EU Risk Management Plan for Yeytuo® (Lenacapavir)

EU Risk Management Plan for Yeytuo® (Lenacapavir) RMP

version to be assessed as part of this application:

Version Number	Data Lock Point for This RMP	Date of Final Sign-off
1.0	21 August 2024	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:	Not applicable

This RMP includes information on the use of lenacapavir for HIV-1 prevention. It does not include information on the use of lenacapavir for the treatment of multidrug resistant HIV-1 infection, which is covered in the separate Sunlenca RMP.

Summary of significant changes in this RMP:

Not applicable

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Not applicable

QPPV name:	Rainer Heissing
QPPV signature:	Refer to ELECTRONIC SIGNATURES

TABLE OF CONTENTS

TABLE OF CONTENTS 3
LIST OF IN-TEXT TABLES 4
LIST OF IN-TEXT FIGURES 4
GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS 6
PART I : PRODUCT OVERVIEW 8
PART II : SAFETY SPECIFICATION 10
PART II: MODULE SI —EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) 10
SI.1. HIV-1 Pre-Exposure Prophylaxis 10
SI.1.1. Incidence of HIV Infection 10
SI.1.2. Populations most affected by HIV 12
SI.1.3. Total Number of People using PrEP 13
SI.1.4. Main Existing PrEP Options 13
SI.1.5. Important Comorbidities 14
PART II: MODULE SII —NONCLINICAL PART OF THE SAFETY SPECIFICATION 16
PART II: MODULE SIII —CLINICAL TRIAL EXPOSURE 20
SIII.1. Clinical Trial Exposure 20
PART II: MODULE SIV —POPULATIONS NOT STUDIED IN CLINICAL TRIALS 24
SIV.1. Exclusion Criteria in Pivotal Clinical Trials Within the Development Program 24
SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs 25
SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs 25
PART II: MODULE SV —POSTAUTHORIZATION EXPERIENCE 27
SV.1. Postauthorization Exposure 27
PART II: MODULE SVI —ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION 28
SVI.1. Potential for Misuse for Illegal Purposes 28
PART II: MODULE SVII —IDENTIFIED AND POTENTIAL RISKS 29
SVII.1. Identification of Safety Concerns in the Initial RMP Submission 29
SVII.1.1. Risk(s) Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 29
SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP 29
SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP 30
SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 30
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks 30
SVII.3.2. Presentation of the Missing Information 30
PART II: MODULE SVIII —SUMMARY OF THE SAFETY CONCERNS 31
PART III : PHARMACOVIGILANCE PLAN 32
III.1 Routine Pharmacovigilance Activities 32
III.2 Additional Pharmacovigilance Activities 32

III.3 Summary Table of Additional Pharmacovigilance Activities....32

PART IV : PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES....34

PART V : RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)....35

V.1 Routine Risk Minimization Measures....35
V.2 Additional Risk Minimization Measures....35
V.3 Summary Risk Minimization Measures....35

PART VI : SUMMARY OF THE RISK MANAGEMENT PLAN....37

I. Summary of risk management plan for Yeytuo....37
II. The Medicine and What Is It Used For....37
III. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks....37
III.A. List of Important Risks and Missing Information....38
III.B. Summary of Important Risks....38
III.C. Postauthorization Development Plan....39

PART VII : ANNEXES....40

REFERENCES....41

ELECTRONIC SIGNATURES....43

LIST OF IN-TEXT TABLES

Table Part I.1. Product Overview....8
Table SI.1. Most Frequent Comorbidities from the Medical Histories of Participants Enrolled in PURPOSE 1 and PURPOSE 2....14
Table SII.1. Table of Key Safety Findings From Nonclinical Studies....16
Table SIII.1. Duration of LEN Exposure in PURPOSE 1....20
Table SIII.2. Exposure to LEN by Age Group and Gender in PURPOSE 1....21
Table SIII.3. Exposure to LEN by Ethnic Origin in PURPOSE 1....21
Table SIII.4. Duration of LEN Exposure in PURPOSE 2....21
Table SIII.5. Exposure to LEN by Age Group and Gender in PURPOSE 2....22
Table SIII.6. Exposure to LEN by Ethnic Origin in PURPOSE 2....22
Table SIV.1. Important Exclusion Criteria in Pivotal Trials in the Development Program....24
Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions....25
Table SIV.3. Exposure of Special Populations Included or Not in Clinical Trial Development Programs....25
Table SVIII.1. Summary of Safety Concerns....31
Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities....32
Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities....32
Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern....35
Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern....35
Table Part VI.1. List of Important Risks and Missing Information....38
Table Part VI.2. Summary of Important Risk(s) and Missing Information....38
Table Part VI.3. Other Studies in Postauthorization Development Plan....39

LIST OF IN-TEXT FIGURES

Figure 1. Change in new HIV infections per year from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024} 10
Figure 2. Distribution of new HIV infections, by region, 2023 from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024} 11
Figure 3. Change in new HIV infections between 2010 and 2023, total population, by region from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}....12
Figure 4. Number of people who used oral PrEP at least once in 2023, by region, and 2025 target from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024} }....13

GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ATC	anatomical therapeutic chemical
APR	Antiretroviral Pregnancy Registry
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BSEP	bile salt export pump
BRCP	breast cancer resistance protein
CA	capsid protein
CI	confidence interval
C_{max}	maximum observed concentration of drug
CYP	cytochrome P450 enzyme
DDI	drug drug interaction
DLP	data lock point
DVY	Descovy
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EEA	European Economic Area
EU	European Union
EU-RMP	EU Risk Management Plan
GGT	Gamma-glutamyl transferase
GSI	Gilead Sciences International Ltd.
HIV	Human immunodeficiency virus
IC_{50}	concentration required to produce 50% inhibition
IV	intravenous
LEN	Lenacapavir
MATE	multidrug and toxin extrusion
MSM	men who have sex with men
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
P-gp	P-glycoprotein
PK	Pharmacokinetics
PL	package leaflet
PrEP	Pre-exposure prophylaxis
PSUR	periodic safety update report
RMP	risk management plan
SC	subcutaneous
SmPC	summary of product characteristics
TGW	transgender women
TVD	Truvada

UGT	UDP-glucuronosyltransferase
UNAIDs	Joint United Nations Programme on HIV and AIDS

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Lenacapavir
Pharmaco-therapeutic group(s) (ATC code):	Other antivirals (J05AX31)
Marketing authorisation applicant:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	2
Invented name(s) in the European Economic Area (EEA):	Yeytuo
Marketing authorization procedure:	Centralized
Brief description of the product:	Chemical class: Capsid Inhibitor
	Summary of mode of action: Lenacapavir is a multistage, selective inhibitor of human immunodeficiency virus type 1 (HIV-1) capsid function that directly binds to the interface between capsid protein (CA) subunits. Lenacapavir inhibits HIV-1 replication by interfering with multiple, essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral deoxyribonucleic acid (DNA) (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of CA subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).
	Important information about its composition: None
Hyperlink to the product information:	Yeytuo Summary of Product Characteristics (SmPC)
Indication(s) in the EEA:	Proposed: Indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents with increased HIV-1 acquisition risk weighing at least 35 kg.
Dosage in the EEA:	Proposed: ***Initiation***: On day 1, the required dose is 927 mg of Yeytuo by subcutaneous injection and 600 mg orally. On day 2, the required dose is 600 mg orally. ***Maintenance:*** The required dose is 927 mg of Yeytuo by subcutaneous injection every 6 months (26 weeks) from the date of the last injection (+/- 2 weeks).

