. This was changed to allow investigators to use their clinical discretion and minimize delays in restarting participants on LEN. This is considered appropriate considering the efficacy data and experience with LEN injections obtained during the RBP.	Section 6.8.2
Language on reporting vertical HIV transmission as serious adverse events was added to provide clearer guidance to sites and ensure that these events are properly reported, if they were to occur.	Section 7.1.2.1
Added text describing “reasonable possibility” of a causal relationship between study drugs and adverse events. This update provides more guidance to investigators on the reporting of adverse events and causality to the sponsor. The added text aligns with the International Conference for Harmonisation (ICH) guidelines on Clinical Safety Data Management E2A.	Section 7.2.1
Updated management of injection site reactions (ISRs). Clarified that investigators will contact the study medical monitor to discuss the evaluation and management of long-lasting or severe (Grade 3 or higher) ISRs if they are determined to be of clinical concern. This change has been made to the protocol to allow the investigators to use their clinical judgement regarding the discussion of ISRs with the medical monitor and to decrease burden on sites so that they do not need to report ISRs that are not of clinical concern.	Section 7.7.5
For primary analysis, updated details of the primary success criteria. Updated the estimation methods for the incidence rate ratio of the LEN study drug group to the background and the incidence rate ratio difference of LEN from F/TDF to account for the possibility that the number of HIV-1 infections in the LEN group is zero. Updated notation definitions of Figure 13 to provide more clarity and remove notations that are not relevant. The updates to the success criteria were required by the United States Food and Drug Administration (US FDA).	Synopsis, Section 8.5.1, Figure 13 (footnotes)
Deleted text related to incidence and weight management.	Section 8.6.1
Updated participant selection language to clarify that the collection of race, ethnicity, gender, and age data allows for the analysis and reporting of safety and efficacy data by demographic subgroups as required by certain health authorities, which is essential for the analysis of the study data.	Section 4.1
Revised the SAE reporting language per latest template to clarify recording and reporting requirements for SAEs. Gilead protocol template language was updated to clarify reporting requirements generally and to note that there is now a Follow-up SAE report form (in addition to the Initial SAE report form).	Section 7.4.1.1

Rationale for Key Changes Included in Amendment 4	Affected Sections
Clarified that the HIV-1 incidence rate of the LEN study drug group is at most 0.8/100 PY higher than the F/TDF study drug group. This change was made to correct a typographical error.	Synopsis, Section 8.5.2
For secondary analysis, updated the estimation methods for the rate ratios of HIV-1 incidence between LEN and F/TDF and between F/TAF and F/TDF and the associated CI if the number of infections is zero. This provides more details on the analysis methods to be used, in alignment with the Statistical Analysis Plan.	Section 8.5.2
Clarified that duration of exposure will be expressed as the number of weeks between the first and last dose of the study drug exposure, inclusive. Given the long acting nature of LEN, any exposure time after SC LEN dosing is considered part of the exposure time.	Section 8.6.1
Removed language related to HIV-1 incidence rate calculation based on weights adjusted for case-cohort sampling to align with the current Statistical Analysis Plan.	Section 8.6.1
Updated DMC criteria for rejection of hypothesis H_{02} and H_{04}. The interim stopping criteria was changed after discussions with the FDA, which requires additionally LEN superiority versus F/TDF.	Section 8.7
Updated name of Study Director.	Appendix 1
Blood sample collection for DBS was removed at the 30-day follow-up visit in the LEN OLE Phase, to correct an error in the prior protocol version. DBS samples are used to measure adherence to F/TDF. Since participants in the LEN OLE Phase are not on F/TDF, collection of blood sample for DBS is unnecessary.	Appendix 3
Urinalyses was removed from the 30-Day Post-HIV Infection Follow-up visit of the LEN OLE Phase as it was listed for that visit in error.	Appendix 3
Updated footnotes for LEN OLE and PK Tail study procedures tables, as applicable. These corrections were made to provide additional clarifications and to align with changes made to the LEN OLE Phase and PK Tail Phase.	Appendix 3
The column “LEN OLE to PK Tail Day 1” was removed from the procedures for PK Tail Phase table to reflect changes to the PK Tail Phase described in Section 3.5.4. This was removed because participants are now able to stay in LEN OLE Phase until LEN becomes available or the sponsor elects to discontinue the study, whichever occurs first.	Appendix 3
Minor changes to correct typographic errors, language, and to provide clarifications.	Throughout, as needed

