Amsterdam, 24 July 2025
EMA/265753/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenacapavir Gilead

International non-proprietary name: lenacapavir

Procedure No. EMEA/H/W/006659/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
AGYW	adolescent girls and young women
AIDS	acquired immunodeficiency syndrome
ARAs	acid reducing agents
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	Atazanavir
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the concentration versus time curve over the dosing interval
bHIV	background HIV-1
BMI	body mass index
CAB	cabotegravir (Apretude®)
CD4	Clusters of differentiation 4
CGM	cisgender men
CGW	cisgender women
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration of drug
COBI	cobicistat
COVID-19	coronavirus disease 2019
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRV	darunavir
DVY	emtricitabine/tenofovir alafenamide (F/TAF; Descovy®)
EEA	European Economic Area
EFV	efavirenz
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EMA	European Medicines Agency
EU	European Union
EU-M4All	European Union Medicines for All

F	Bioavailability
FAM	famotidine
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTC	emtricitabine (Emtriva®)
GAHT	gender-affirming hormone therapy
GBMSM	gay, bisexual, and other men who have sex with men
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
ISR	injection site reaction
ISS	Integrated Summary of Safety
LEN	lenacapavir
MedDRA	Medical Dictionary for Regulatory Activities
MDZ	midazolam
N/A	Not applicable
OL	open label
$paEC_{95}$	protein adjusted 95% effective concentration
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PIT	pitavastatin
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
PrEP	pre-exposure prophylaxis
PT	preferred term
PTM	placebo to match
PWBP	people who would benefit from PrEP
PWID	people who inject drugs
PY	person-years
Q1	first quartile
Q3	third quartile
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
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RIF	rifampicin

RITA	recent infection testing algorithm
RNA	ribonucleic acid
ROS	rosuvastatin
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SmPC	summary of product characteristics
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TFV	tenofovir
TGM	transgender men
TGW	transgender women
T_{max}	time (observed time point) of C_{max}
TQT	thorough QT
TVD	emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
VORI	voriconazole
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

1. Executive summary

On 24 July 2025, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion in accordance with Article 58 of Regulation (EC) No 726/2004 for the medicinal product Lenacapavir Gilead (lenacapavir) intended for the prophylaxis against sexually acquired human immunodeficiency virus type 1 (HIV-1) infection. Lenacapavir Gilead was reviewed under EMA's accelerated assessment programme.

Lenacapavir Gilead will be available as a 464 mg solution for injection and as 300 mg film-coated tablets, both are essential for the treatment course. After the initiation dose (consisting of both injection and tablets), the frequency of injections is once every 6 months. The active substance of Lenacapavir Gilead is lenacapavir, an antiviral for systemic use. Lenacapavir is a multistage, selective inhibitor of HIV-1 capsid function that ultimately inhibits HIV-1 replication.

The main evidence of efficacy of Lenacapavir Gilead was based on two phase 3 clinical trials: PURPOSE 1, involving adolescent (from 16 years of age) and adult women, and PURPOSE 2, involving adolescent (over 16 years of age) and adult men and gender-diverse persons.

The results showed a reduction in the incidence of HIV-1 infections with Lenacapavir Gilead compared with once daily emtricitabine/tenofovir alafenamide (FTC/TDF) (PURPOSE 1: rate ratio (RR): 0.000; 95% confidence interval (CI): 0.000, 0.101; p <0.0001; PURPOSE 2: RR: 0.111; 95% CI: 0.024, 0.513; p = 0.00245).

The most relevant safety concerns were slow or non-resolving injection site nodules and indurations, and the most commonly reported adverse events were local injection site reactions, headache, nausea, and diarrhoea.

The full indication for Lenacapavir Gilead solution for injection is:
Lenacapavir Gilead injection is 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 (see sections 4.2, 4.4 and 5.1).

The full indication for Lenacapavir Gilead film-coated tablets is:
Lenacapavir Gilead tablet is 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 for:

- *oral loading*
- *oral bridging*

(see sections 4.2, 4.4 and 5.1).

Lenacapavir Gilead should be prescribed by a healthcare professional experienced in the management of HIV prevention.

Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which will be published on the EMA website.

Lenacapavir Gilead is intended exclusively for markets outside the European Union.

This report summarises the scientific review leading to the opinion adopted by the Committee for Medicinal Products for Human Use (CHMP).

2. Administrative/regulatory information and recommendations on the procedure

2.1. Information on the product

Table 1. Product data

Product data	
Product name	Lenacapavir Gilead
Active substance	lenacapavir sodium
INN or common name	lenacapavir
Applicant	Gilead Sciences Ireland Unlimited Company IDA Business and Technology Park Carrigtohill T45 DP77 IRELAND
EMA Product Number	EMEA/H/W/006659
ATC code and Pharmacotherapeutic group	J05AX31 Antivirals for systemic use, other antivirals
Pharmaceutical form(s) and strength (s)	300 mg film-coated tablets; 464 mg solution for injection
Packaging	Film-coated tablets: bottle (HDPE); Solution for injection: vial (glass)
Package size(s)	Film-coated tablets: 4 tablets; Solution for injection: 2 single-dose vials 2 withdrawal needles 2 syringes 2 injection needles
Route of administration	Oral use and Subcutaneous use
Device or diagnostic	Lenacapavir Gilead solution for injection (2 vials) will be packaged with the following medical devices: syringes, withdrawal needles and injection needles. The medical devices are included to enable the healthcare provider to administer the subcutaneous injections correctly, the injection safety needles have a bore size that is appropriate for administering the solution and the withdrawal needles assist withdrawal of the solution from the vial into the syringe.

Product data	
	All of the devices that will be co-packaged with the medicinal product are compliant with MDR Regulation (EU) 2017/745. Evidence of compliance has been provided in the application and is explained further below. <u>Disposable Syringe and Injection Needles</u> Section 3.2.R.2 Medical Device has been updated to include a copy of the EU certificate issued by the Notified Body that was referenced in the manufacturer's EU declaration of conformity for each component, disposable syringe and injection needles. The eAF has been updated for both components to indicate that EU certificate issued by a Notified Body is provided. <u>Withdrawal Needles</u> Section 3.2.R.2 Medical Device includes the EC declaration of conformity from the manufacturer in accordance with Directive 93/42/EEC (MDD), the manufacturer's declaration of MDD certificate extension validity, and their notified body's confirmation of formal application, written agreement and appropriate surveillance. As explained in Section 3.2.R.2 Medical Device, the manufacturer's declaration of MDD certificate extension and the notified body's confirmation have fulfilled requirements in Regulation (EU) 2023/607, amending MDR in regards to Article 120 Transitional Provisions, paragraphs 2 and 3. This extends the validity of the MDD certificate until 31 December 2028 for class IIa devices. The applicant anticipates that the manufacturer will conduct conformity assessment procedures per MDR, Article 52(6) prior to 31 December 2028, the end of their transitional period. The eAF states that the withdrawal needle complies with Regulation 2023/607 extending the validity of MDD certificate to 31 Dec 2028.
Orphan designation	Not applicable
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	EU-M4All scientific opinion
Legal basis	Article 58 of Regulation (EC) No 726/2004 (by analogy to Article 8(3) of Directive 2001/83/EC)
Final indication	Solution for injection: *Lenacapavir Gilead injection is 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 (see sections 4.2, 4.4 and 5.1).* Film-coated tablets: *Lenacapavir Gilead tablet is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of*

Product data	
	sexually acquired HIV-1 infection in adults and adolescents with increased HIV-1 acquisition risk, weighing at least 35 kg for: • *oral loading* • *oral bridging* *(see sections 4.2, 4.4 and 5.1).*
New active substance status	Not applied for

2.2. Scientific advice

The applicant did not seek scientific advice from the CHMP.

2.3. Eligibility to the CHMP scientific opinion

The applicant Gilead Sciences Ireland Unlimited Company submitted on 31 January 2025 an application in accordance with Article 58 of Regulation (EC) No 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organization for Lenacapavir Gilead (lenacapavir).