Pharmaceutical form(s) and strengths:	Proposed: Injection: Each single-dose vial contains sufficient volume to allow withdrawal of 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (equivalent to 473.1 mg/1.5 mL of lenacapavir sodium). Sterile, preservative-free, clear, yellow to brown solution with no visible particles. Oral: Each tablet contains 300 mg of lenacapavir (equivalent to 306.8 mg lenacapavir sodium). Beige, capsule-shaped, film-coated tablets, debossed with 'GSI' on one side of the tablet and '62L' on the other side of the tablet.
Is/Will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

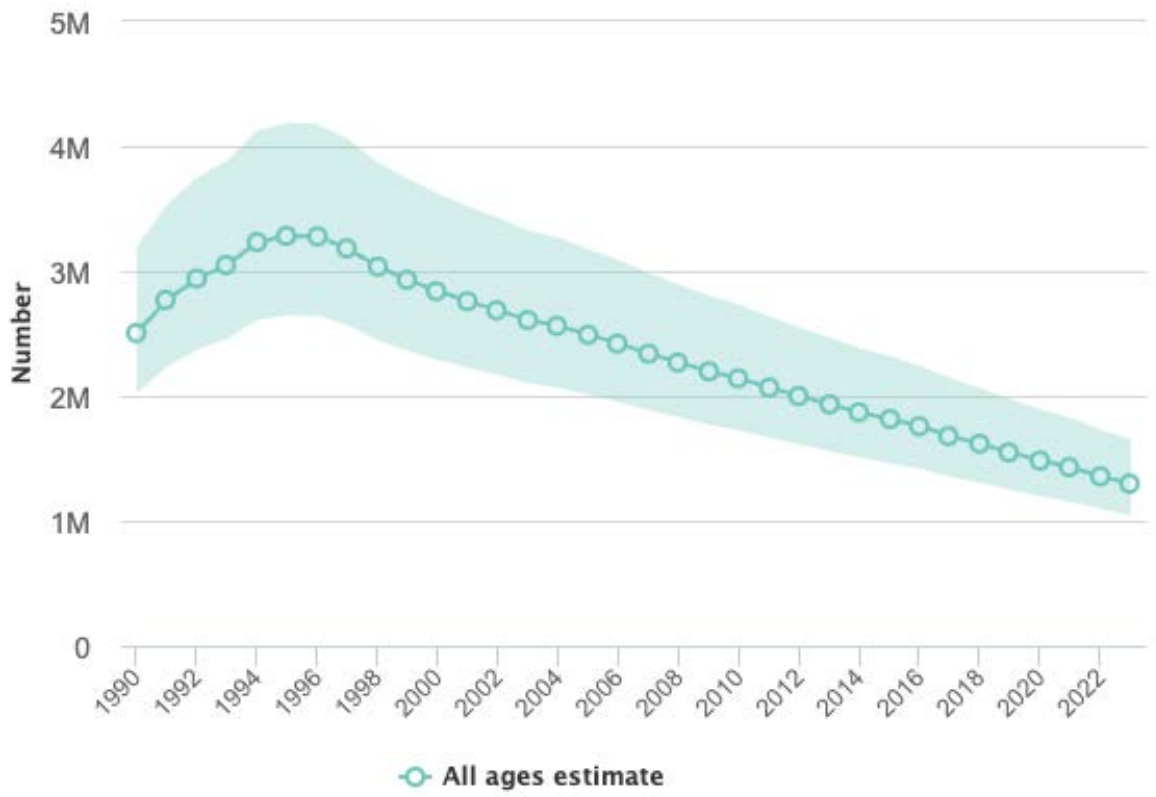
PART II: MODULE SI—EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1. HIV-1 Pre-Exposure Prophylaxis

SI.1.1. Incidence of HIV Infection

HIV-1 infection is a serious and life-threatening disease of major public health significance. While the number of worldwide new HIV infections continues to decrease over time, the Joint United Nations Programme on HIV/AIDS estimates that approximately 1.3 million (95% CI: 1.0-1.7 million) new HIV infections occurred in 2023 (Figure 1; {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}.

Figure 1. Change in new HIV infections per year from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}



Almost half of the people who acquired HIV in 2023 were living in eastern and southern Africa and western and central Africa (Figure 2), the regions that have together achieved the steepest decline (56%) in new infections since 2010 (Figure 3). Compared with 2010, the number of people acquiring HIV has risen in eastern Europe and central Asia, the Middle East and North Africa and Latin America (Figure 3).

Figure 2. Distribution of new HIV infections, by region, 2023 from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}