2) Amendment 3 (25 October 2023)

Rationale for Key Changes Included in Amendment 3	Affected Sections
Country-specific requirements for the United States were added to the protocol.	Synopsis; Sections 1.2.2, 1.2.4.1, 1.2.5.2, 1.2.6.2, 1.2.7.1, 1.4, 1.6, 3.3, 3.3.4, 3.5, 5.2.1.3, 5.2.2.3, 5.2.3.3, 5.3.3, 5.4, 6.2.2, 6.3.1, 6.3.2, 6.4, 6.5, 6.7.1, 6.13.1, 6.15, 6.16, Figure 11; Table 22; Appendices 3, 6, and 7
Country-specific requirements for Mexico were added to the protocol.	Study Procedures Table
Updated the lenacapavir (LEN) clinical history with the latest information from ongoing studies.	Sections 1.2.3.4.2, 1.2.3.4.3, 1.2.3.4.4, 1.2.3.4.6, and 1.2.3.4.7
Updated the rationale for Oral Weekly Bridging of LEN for missed subcutaneous (SC) injection with the preliminary Oral Bridging PK data available from Phase 2/3 Studies GS-US-200-4625 and GS-US-200-4334.	Section 1.5
Postinjection observation text was revised to clarify that observation for approximately 30 minutes pertains to all study drug injection visits.	Synopsis, Sections 3.3.2, 3.3.3, 6.3.1, 6.3.2, and 6.4
CCI	
Text was revised to clarify that the study will only proceed to the LEN Open-Label Extension (OLE) Phase if LEN demonstrates acceptable safety and efficacy in the Randomized Blinded Phase.	Synopsis, Section 3.3.3
The Incidence Phase exclusion criterion pertaining to pre-exposure prophylaxis (PrEP) use in the past 12 weeks was revised to include HIV postexposure prophylaxis (PEP) because PEP use in the period prior to randomization, like PrEP use, may interfere with accurate HIV incidence rate estimation.	Synopsis, Section 4.2.2
Updated the nomenclature of the Sexual Risk and Behavior Questionnaire to “Integrated sexual behaviors and alcohol and substance use.”	Synopsis, Sections 6.2.2, 6.3.1, 6.3.2, 6.4, 6.5, 6.7.1, and 6.16
Clarified that only participants in the open label extension phase will perform ‘Experienced Preference for PrEP Medication’ questionnaire.	Synopsis, Sections 3.2, 6.5, 8.1.4, and Appendix 3 (Study Procedure Table [Procedures for PK Tail Phase])
Tablet storage conditions were revised for clarity to indicate that tablets must be stored at a controlled room temperature below 25 °C.	Section 5.2.3.2
Text pertaining to PEP, HIV vaccine, and HIV broadly neutralizing antibody use was deleted due to redundancy; this information is provided in the protocol eligibility criteria.	Section 5.4