The eligibility to an application for a CHMP scientific opinion in accordance with Article 58 of Regulation (EC) No 726/2004 was granted by the CHMP, after having consulted the World Health Organisation, on 14 November 2024.

Lenacapavir Gilead will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication:

Solution for injection:
Lenacapavir Gilead injection is indicated for pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg (see sections 4.2 and 5.1).

Film-coated tablets:
Lenacapavir Gilead tablet is indicated for pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg for:

- *oral loading*
- *oral bridging*

(see sections 4.2 and 5.1).

2.4. Legal basis, dossier content and multiples

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

2.5. Information on paediatrics

Not applicable

2.6. Information on orphan market exclusivity

2.6.1. Similarity with authorised orphan medicinal products

Not applicable

2.7. Applicant's request(s) for consideration

2.7.1. Accelerated assessment request

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following considerations:

Lenacapavir is a long-acting first-in-class inhibitor of human immunodeficiency virus type 1 (HIV-1) capsid function. It is already approved in the EU under the tradename of Sunlenca in combination with other antiretrovirals for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen.

Due to its long half-life it may provide a novel option for HIV prevention, with a longer duration of action. Lenacapavir for PrEP can be administered twice-yearly by subcutaneous injection. Lenacapavir is a therapeutic innovation for PrEP insofar as no available options use the mechanism of HIV-1 capsid inhibition.

HIV-1 infection remains a significant, serious, and life-threatening disease of major public health. HIV remains a chronic infection where complete viral clearance is not anticipated. Thus, life-long therapy is anticipated. This makes preventive strategies highly relevant. PrEP for persons at particular risk is recommended by public health bodies, but significant transmission still remains. The most readily available PrEP option, Truvada, is not suitable for all. PrEP options that are highly effective with improved/optimised administration forms are considered to fulfil an unmet need.

The efficacy of lenacapavir was superior to tenofovir-based PrEP in two large studies covering cisgender women in sub-Saharan Africa, and cisgender men and gender diverse people who have sex with men. This is likely due to improved adherence with a long acting injectable given at six-month intervals. The superior efficacy of lenacapavir over the dapivirine ring was evident on cross study comparison; moreover, the ring is not relevant for a large proportion of the target population. The comparative efficacy of lenacapavir and

cabotegravir has not been studied. However, cross study comparison indicates similar, very high efficacy. Lenacapavir provides an advantage over cabotegravir with respect to six-month rather than two-month injection intervals, which may facilitate and increase adherence.

Thus, lenacapavir was assumed to address an unmet medical need and to be of major public health interest.

2.7.2. Request for additional data exclusivity/marketing protection

Not applicable

2.7.2.1. CHMP recommendation on additional data exclusivity /marketing protection

Not applicable

2.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Filip Josephson
Co-Rapporteur:	Patrick Vrijlandt

Table 2. Steps taken for the assessment of the product

The application was received by the EMA on	31 January 2025
An application for accelerated assessment was filed by the applicant. Accelerated assessment procedure was agreed-upon by CHMP on	31 January 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was received on	22 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	22 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	29 April 2025
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	not applicable
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 May 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 June 2025

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	10 July 2025
The List of Questions were addressed by the applicant via Eudralink on	15 July 2025
The Quality Working Party agreed on the Assessment Overview during their meeting on	15 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Lenacapavir Gilead on	24 July 2025

During the assessment of the application for a scientific opinion of Lenacapavir Gilead under Article 58 of Regulation (EC) No 726/2004 (i.e., EU-M4all), experts from the WHO and the national regulatory authorities of Kenya, Nigeria, South Africa, Thailand, Uganda, Viet Nam, Zambia and Zimbabwe contributed to the scientific discussions. The final scientific opinion was adopted by CHMP.

2.9. Final CHMP outcome

2.9.1. Considerations related to paediatrics

Not applicable

2.9.2. Considerations related to orphan market exclusivity

Not applicable

2.9.3. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lenacapavir Gilead is favourable in the following indication(s):

Solution for injection:

Lenacapavir Gilead injection is 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 (see sections 4.2, 4.4 and 5.1).

Film-coated tablets:

Lenacapavir Gilead tablet is 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 for:

- *oral loading*
- *oral bridging*

(see sections 4.2, 4.4 and 5.1).