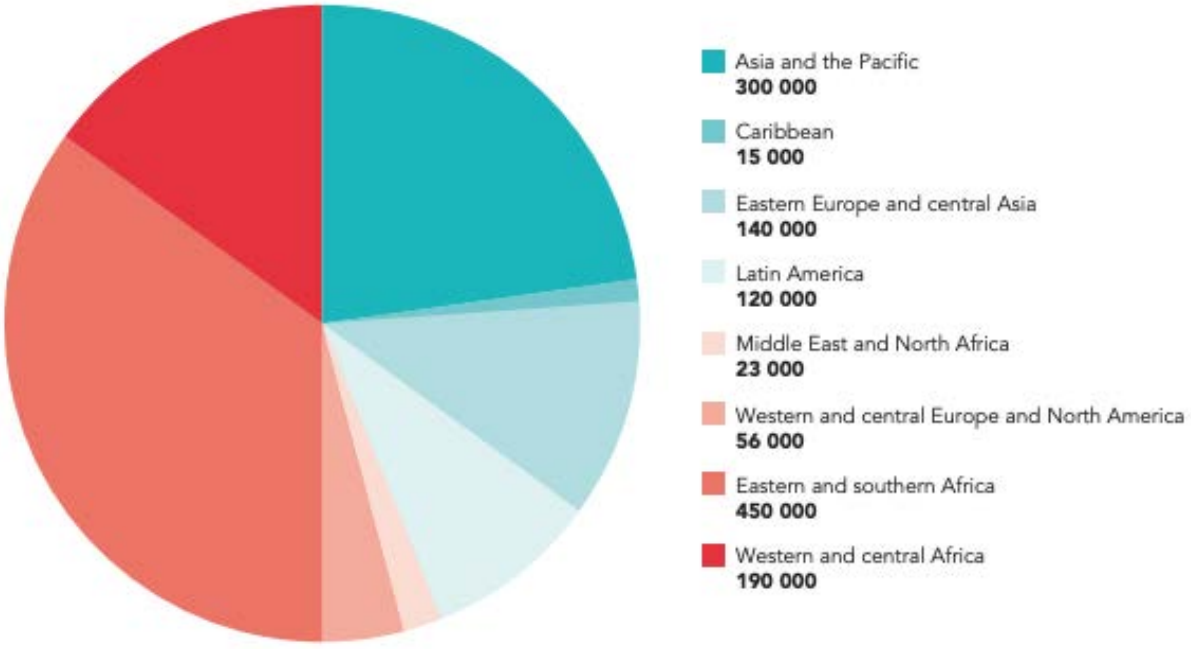
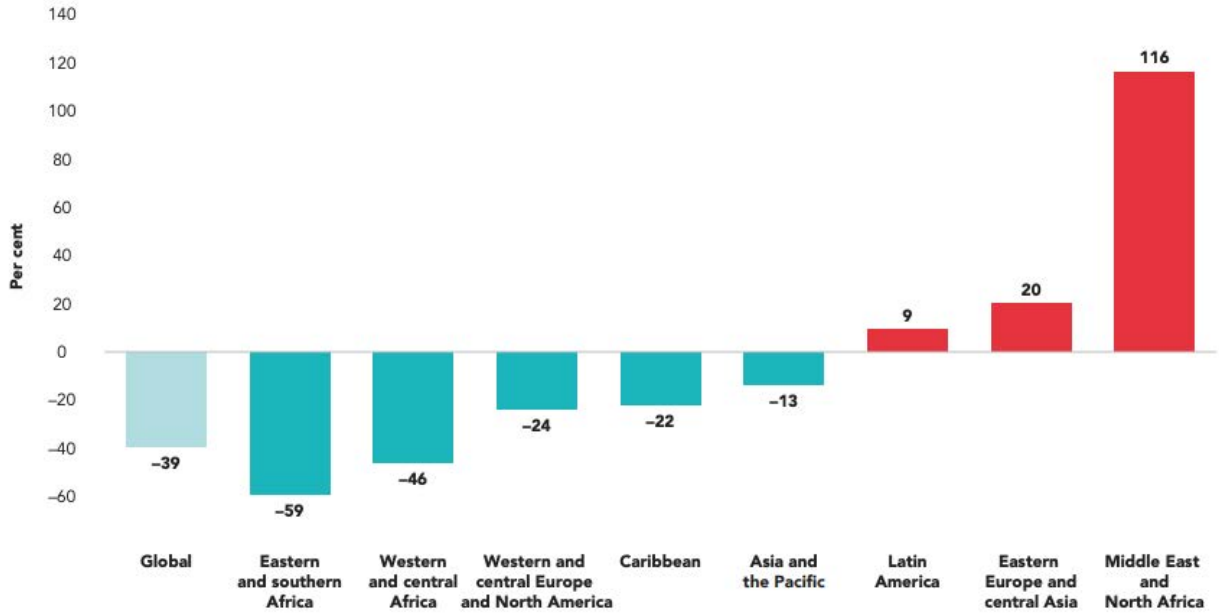


Figure 3. Change in new HIV infections between 2010 and 2023, total population, by region from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}



SI.1.2. Populations most affected by HIV

Median HIV prevalence among the adult population (ages 15–49) was 0.8% globally in 2023 {UNAIDS 2024}. However, because of marginalization, discrimination and in some cases criminalization, median prevalence was higher among certain groups of people:

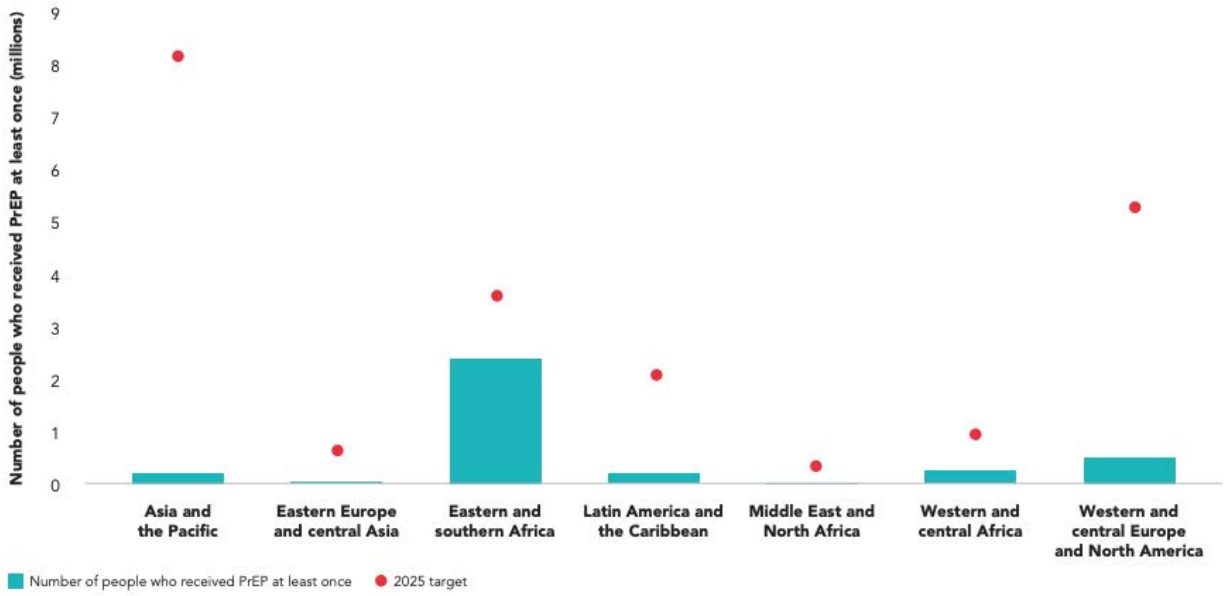
- 2.3% higher among young women and girls aged between 15 and 24 in eastern and southern Africa
  - — Globally, 44% of all new HIV infections were among women and girls (all ages) in 2023.
  - — In sub-Saharan Africa, women and girls (all ages) accounted for 62% of all new HIV infections. In all other geographical regions, over 73% of new HIV infections in 2023 occurred among men and boys.
  - — Every week, 4000 adolescent girls and young women aged 15–24 years became infected with HIV globally in 2023. 3100 of these infections occurred in sub-Saharan Africa.
- 7.7% higher among gay men and other men who have sex with men (MSM)
- 3% higher among sex workers

- 5% higher among people who inject drugs
- 9.2% higher among transgender people
- 1.3% higher among people in prisons

SI.1.3. Total Number of People using PrEP

The total number of people using oral PrEP rose from a little over 200,000 in 2017 to about 3.5 million in 2023, short of the Joint United Nations Programme on HIV/AIDS (UNAIDS) global 2025 target of 21.2 million people {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024}. The number of people who used PrEP at least once in 2023, by region, and 2025 target is presented in Figure 4.

