Project Brief: PURPOSE 2

Full Title of Study/Programme	A phase 3, double-blinded, multicentre, randomised study to evaluate the safety and efficacy of twice yearly long-acting subcutaneous Lenacapavir, and daily oral Emtricitabine/Tenofovir Alafenamide for pre-exposure prophylaxis in cisgender men, transgender women, transgender women, transgender men and gender non-binary at risk of HIV infection.
Technical Focus Area/Key Words	Long -acting HIV pre-exposure prophylaxis
Rationale	Both daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®; TVD) and emtricitabine/tenofovir alafenamide (F/TAF; Descovy®; DVY) 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 . 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 . 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. 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. 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.
Primary Objective	To evaluate the efficacy of LEN in preventing the risk of HIV-infection relative to the background HIV-1 incidence rate. Participants are CGM, TGW, TGM, and GNB.
Incidence Phase Objectives	The primary objective for the Incidence Phase of this study is to estimate the HIV-1 background incidence rate.
Randomised Blinded Phase Primary Objectives	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
Randomised Blinded Phase Secondary Objectives	• 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.
Exploratory Objectives for the Randomised Blinded phase	• To assess the adherence rate to LEN as assessed by on-time LEN injection.

	• To assess LEN plasma levels. • To assess the adherence rate to F/TDF using intracellular TFV-DP levels in DBS. — To evaluate the acceptability of a once every 6 months (Q6M) LEN injection for HIV-1 PrEP in participants at risk of HIV-1. — To explore concentrations of LEN in participants on exogenous hormones. — To explore concentrations of estradiol and testosterone in LEN participants on exogenous hormones.
Incidence Phase Endpoint	• The primary endpoint for the Incidence Phase of this study is the background HIV-1 incidence reported per 100 person-years (PY) computed based on the recency assay algorithm.
Randomised Blinded Phase Primary Endpoints/Outcomes	• HIV-1 incidence based on the Full Analysis Set (FAS) (HIV-1 infections per 100 PY of follow-up
Randomised Blinded Phase Secondary Endpoints/Outcomes	• HIV-1 incidence among participants while adherent to study drug (as defined by medium and high TFV-DP levels DBS at the time of HIV-1 diagnosis for the F/TDF study drug group and by LEN administration in the past 26 weeks for the LEN study drug group), reported as per 100 PY of exposure to study drug • Incidence 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
Randomised Blinded Phase Exploratory Endpoints/Outcomes	• The adherence to LEN as assessed by on-time LEN injection • The assessment of LEN plasma levels • The adherence to F/TDF assessed using the intracellular TFV-DP concentration in DBS • The assessment of LEN plasma levels in participants on exogenous hormones • The assessment of estradiol and/or testosterone levels in LEN participants on GAHT • Questionnaire outcomes pertaining to the following: o Adherence o Integrated sexual behaviors and alcohol and substance use o Numeric pain rating scale – injection pain o Experienced preference for PrEP medication o Administration and dosing for PrEP medication o PrEP impacts and administration preference
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 external 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.
Study arms	Not applicable

Study population	HIV-negative 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, over the age of 16.
Study sample size	75
Follow up/duration	~ 5.5 years
Study/Programme sites	Hillbrow, Johannesburg
Study/Programme duration	~6 years
Intervention	SC Lenacapavir, F/TAF , F/TDF
Operations	Not applicable
Investigators	Wits RHI Prof. Thesla Palanee-Phillips, Co-Principal Investigator Dr. Nkosiphile Ndlovu, Co-Investigator Dr. L Kew, Co-Investigator Dr. L Kgoa, Co-Investigator Dr. H Ismail, Co-Investigator
Other Partners & Collaborators	
Sponsors/Donors	Gilead Sciences, Inc IND Number: 153858
Linked Sub Studies and post grad projects	Not applicable
Publications/key presentations to date	Not applicable
Progress Update as at 20 February 23	Accrual in progress: 87/75 participants enrolled
Frequency of donor narrative report	Every six months
Overall Study/Project Contact	Prof. Thesla Palanee-Phillips
Briefing owner and date	La-Donna Kapa, 11 April 2024