The CHMP, therefore, recommends the granting of the scientific opinion subject to the conditions described

in the following sections.

2.9.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

2.9.5. Other conditions and requirements of the marketing authorisation

2.9.5.1. Periodic safety update reports

The scientific opinion holder shall submit periodic safety update reports for this product in line with the requirements for the existing active substance as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

2.9.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

2.9.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

2.9.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

2.9.8. Proposed list of recommendations

Table 3. Proposed list of recommendations

Description of recommendations
The Applicant should collect pre-dose PK samples (C_{trough}) in ongoing clinical studies of lenacapavir, from subjects that had lenacapavir injected into the upper arm or buttocks, to further support a

Description of recommendations
change in the SmPC regarding these as alternative injection sites. The data should be submitted as soon as it is available.
The Applicant should conduct a non-interventional drug utilization study of lenacapavir for PrEP in a real-world setting. Details of this study should be provided as soon as it is available.

3. Introduction

3.1. Therapeutic context

HIV-1 infection is a serious, and life-threatening disease of major public health significance. In the European region, an estimated 160,000 (range: 140,000-190,000) people acquired HIV in 2023. Other global regions of focus for HIV prevention efforts include sub-Saharan Africa, which was the region most affected by HIV in 2023, accounting for two-thirds of all global HIV infections and 640,000 (range: 490,000-860,000) new infections. In Eastern Europe and Central Asia, new HIV infections have risen by 20% since 2010, reaching 140,000 in 2023. The Middle East and North Africa have seen a 116% increase in new infections from 2010 to 2023. Despite progress in Eastern and Southern Africa, where new infections have dropped by 59%, the region still has a high HIV burden, especially among young women.

Biomedical HIV prevention using PrEP is a cornerstone of HIV-control efforts in Europe and worldwide. While effective options exist for HIV PrEP, uptake and adherence have been suboptimal, and several key populations in the EU and globally remain underserved by existing PrEP options, highlighting an urgent need to develop additional PrEP modalities.

Daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®; TVD) is approved in the EU, and several other regions globally for PrEP in adults and adolescents and is recommended by the World Health Organization (WHO) as part of the HIV-1 prevention standard of care. Daily oral emtricitabine/tenofovir alafenamide (F/TAF; Descovy®; DVY) is approved in the US and other regions for PrEP in adults and adolescents weighing $\geqslant$ 35 kg; however, it is currently not indicated for PrEP in individuals who are at risk of HIV-1 due to receptive vaginal sex. TVD and DVY, have high efficacy when taken as directed. However, the requirement for daily adherence to oral PrEP has limited uptake of and persistence on PrEP.

There are currently 2 options for PrEP that are not daily oral pills: cabotegravir (CAB; Apretude®), which is administered by intramuscular injection every 2 months and the dapivirine ring, which is inserted intravaginally each month. However, regulatory approval and access to these products are limited. While CAB was highly efficacious in Phase 3 studies, the requirement for bimonthly injections increases the frequency of clinic visits beyond the quarterly standard of care for PrEP, which appears to result in implementation challenges and negatively impacts uptake and persistence, particularly among populations that face multiple barriers to care. Currently, the dapivirine vaginal ring has only been approved for use in Africa and requires monthly replacement.

3.2. Aspects of development

In the European Union (EU), United States (US), and other regions, lenacapavir (Sunlenca) is approved in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1 infection.

The Applicant is submitting this application in support of a new indication for the subcutaneous (SC) injection and oral tablet formulations of lenacapavir (LEN) for pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1. The proposed indication for LEN for PrEP is primarily based on efficacy and safety data from two Phase 3 studies being conducted in cisgender women including pregnant, lactating, and postpartum women (Study GS-US-412-5624 [PURPOSE 1]) and cisgender men and gender-diverse people (Study GS-US-528-9023 [PURPOSE 2]).

The data provided are from the planned interim efficacy analyses of Studies GS-US-412-5624 and GS-US-528-9023, which served as the primary analysis for each study, as specified in the clinical study protocols.