Figure 4. Number of people who used oral PrEP at least once in 2023, by region, and 2025 target from {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2024} }



SI.1.4. Main Existing PrEP Options

Four PrEP options (Truvada®, Descovy®, Apretude® and DapiRing®) are currently available; however, they are not licensed and commercialized globally and do not meet the needs of all individuals who want or could benefit from PrEP. Despite having high efficacy when taken as prescribed {Centers for Disease Control and Prevention 2023} {Centers for Disease Control and Prevention (CDC) 2023} {Descovy 2022}, {Grulich 2018}, {International AIDS Society (IAS). 2023}, {Nwokolo 2017a}, {Nwokolo 2017b}, {Sullivan 2018}, {Truvada 2023} the uptake of, adherence to, and persistence on oral PrEP options remains a real challenge for some individuals due to concerns with tolerability (large pill size), safety, privacy, or stigma of using a drug taken by people with HIV. While 2-monthly injection with cabotegravir can address some of these

barriers, the increased frequency of clinic visits required for cabotegravir administration has resulted in implementation challenges and has negatively impacted uptake and persistence. The lower efficacy of the dapivirine vaginal ring compared with other PrEP options, as well as the requirement for vaginal insertion and monthly replacement have limited its regulatory approvals and uptake {Boerner 2022}, {Gollub 2022}.

SI.1.5. Important Comorbidities

Yeytuo was studied in two large pivotal studies, GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2), that included a broad and diverse population: adolescents; cisgender women, including pregnant, lactating, and postpartum women; cisgender men; and gender-diverse people, including transgender women and transgender men. The studies were conducted in regions and populations that are disproportionately affected by HIV incidence and include sites across 4 continents (Africa, Asia, North America, and South America). The most frequent medical histories among the 5,368 participants enrolled in PURPOSE 1 and 3,295 participants enrolled in PURPOSE 2 are presented in Table SI.1. In adolescents and cisgender women, including pregnant, lactating, and postpartum women, frequent comorbidities included STIs, headache, urinary tract infection, dysmenorrhoea, and caesarean section. In cisgender men and gender-diverse people, including transgender women, transgender men, and gender nonbinary people, frequent comorbidities included STIs, depression, anxiety, and hypertension.

Table SI.1. Most Frequent Comorbidities from the Medical Histories of Participants Enrolled in PURPOSE 1 and PURPOSE 2

PURPOSE 1 (n = 5,368)		PURPOSE 2 (n = 3,295)	
Medical History	**%**	**Medical History**	**%**
Genitourinary chlamydia infection	11.4	Syphilis	16.4
Chlamydial infection	11.1	Latent syphilis	9.7
Headache	5.6	Anal chlamydia infection	8.4
Urinary tract infection	4.9	Depression	8.1
Trichomoniasis	4.7	Anxiety	7.6
Dysmenorrhoea	4.4	Oropharyngeal gonococcal infection	7.5
Caesarean section	4.3	Hypertension	6.9
Syphilis	3.8	Drug hypersensitivity	5.9
Genitourinary tract gonococcal infection	3.5	Asthma	5.5
Upper respiratory tract infection	3.3	Rhinitis allergic	5.3
Gonorrhoea	2.6	Obesity	4.9
Anaemia	2.6	Anal gonococcal infection	4.3
Acne	2.2	Seasonal allergy	3.9
Vulvovaginal candidiasis	2.2	Gonorrhoea	3.9

PURPOSE 1 (n = 5,368)		PURPOSE 2 (n = 3,295)	
Medical History	**%**	**Medical History**	**%**
Allergic sinusitis	2.1	Insomnia	3.8
Gonococcal infection	2.1	Headache	3.4
Abnormal uterine bleeding	2.0	Chlamydial infection	3.4
Vaginal discharge	1.8	Attention deficit hyperactivity disorder	3.4
Gynaecological chlamydia infection	1.8	Myopia	3.3
Amenorrhoea	1.8	Substance use	3.2
Obesity	1.5	Proctitis chlamydial	3.0
Heavy menstrual bleeding	1.5	Gastrooesophageal reflux disease	2.8
Vulvovaginitis trichomonal	1.4	Proctitis gonococcal	2.6
Food allergy	1.4	Migraine	2.6
Latent syphilis	1.2	Pharyngeal chlamydia infection	2.3

PART II: MODULE SII—NONCLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1. Table of Key Safety Findings From Nonclinical Studies