Rationale for Key Changes Included in Amendment 3	Affected Sections
Text pertaining to drug-drug interactions (DDI) was updated for consistency with the IB, based on the available DDI data, and our current understanding of LEN disposition. Specifically, removed rosuvastatin 10 mg and pravastatin 40 mg from the "Use Discouraged and To Be Used with Caution" list. Clarified that there is no clinically relevant interactions between LEN and lopinavir (LPV) with ritonavir (RTV) or cobicistat and darunavir (DRV) with RTV, also clarified that the use of these drug(s) is acceptable for PEP.	Section 5.4, Tables 22 and 23
A provision allowing noninjection visits to be performed at an off-site location in exceptional circumstances was added. This provision will improve the ability to perform rigorous participant follow-up.	Section 6
Protocol language was revised for clarity to explicitly state that PrEP use between the Incidence Phase and Randomization is allowable. The use of PrEP after Incidence Phase HIV testing has been completed has no impact on HIV incidence rate determination, and is an important allowance to minimize HIV acquisition risk during the screening period.	Section 6.2.1
Recency assay text was updated to reflect that the assay will be run as indicated based on HIV testing results (ie when HIV testing indicates HIV infection).	Synopsis, Section 6.2.1, 6.3.1, and Appendix 3 (Study Procedure Table [Procedures for Incidence Phase and Randomized Blinded Phase; Footnote 'j'])
Updated the text to clarify that the SC LEN/placebo administration at Week 26/Injection 2, Week 52, and every 26 weeks (± 7 days) are always administered 26 weeks (± 7 days) from the prior SC injection.	Sections 6.3.2 and 6.4
Text pertaining to urine storage sample visits was updated to include Oral Bridging visit in addition to End of Randomized Blinded Phase visit and LEN OLE Day 1 visit to align with the study procedures table.	Sections 6.4 and 6.5
Text was added to clarify that glucose will be collected in a fasting state only on visits when metabolic assessments are performed.	Section 6.9.2
The name of the rapid HIV test was corrected to reflect that it is an HIV-1/2 test. Reflexive RNA quantitative nucleic acid amplification test (NAAT) was added for positive rapid HIV-1/2 Ab/Ag tests and central laboratory HIV-1/2 Ab/Ag tests occurring after Day 1; this provision was added to accelerate the interpretation of discordant HIV tests results (eg, suspected false positive rapid HIV-1/2 tests).	Section 6.13, Appendix 5; Appendix 3 - Procedures for Incidence Phase and Randomized Blinded Phase (Footnote 't'), Procedures for LEN OLE Phase (Footnote 'r'), Procedure for PK Tail Phase (Footnote 'r')
Text describing additional HIV testing and ART initiation was reorganized for clarity. The revised text allows the investigator to perform additional local testing if the participant has a positive local rapid HIV test; this provision may allow ART to be initiated more quickly in the case of HIV acquisition, which is in the interest of participant wellbeing	Section 6.13
The text pertaining to the performing of recency assays was consolidated into separate bullets and revised to clarify that recency assays will be performed based on laboratory testing indicative of HIV infection.	Section 6.13
Post-Day-1 HIV diagnosis procedures were revised to clarify that participants who have a positive rapid HIV test should not receive injection study drug.	Section 6.13

Rationale for Key Changes Included in Amendment 3	Affected Sections
A provision was added to indicate that participants with a positive rapid HIV test after Day 1 may receive injection study drug if central HIV testing, including an HIV-1 RNA quantitative NAAT, is negative, ie, in the case of a false positive local rapid HIV test.	Section 6.13
Recency assay language was removed from the chart and HIV diagnoses at screening since it is not relevant to the determination of study eligibility.	Figure 12
Clarification added to HIV testing strategy and injection restrictions.	Section 6.13
Additional guidance was added to the adverse event reporting procedures to clarify the interpretation of Division of AIDS adverse event grading scale entries pertaining to injection site reactions.	Sections 7.2.2 and 7.7.1
Updated the language pertaining to injection site reactions (ISRs) of Grade 3 or higher or persisting for more than 26 weeks to clarify that the investigator must contact and discuss the appropriate next steps with the medical monitor, that ISRs will be followed until resolution or study completion, and that documentation of any ISR evaluation, including photographic documentation, may be shared with the sponsor and study team.	Section 7.7.5
Updated to clarify the language pertaining to the primary and secondary endpoints; the endpoints were not changed; however the language was revised for clarity to distinguish between endpoints (observed at the individual participant level) and how each will be estimated and reported at the study population level.	Sections 3, 8.1.2.1, 8.1.2.2, 8.1.3
The Interim Analyses of Efficacy Data section was edited for clarity to indicate that the interim efficacy analysis will serve as the study's primary analysis in the event that the Randomized Blinded Phase is stopped early due to an efficacy outcome.	Section 8.2.1.2
Updated to clarify the criteria for All Screened Set.	Section 8.3.1.1
Updated the language to clarify that LEN plasma concentrations will be summarized by timepoint for SC and oral LEN. Additionally, population PK analysis of LEN is planned.	Section 8.8
Text was updated to align with the Gilead clinical trial agreement and publication policies.	Section 9.2.2
Updated the number of sites.	Synopsis
The relative standard error was corrected to 6.5 due to a typographical error.	Synopsis, Section 8.9
Timing of visits for each study phase clarified	Appendix 3 (Study Procedures Tables)
Clarified timing of routine asymptomatic sexually transmitted infection testing is only every 26 weeks for Oral Bridging Visit.	Appendix 3 (Study Procedure Tables [Procedures for Incidence Phase and Randomized Blinded Phase])
Minor changes to correct typographic errors, language, and to provide clarifications.	Throughout, as needed

Prot GS-US-528-9023 amd-4

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	PPD eSigned	22-Oct-2024 18:48:03