In addition, 3 Phase 1 studies (GS-US-200-4538, GS-US-200-4540, and GS-US-200-5709) provide clinical pharmacology data that contribute to the characterization of LEN PK. Study GS-US-200-4540 also provides supportive safety data for SC LEN in alternative injection sites. Two studies from the LEN HIV-1 treatment program (Studies GS-US-200-4625 and GS-US-200-4334) are provided to support oral bridging.

3.3. Description of the product

Lenacapavir is a selective inhibitor of HIV-1 capsid function and directly binds to the interface between capsid protein (CA) subunits. It thereby inhibits HIV-1 replication by interfering with multiple, essential steps of the viral lifecycle.

The proposed indication in this application is for PrEP to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg.

The LEN PrEP dosing regimen is SC LEN 927 mg (309 mg/mL; 2 x 1.5 mL injections) which is administered on Day 1 and every 6 months (26 ± 2 weeks), and oral LEN 600 mg (2 x 300 mg tablets) which is required for pharmacokinetic (PK) loading on Days 1 and 2.

In the European Union (EU), United States (US), and other regions, lenacapavir (Sunlenca) is approved in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection in heavily treatment-experienced (HTE) adults with multidrug-resistant HIV-1 infection.

The initiation of LEN PrEP differs from the approved dosing for Sunlenca. The Sunlenca dosing regimen is as follows: on treatment Day 1 and Day 2, 600 mg per day is taken orally. On Day 8, 300 mg is taken orally. Then, on Day 15, SC LEN 927 mg is administered and thereafter every 6 months (26 ± 2 weeks).

3.4. Inspection issues

3.4.1. GMP inspection(s)

No inspection required.

FDA performed a GMP inspection at Gilead Sciences Inc. 333 Lakeside Drive Foster City CA 94404-1147 United States in February 2025 covering the activities intended to be carried out at this site in the context of this procedure. A screenshot from the FDA inspection classification database that include this inspection has been provided.

3.4.2. GLP inspection(s)

No inspection required.

3.4.3. GCP inspection(s)

No inspection required.

4. Quality aspects

4.1. Introduction

4.1.1. Introduction

There are two proposed presentations of lenacapavir finished product: solution for injection and film-coated tablet containing respectively 463.5 mg and 300 mg of lenacapavir (as sodium salt) as active substance.

Other ingredients are:

Solution for injection: macrogol (E1521) and water for injections

The finished product is packaged in a dosing kit containing:

- 2 clear glass vials, each containing 1.5 mL solution for injection. Vials are sealed with an elastomeric butyl rubber closure and aluminium overseal with flip off cap;
- 2 withdrawal needles (18-gauge, 40 mm), 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, 13 mm).

Film-coated tablets:

Tablet core: mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), copovidone, magnesium stearate, poloxamer.

Tablet coating: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172), iron oxide red (E172).

The tablets are packaged in white high-density polyethylene (HDPE) bottles containing polyester coils and silica gel desiccants. Each bottle is capped using a white, continuous thread, child-resistant polypropylene (PP) screw cap with an induction sealed, aluminium-faced liner.

4.1.2. Active substance

General information

The chemical name of lenacapavir sodium is sodium (4-chloro-7-(2-((*S*)-1-(2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-3-yl)(methylsulfonyl)amide corresponding to the molecular formula $C_{39}H_{31}ClF_{10}N7NaO_5S_2$. It has a molecular mass of 990.3 g/mol and the following structure:

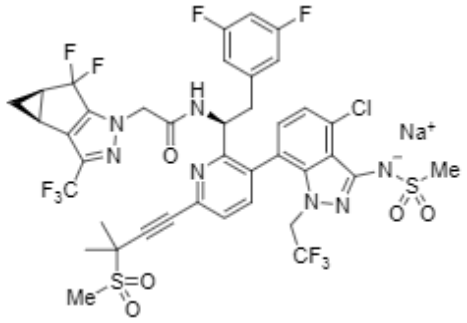


Figure 1. Active substance structure

The chemical structure of lenacapavir was elucidated by ^{1}H-, ^{13}C-, and ^{19}F-NMR, MS, IR, UV, elemental analysis, and X-ray crystallography.