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Toxicity	
Single and repeat dose toxicity: No systemic toxicity was observed in rats after SC or oral administration of LEN, or in dogs after oral administration of LEN. Reversible changes in liver function were observed in Beagle dogs after very large single intravenous (IV) doses and SC repeat doses, consistent with the inhibition of the Bile Salt Export Pump (BSEP) transporter: • In dogs, after a single IV dose of 10 or 30 mg/kg, LEN-related serum chemistry changes were observed 24 hours after dosing and included mildly to markedly increased serum alanine (ALT) and aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) activity, and total bilirubin with correlative microscopic findings of hepatocyte degeneration and hepatocyte necrosis (TX-200-2030). At the 14-day terminal sacrifice, clinical pathology changes had partially or fully reversed and there were no LEN-related microscopic findings. The no observed adverse effect level (NOAEL) was determined to be 3 mg/kg in this study. Based on the time course, the liver changes appear to be C_{max} related. The C_{max} achieved at the 3 mg/kg NOAEL (5.1 µg/mL) is 38-fold higher than the clinical C_{max} observed after the 6-month clinical oral loading and SC dosing regimen. • Two repeat toxicity studies in dogs were conducted via monthly SC injection of LEN for up to 9 months (10 doses). In the first study (TX-200-2017), LEN was well tolerated when administered as 10 monthly SC injections of 20 mg/kg/dose with or without NaOH or 40 mg/kg/dose without NaOH, and no systemic toxicity was observed at LEN exposures up to 8-fold higher than clinical exposure based on the $AUC_{Day1\text{-}week26}$. The NOAEL was determined to be 40 mg/kg in this study. • In the second study (TX-200-2047), animals were administered LEN at dosages of 0 (vehicle control), 130, or 411 mg/kg/dose. In the 411 mg/kg/dose group, clinical observations, clinical pathology and anatomic pathology data indicated hepatobiliary changes indicative of cholestasis and hepatobiliary injury. Less severe changes in clinical pathology test results, and fewer and less severe liver and gall bladder microscopic findings were observed in the 130 mg/kg/dose group, but included periductular fibrosis in one dog, considered adverse. Mean LEN exposures in the 411 mg/kg/dose group were ≥ 51-fold higher than the clinical exposure based on the $AUC_{Day1\text{-}week26}$.	The transient acute toxicity and the clinical, clinical pathology and histopathology observations in study TX-200-2047 are consistent with disruption in secretion of bilirubin into bile. Inhibition of the BSEP transporter induces hepatotoxicity by causing intracellular concentrations of bile acids to rise above a toxic threshold. Lenacapavir is a much more potent inhibitor of dog BSEP (dBSEP) transporter (IC_{50} = 0.124 µg/mL) than the human BSEP (hBSEP) transporter (IC_{50} = 1.15 µg/mL); the average dog plasma LEN concentration (C_{ave}) after 9 months of 130 mg/kg/dose or 3 months of 411 mg/kg is at least 39-fold higher than the dBSEP transporter IC_{50}, while the average clinical plasma LEN concentration is 27-fold lower than the hBSEP transporter IC_{50}. Given the significant exposure margins observed in the single dose IV and repeat dose SC studies, and the higher sensitivity of the dBSEP to LEN compared to the hBSEP, these findings do not suggest a significant risk of organ toxicity at or near the expected clinical exposure.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Genotoxicity: A standard battery of in vitro and in vivo studies was performed to assess the genotoxic potential of LEN. Lenacapavir was not genotoxic in the bacterial reverse mutation test (TX-200-2007), the in vitro chromosomal aberrations assay using cultured human peripheral blood lymphocytes (TX-200-2008) and the in vivo micronucleus assay in rats conducted as part of the repeat dose toxicity study (TX-200-2005).	There were no specific concerns raised by nonclinical genotoxicity studies.
Carcinogenicity *Six-month transgenic mouse carcinogenicity study:* A 6-month transgenic mouse carcinogenicity study was conducted to evaluate the carcinogenic potential of LEN when administered once every 13 weeks at SC injection to 001178-T (hemizygous) RasH2 mice for at least 26 weeks (TX-200-2068). Subcutaneous injection of LEN at levels of 0 (control), 30, 100, and 300 mg/kg/dose resulted in no carcinogenic effect by Day 183, and no effect of LEN on survival or the incidence of neoplasms was observed. *Two-year rat carcinogenicity study:* Male and female Wistar Han rats were administered saline control article, vehicle control article, or a 102, 309, or 927 mg/kg/dose of LEN via SC injection once every 13 weeks (TX-200-2046). Lenacapavir-related mortality (both sexes) and decreased survival (females only) were noted for animals administered the single 927 mg/kg/dose every 13 weeks, but a sufficient number of animals survived to the end of the dosing phase to adequately evaluate the carcinogenic potential of LEN. An increased incidence of SC injection site primary sarcomas was noted for both sexes administered the single 927 mg/kg/dose every 13 weeks and was considered secondary to the local, chronic (granulomatous) inflammatory reaction to LEN; these findings correlated with clinical observations of abnormal color, scab, sore, or ulceration of the dose site and macroscopic findings of raised area, thickened, and/or discolored at necropsy. No neoplasms were noted to be directly LEN-related; thus, no dose level resulted in a carcinogenic effect.	An increased incidence of injection site sarcoma in the rat carcinogenicity study was only observed at a very high multiple of the expected human systemic LEN exposure (approximately 44-fold). Rats are well known to produce a fibrotic response to SC injections of various substances that can progress to sarcomatous neoplasms {Bartholomew 2014, GRASSO 1966}. Injection site sarcomas have not been observed in the LEN clinical development program. The rat carcinogenicity study results are included in Section 5.3 of the SmPC with guidance that rats are prone to sarcoma formation from subcutaneous injections, but a clinical relevance cannot be excluded considering the long clinical depot duration.
Reproductive/developmental toxicity: No changes in reproductive organ weights and no macroscopic or microscopic findings were noted in rat and rabbit repeat-dose studies. In a SC rat fertility study (TX-200-2043), no adverse effects occurred in male or female fertility at 100 mg/kg, the highest dose administered. No LEN-related effects on mean body weights, body weight gains, and food consumption were noted, and no effects on male and female reproductive performance (mating, fertility, and pregnancy), male spermatogenesis (sperm numbers, sperm production rate, and motility), and male or female organ weights were noted. No LEN related macroscopic findings were noted. Intrauterine survival of the embryos was unaffected by LEN administration at all doses. Oral administration of LEN to pregnant rats during gestation day (GD) 6 through 17 at dose levels of 3, 10, and 30 mg/kg/day resulted in no LEN-related effects on maternal animals or embryo/fetal development (TX-200-2031, TX-200-2036). Intravenous administration of LEN to pregnant rabbits during GD 7 through 19 at dose levels of 5, 10 and 20 mg/kg/day also resulted in no LEN-related effects on maternal animals or embryo/fetal development (TX-200-2032, TX-200-2037). In a rat SC peri- and postnatal toxicity study (TX-200-2049), pregnant rats were administered a single dose of either 30 or 300 mg/kg LEN on GD 6. Parameters evaluated included pregnancy,	There were no specific concerns raised by nonclinical reproductive/developmental toxicity studies.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
parturition, and lactation of the maternal (F_0) animals and on the growth, viability, and development of the F_1 neonates. Reproductive performance of the F_1 generation was also assessed. No LEN-related systemic effects were noted at any dose level tested in the F_0 or F_1 generation.	
Safety Pharmacology	
In safety pharmacology studies, LEN did not show significant effects on the cardiovascular (dogs), respiratory (rats), or central nervous system (rats) at NOAEL exposures that were 20-, 1.4- and 1.4-fold higher, respectively, than the free LEN C_{max} after the 6-month clinical oral loading and subcutaneous dosing regimen.	There were no specific concerns raised by nonclinical safety pharmacology studies.
Local tolerance	
In single and repeat-dose nonclinical local tolerance studies, the macroscopic observation of thickening and the microscopic observations of mixed cell or granulomatous inflammation, necrosis, and mononuclear cell infiltrates were observed at the subcutaneous injection site of animals administered various SC formulations of LEN. These observations were expected reactions of SC depots.	There were no specific concerns raised by nonclinical local tolerance studies. Injection site reactions have been observed in clinical studies and are listed adverse drug reactions (ADRs) for LEN in the SmPC.
Other toxicity studies	
Antigenicity: In in vitro studies, LEN was positive with low reactivity in the Direct Peptide Reactivity Assay (TX-200-2071), negative in the ARE-Nrf2 Luciferase assay (TX-200-2072) and positive in the Human Cell Line Activation Test (TX-200-2073). In vivo, LEN was not a sensitizer in the mouse local lymph node assay (TX-200-2053). Immunotoxicity: Data from repeat-dose toxicity studies with LEN (hematology, lymphoid organ weights, microscopy of lymphoid tissues, bone marrow cellularity) did not suggest immunotoxic potential. Dependence: No specific studies on dependency of LEN were conducted. There was no evidence of development of dependence in nonclinical studies with LEN. Tissue distribution studies using radiolabeled LEN in both rat and dog indicated that very low concentrations of radioactivity at C_{max} were observed in the central nervous system. Impurities: Two repeat-dose toxicity studies were conducted in rats to determine if there were unexpected adverse effects from LEN-related process impurities. Male and female rats were administered a single SC dose of 100 mg/kg LEN solutions using a pure (at least 98.7%) LEN batch or batches with added impurities and observed for 4 weeks (TX-200-2042) or 13 weeks (TX-200-2050). Lenacapavir plasma exposure was confirmed for the duration of observation. No adverse LEN-related effects were observed and there were no differences in findings in animals treated with lots containing LEN related impurities to those observed in previous studies, or to a comparator lot.	There were no specific concerns raised by other nonclinical toxicology studies.

Key Safety Findings from Nonclinical Studies	Relevance to Human Usage
Pharmacokinetic Drug-Drug Interactions	
Nonclinical assessment of LEN as a victim of drug-drug interactions (DDIs) showed inhibitors or inducers of cytochrome P450 3A (CYP3A) and UDP Glucuronosyltransferase Family 1 Member A1 (UGT1A1) may affect the pharmacokinetics (PK) of LEN. Assessment of LEN as a perpetrator of drug interactions indicates low potential for reversible inhibition of CYP enzymes or UGT1A1 at the clinical systemic concentrations observed following oral or SC administration. Inhibition of intestinal efflux transporters (P-glycoprotein [P-gp] and breast cancer resistance protein [BCRP]) following oral dosing of LEN cannot be ruled out from in vitro data as the maximum concentration that could be tested in vitro was 1 μM wherein no inhibition of either transporter was observed. While LEN was a potent inhibitor of hepatic uptake transporters organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 in vitro, there was no effect of orally administered LEN on the PK of pitavastatin in humans. From potencies determined in vitro, LEN exhibits no potential for inhibition of renal transporters (organic anion transporter 1 (OAT1), OAT3, organic cation transporter 1 (OCT2), multidrug and toxin extrusion protein 2K (MATE2K) and weak inhibition of MATE1.	In a Phase 1 clinical DDI study (GS-US-200-4333), CYP3A/P-gp inhibitor, cobicistat, increased exposure of orally administered LEN, but the CYP3A selective inhibitor, voriconazole, had less effect. Coadministration of LEN and medicinal products that potently induce CYP3A, P-gp, and UGT1A1 may significantly decrease plasma concentrations of LEN, which may result in reduced effectiveness. Moderate inducers of CYP3A and P-gp may also decrease plasma concentrations of LEN. Lenacapavir exposures may significantly increase upon coadministration with strong inhibitors of CYP3A, P-gp, and UGT1A1 together (i.e., all 3 pathways). Lenacapavir is a moderate inhibitor of CYP3A and a P-gp inhibitor. Caution is advised if LEN is coadministered with a sensitive CYP3A and/or P-gp substrate with a narrow therapeutic index. There was no clinically meaningful effect of orally administered LEN on tenofovir alafenamide (a P-gp substrate) or rosuvastatin (a BCRP substrate). Guidance on established and other potentially significant DDIs is included in Sections 4.3, 4.4 and 4.5 of the SmPC.

PART II: MODULE SIII—CLINICAL TRIAL EXPOSURE

SIII.1. Clinical Trial Exposure

The indication is primarily based on data from Study GS-US-412-5624 (PURPOSE 1), an ongoing Phase 3, randomized, double blind, multicenter study of LEN and DVY for PrEP in cisgender adolescent girls and young women who have sex with partners assigned male at birth, and Study GS-US-528-9023 (PURPOSE 2), an ongoing Phase 3, randomized, double blind, multicenter study of LEN for PrEP in cisgender men, transgender women, transgender men, and gender nonbinary people who have sex with partners assigned male at birth.

The tables in this section present exposure to LEN up to data cut dates of 08 May 2024 for PURPOSE 1 and 05 August 2024 for PURPOSE 2. Safety data for the primary analyses of these studies was based on the randomized blinded phase of each individual study, and the exposure is presented here separately. The combined number of participants exposed to LEN from a supplementary pooled analysis of the PURPOSE 1 and PURPOSE 2 randomized blinded phase was 4,323.

Table SIII.1. Duration of LEN Exposure in PURPOSE 1

	Cumulative for PURPOSE 1	
Duration of Exposure	**Participants**	**Person-days**
>= 1 Day	2140	706,430
>= 4 Weeks (28 Days)	2129	706,278
>= 8 Weeks (56 Days)	2110	705,625
>= 13 Weeks (91 Days)	2076	702,995
>= 26 Weeks (182 Days)	2015	695,444
>= 39 Weeks (273 Days)	1411	544,754
>= 52 Weeks (364 Days)	808	357,990
>= 65 Weeks (455 Days)	255	140,994
>= 78 Weeks (546 Days)	133	82,389
>= 91 Weeks (637 Days)	36	27,078
>= 104 Weeks (728 Days)	18	15,403
>= 117 Weeks (819 Days)	13	11,447
>= 130 Weeks (910 Days)	4	3668

Table SIII.2. Exposure to LEN by Age Group and Gender in PURPOSE 1

	Cumulative for PURPOSE 1	
	Participants	Person-days
Age Group	Female	Female
16 - < 18 years	56	15,366
>= 18 years	2084	691,067

Table SIII.3. Exposure to LEN by Ethnic Origin in PURPOSE 1

	Cumulative for PURPOSE 1	
Ethnic Origin	Participants	Person-days
Black	2137	705,521
Multiracial - Other	3	912

Table SIII.4. Duration of LEN Exposure in PURPOSE 2

	Cumulative for PURPOSE 2	
Duration of Exposure	Participants	Person-days
>= 1 Day	2183	694,706
>= 4 Weeks (28 Days)	2156	694,410
>= 8 Weeks (56 Days)	2126	693,281
>= 13 Weeks (91 Days)	2084	690,331
>= 26 Weeks (182 Days)	1993	679,078
>= 39 Weeks (273 Days)	1226	507,387
>= 52 Weeks (364 Days)	769	372,969
>= 65 Weeks (455 Days)	383	222,028
>= 78 Weeks (546 Days)	230	149,219
>= 91 Weeks (637 Days)	85	66,064
>= 104 Weeks (728 Days)	36	33,873
>= 117 Weeks (819 Days)	28	27,862
>= 130 Weeks (910 Days)	27	26,953
>= 143 Weeks (1001 Days)	12	12,659
>= 156 Weeks (1092 Days)	4	4477

Table SIII.5. Exposure to LEN by Age Group and Gender in PURPOSE 2

	Cumulative for PURPOSE 2			
	Participants		Person-days	
Age Group	Male	Female	Male	Female
16 - < 18 years	3	0	979	0
18 - <=25 years	733	16	215,740	5628
>25 - <35 years	896	16	288,024	6108
35 - <50 years	444	10	149,277	3623
>=50 years	64	1	24,953	366

Table SIII.6. Exposure to LEN by Ethnic Origin in PURPOSE 2

	Cumulative for PURPOSE 2	
Ethnic Origin	Participants	Person-days
American Indian or Alaska Native	20	6279
Asian	269	66,328
Black	584	206,492
Native Hawaiian or Pacific Islander	3	927
White	722	251,550
Hispanic or Latino	592	197,119
Not Hispanic or Latino	130	54,431
Black/White	185	64,839
Black/Asian	1	328
Black/American Indian or Alaska Native	5	3292
Black/Native Hawaiian or Pacific Islander	2	532
Asian/White	3	2115
Asian/Native Hawaiian or Pacific Islander	1	547
White/American Indian or Alaska Native	316	69,714
White/Native Hawaiian or Pacific Islander	1	1
Multiracial - Other	53	15,569
Coloured	5	1912
Pardo	1	276
Black/Brown	12	3694
Black/Coloured	7	2533
Black/Pardo	15	3506

	Cumulative for PURPOSE 2	
Ethnic Origin	**Participants**	**Person-days**
White/Brown	6	1485
Any Other	7	2163
Not Multiracial - Other	10	4040
Unknown	10	4040
Not permitted	8	2145

PART II: MODULE SIV—POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1. Exclusion Criteria in Pivotal Clinical Trials Within the Development Program

Table SIV.1. Important Exclusion Criteria in Pivotal Trials in the Development Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Body weight	The inclusion criteria for both studies GS-US-412-5624 and GS-US-528-9023 is body weight ≥ 35 kg.	No Rationale: Yeytuo is indicated for use in people ≥ 35 kg body weight.
Renal impairment	TVD is used as the comparator in studies GS-US-412-5624 and GS-US-528-9023. The inclusion criteria for both studies is an eGFR ≥ 60 mL/min based on the safety profile of TVD.	No Rationale: No safety concerns for LEN are anticipated in individuals with severe renal impairment. LEN is not renally eliminated, and no clinically relevant changes in LEN PK were observed in participants with severe renal impairment ($eGFR_{CG}$ between 15 and 29 mL/min [inclusive]) in a dedicated renal impairment study (GS-US-200-4330). As LEN is highly protein bound, it is unlikely to be removed by dialysis.
Hepatic impairment	An exclusion criteria for both studies GS-US-412-5624 and GS-US-528-9023 is severe hepatic impairment or a history of or current clinical decompensated liver cirrhosis (eg, ascites, encephalopathy, variceal bleeding).	No Rationale: The effect of hepatic impairment was evaluated in a dedicated Phase 1 study in participants with mild to moderate hepatic function matched to healthy controls (GS-US-200-4331). No clinically relevant changes in LEN PK were observed in this study and based on cumulative PK data from the LEN development program, no dose adjustment of LEN is recommended in people with mild to moderate hepatic impairment (Child-Pugh Class A or B). LEN has not been studied in participants with severe hepatic impairment (Child-Pugh Class C). However, no safety concerns for LEN are anticipated in individuals with severe hepatic impairment, and no additional studies are planned in this population.
Hepatitis	An exclusion criteria for both studies GS-US-412-5624 and GS-US-528-9023 is acute viral hepatitis A, B, or C or	No Rationale: The safety profile of LEN in this patient population is not expected to differ from the known safety profile of LEN in the indicated population.

Criterion	Reason for Exclusion	Considered to be Missing Information
	evidence of chronic hepatitis B or C infection.	

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

Table SIV.2. Ability of the Clinical Trial Development Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare	4323 participants have been exposed to LEN for PrEP in the clinical development program.	ADRs with a frequency of 1 in 1441 could be detected if there were no background incidence.
Due to prolonged exposure	54 participants have been exposed to LEN for PrEP for ≥ 2 years in studies in the clinical development program.	No ADRs associated with prolonged exposure have been identified in the clinical trial program.
Due to cumulative effects	54 participants have been exposed to LEN for PrEP for ≥ 2 years in studies in the clinical development program.	No cumulative effects have been identified in the clinical trial program.
Which have a long latency	54 participants have been exposed to LEN for PrEP for ≥ 2 years in studies in the clinical development program.	No ADRs with a long latency have been identified in the clinical trial program.

SIV.3. Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table SIV.3. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure	Considered to Be Missing Information
Pregnant women	As of 08 May 2024, 105 of 193 (54%) of pregnancies exposed to LEN in the randomized blinded phase of PURPOSE 1 had completed. A cumulative review of use of LEN in pregnancy and lactation to 01 October 2024 included 369 pregnancy exposures to LEN of which 231 were completed.	Yes

Type of Special Population	Exposure	Considered to Be Missing Information
Breastfeeding women	From a cumulative review including lactation exposures to 01 October 2024, there were 89 cases in which infants were reported to have been exposed to LEN via breast milk, all of which came from PURPOSE 1.	Yes
Pediatrics	There were 56 adolescent participants aged ≥ 16 to < 18 years in PURPOSE 1 and 3 adolescent participants aged ≥ 16 to < 18 years in PURPOSE 2 who received LEN.	No Rationale: The safety profile of LEN in adolescents weighing ≥ 35 kg is anticipated to be similar to that in adults. Population PK analyses did not identify any clinically relevant differences due to age on the PK of LEN, and no dose adjustment is required for adolescents.
Elderly	19 participants were ≥ 65 to ≤ 78 years of age.	No Rationale: The safety profile in elderly people is expected to be similar to the safety profile in non-elderly adults. Population PK analyses did not identify any clinically relevant differences due to age on the PK of LEN, and no dose adjustment is required for elderly people.

PART II: MODULE SV—POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

As Yeytuo is not yet approved, there is currently no information on postauthorization exposure of Yeytuo.

PART II: MODULE SVI—ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for Yeytuo to be misused for illegal purposes.

PART II: MODULE SVII—IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risk(s) Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII 1. Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason	List of Risks	Comment
Risks with minimal clinical impact (in relation to the severity of the indication)	*Identified Risk* Development of resistance to LEN if an individual acquires HIV-1 either before or when receiving Yeytuo, or following discontinuation of Yeytuo.	Lenacapavir-resistant HIV-1 variants retain susceptibility to all first-line antiretroviral (ARV) classes owing to LEN's novel mechanism of action; therefore, the risk is considered to have minimal clinical impact.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

There are no important identified risks for LEN for inclusion as a safety concern.

SVII.1.2.2. Important Potential Risks

There are no important potential risks for LEN.

SVII.1.2.3. Missing Information

Table SVII 2. Missing Information

Missing Information	Risk-Benefit Impact
Safety in Pregnancy and Lactation	In PURPOSE 1, as of the data cut of 08 May 2024, 193 pregnancies were reported in participants who received LEN, including 105 completed pregnancies. The rates of adverse pregnancy outcomes in participants who received LEN were similar to reported background rates. Lenacapavir exposures during each trimester of pregnancy and postpartum were comparable to those in non-pregnant participants. Based on a cumulative review of the Gilead Global Safety Database through 01 October 2024, including 369 pregnancies in 366 individuals with maternal exposure to LEN, the prevalence of adverse pregnancy outcomes and pregnancy-related maternal AEs on LEN was consistent with the background prevalence.

Missing Information	Risk-Benefit Impact
	Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with lenacapavir during pregnancy, there were no toxicologically significant effects on developmental endpoints. Lenacapavir is present in human milk. In PURPOSE 1, LEN was detected at very low levels in infants who were breastfed by individuals who became pregnant while receiving LEN. No adverse effects of LEN in breastfed infants were observed in 89 cases of LEN use in lactating women.
Long-term safety information	Limited safety data are available for LEN for PrEP beyond 52 weeks of exposure.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for LEN for inclusion as a safety concern.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for LEN.

SVII.3.2. Presentation of the Missing Information

Table SVII 3. Missing Information

Missing Information	Evidence Source
Safety in Pregnancy and Lactation	Population in need of further characterization: No safety concerns have been identified with the exposure of LEN during pregnancy or lactation. Additional information will be provided in the Antiretroviral Pregnancy Registry (APR).
Long-term Safety Information	Limited safety data are available for LEN for PrEP beyond 52 weeks of exposure. LEN for PrEP was well tolerated through 52 weeks in cisgender adolescent girls and young women who have sex with partners assigned male at birth in study GS-US-412-5624 (PURPOSE 1) and in cisgender men, transgender women, transgender men, and gender nonbinary people who have sex with partners assigned male at birth in study GS-US-528-9023 (PURPOSE 2).

PART II: MODULE SVIII—SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in pregnancy and lactation
	Long-term safety information

PART III: PHARMACOVIGILANCE PLAN

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Drug Reactions Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

There are no specific adverse reaction follow-up questionnaires for any of the safety concerns.

Other Forms of Routine Pharmacovigilance Activities

There are no other forms of routine pharmacovigilance activities for any of the safety concerns.

III.2 Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Antiretroviral Pregnancy Registry (APR)	
Rationale and Study Objectives	Safety concern addressed: Safety in pregnancy and lactation (missing information). Objectives: To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.
Study Design	Prospective, observational, exposure registration, and follow-up study.
Study Populations	Pregnant women exposed to antiretroviral drugs.
Milestones	Submission of interim reports in the LEN periodic safety update report (PSUR) (data lock point [DLP] and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1—Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2—Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3—Required additional pharmacovigilance activities				
Antiretroviral Pregnancy Registry (APR) Ongoing	To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.	Safety in pregnancy and lactation (missing information)	Submission of interim reports	In the LEN PSUR (DLP and periodicity described in the list of EU Reference Dates and frequency of submission of PSURs)

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorization efficacy studies.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine Risk Minimization Measures

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Safety in Pregnancy and Lactation (missing information)	Routine risk communication: SmPC section 4.6 PL section 2
Long-term Safety Information	Routine risk communication: None

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary Risk Minimization Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None	N/A	N/A
Important potential risk(s)		
None	N/A	N/A
Missing information		
Safety in pregnancy and lactation	Routine risk minimization measures: SmPC section 4.6 PL section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR)
Long-term safety information	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None Additional risk minimization measures: None	reporting and signal detection: None Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

I. Summary of risk management plan for Yeytuo

This is a summary of the risk management plan (RMP) for Yeytuo. The RMP details important risks of Yeytuo, how these risks can be minimized, and how more information will be obtained about Yeytuo's risks and uncertainties (missing information).

Yeytuo's summary of product characteristics (SmPC) and its PL give essential information to health care professionals and patients on how Yeytuo should be used.

This summary of the RMP for Yeytuo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Yeytuo's RMP.

II. The Medicine and What Is It Used For

Yeytuo is authorized in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents with increased HIV-1 acquisition risk weighing at least 35 kg (see SmPC for the full indication). It contains lenacapavir as the active substance and it is given subcutaneously as well as orally for loading and bridging.

Further information about the evaluation of Yeytuo's benefits can be found in Yeytuo's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage*:*

III. Risks Associated With the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Yeytuo, together with measures to minimise such risks and the proposed studies for learning more about Yeytuo's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and health care professionals
- Important advice on the medicine's packaging
- The authorized pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

- The medicine's legal status—the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Yeytuo is not yet available, it is listed under 'missing information' below.

III.A. List of Important Risks and Missing Information

Important risks of Yeytuo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Yeytuo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in pregnancy and lactation
	Long-term safety information

III.B. Summary of Important Risks

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Missing information	**Safety in pregnancy and lactation**
Risk minimization measure(s)	Routine risk minimization measures: SmPC section 4.6 PL section 2 Additional risk minimization measures: None

Additional pharmacovigilance activities.	Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR) See Section III.C of this summary for an overview of the postauthorization development plan.
Missing information	**Long-term safety information**
Risk minimization measure(s)	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities.	Additional pharmacovigilance activities: None

III.C. Postauthorization Development Plan

III.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Yeytuo.

III.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Short Study Name	Purpose of the Study
Antiretroviral Pregnancy Registry (APR)	To collect information on the risk of birth defects with antiretroviral drugs, including LEN, to which pregnant women are exposed.

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

None.

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None.

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None.

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material (Refer to REFERENCES)

Annex 8. Summary of Changes to the Risk Management Plan Over Time

Not applicable.

REFERENCES

Bartholomew PM, Kreeger JM, Morton D. Injection-site malignant fibrous histiocytomas in a pegvisomant carcinogenicity study in SD rats. Toxicol Pathol 2014;42 (7):1082-91.

Boerner H. Dapivirine Vaginal Ring for HIV Prevention No Longer Under Consideration by the FDA. Available at: https://www.medscape.com/viewarticle/967175?form=fpf#vp_1. Accessed on: 6 Aug, 2024. Last Reviewed: 24 January 2022:

Centers for Disease Control and Prevention. Estimated HIV Incidence and Prevalence in the United States, 2017–2021. HIV Surveillance Supplemental Report 2023. Available at: https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-28-no-3/index.html. Accessed: 10 September 2023. Last Updated: 23 May. 2023:

Centers for Disease Control and Prevention (CDC). Expanding PrEP Coverage in the United States to Achieve EHE Goals. Available at: https://www.cdc.gov/nchhstp/dear_colleague/2023/dcl-101723-prep-coverage.html Accessed:23 October 2023. Last Updated: 17 October. 2023:

Descovy, Gilead Sciences Ireland UC. Descovy 200mg/25mg or 200mg/10mg film-coated tablets. Summary of Product Characteristics. County Cork, Ireland Revised November. 2022:

Gollub EL, Vaughan R. U.S. Women Need the Dapivirine Ring, Too: FDA as Structural Barrier to HIV Prevention for Women. AIDS Educ Prev 2022;34 (4):311-24.

GRASSO P, GOLBERG L. Subcutaneous Sarcoma as an Index of Carcinogenic Potency. Fd Cosmet Toxicol 1966;4:297-320.

Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV 2018;5 (11):e629-e37.

International AIDS Society (IAS). HIV transmission virtually eliminated in Inner Sydney, Australia New evidence that Australia may become world's first nation to end HIV epidemic. Available at: https://www.iasociety.org/news-release/hiv-transmission-virtually-eliminated-inner-sydney-australia#:~:text=From%202017%20to%202021%2C%20the,according%20to%20a%20new%20study Accessed: 09 October 2023. Last Updated: 24 July. 2023:

Joint United Nations Programme on HIV/AIDS (UNAIDS). The urgency of now: AIDS at a crossroads. Geneva, Switzerland. 2024.

Nwokolo N, Hill A, McOwan A, Pozniak A. Rapidly declining HIV infection in MSM in central London. Lancet HIV 2017a;4 (11):e482-e3.

Nwokolo N, Whitlock G, McOwan A. Not Just PrEP: Other Reasons for London's HIV Decline. The Lancet HIV 2017b;4 (4):e153.

Sullivan PS, Smith DK, Mera-Giler R, Siddiqi A, Gunnels B, Harris N, et al. The impact of pre-exposure prophylaxis with TDF/FTC on HIV diagnoses, 2012-2016, United States [Abstract LBPEC036]. International AIDS Conference (IAC); 2018 23-27 July; Amsterdam, the Netherlands.

Truvada, Gilead Sciences Ireland UC. Truvada 200 mg/245 mg film-coated tablets. Summary of Product Characteristics. Carrigtohill County Cork, T45 DP77 Ireland. Revised February. 2023:

UNAIDS. FACT SHEET 2024 Global HIV statistics. 2024:

ELECTRONIC SIGNATURES

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
[redacted]	Patient Safety eSigned	10-Jun-2025 22:00:01
Rainer Heissing	QPPV eSigned	10-Jun-2025 22:37:37
[redacted]	Global Development Lead (GDL) eSigned	11-Jun-2025 17:30:24