The active substance is a light yellow to yellow solid. Lenacapavir is a weak acid and exhibits pH-dependent solubility (increase solubility with increased pH). Lenacapavir undergoes pH-dependent hydrolysis in solution. Lenacapavir solutions are most stable at pH $\geq$ 5.

Lenacapavir sodium has three stereogenic centres with defined configuration and is produced as a single stereoisomer of an interconvertible mixture of two atropisomers. Enantiomeric purity is ensured by the combined control strategy at the level of starting materials and synthetic process as further described in detail below.

Polymorphism has been observed for lenacapavir. During screening, fourteen different solvates were identified. Upon drying, these solvates give three solvent-free forms (Form I - III) or an amorphous form. Direct interconversion between the different forms is not possible in the solid state. Form I is the proposed commercial polymorphic form and is consistently obtained by the proposed manufacturing process.

Isolation of lenacapavir sodium Form I is important for impurity control, but the physical form of the active substance is not considered critical for the finished product manufacture, since the active substance is completely dissolved during processing for both pharmaceutical forms. Similarly, the particle size of the active substance is not considered critical.

Manufacture, characterisation and process controls

Two active substance manufacturers are proposed. GMP compliance of the sites has been confirmed via the QP declaration. Lenacapavir sodium is synthesised using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis, and the critical controls identified. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered satisfactory. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Impurity levels comply with ICH Q3A. The active substance is packaged in polyethylene bags which comply with the European Pharmacopoeia and with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are then contained in a heat sealed, polyethylene-lined aluminium foil bag. The foil bags are held in high-density polyethylene drums (or other suitable secondary containment) with lids of appropriate size and fitted with a security seal.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, LC), clarity of solution (visual), water content (Ph. Eur.), sodium content (LC), assay (LC), impurity content (LC), GS-832186 content (LC), residual solvents (GC), organic volatile impurities (GC), bacterial endotoxins (Ph. Eur.) and microbial examination (Ph. Eur.).

The active substance specifications are based on the CQA of the active substance.

The specification has been justified in line with ICH guidelines and Ph. Eur. requirements.

The proposed impurity limits for specified impurities are supported by toxicology studies based on a maximum subcutaneous dose of 927 mg of the active substance. A maximum daily dose has been set based on the theoretical systemic exposure of the subcutaneous dose of 927 mg. There is no need to control particle size since the active substance is dissolved for manufacture of both the tablets and the solution for injection. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (13 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The stability studies were conducted using active substance from one of the two proposed manufacturers stored in two different configurations: the proposed container closure system (three batches) and the proposed primary packaging, without the outer, sealed polyethylene-lined aluminum foil bag (four batches), considered to be the worst case scenario. Stability data has been provided for up to 36 months under long term conditions (30 ºC / 75 % RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines.

Stability samples were tested for appearance, water content, assay, impurity content and microbial quality with acceptance limits according to the release specification. All results from the stability studies are within specification limits and no trends are observed.

Photostability testing following ICH Q1B was performed on one commercial batch of the active substance. The active substance is considered to be photostable.

Results under stressed conditions acid, base, oxidative agents were also provided on samples of the active substance.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months "Store below 30 °C" in the proposed container. The proposed temperature restriction, store below 30 °C, is not expressly justified by the stability data, however, no objections are raised.

4.1.3. Finished medicinal product (solution for injection)

Description of the product and pharmaceutical development

Lenacapavir injection, 309 mg/mL corresponding to 463.5 mg in 1.5 ml, is a sterile, preservative-free, clear, yellow to brown solution for subcutaneous (SC) administration. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The formulation is considered suitable for the intended patient population.

The overall goal of lenacapavir pharmaceutical development was to develop a formulation suitable for SC injection that would provide a clinically relevant steady-state and minimize dose volume. Additionally, the finished product should withstand terminal sterilisation and meet pharmacopoeial requirements for small volume parenteral dosage forms, including sterility, bacterial endotoxins, and particulate matter. The finished product should also remain physically and chemically stable for 2 years or longer when stored at 30 °C/75% RH.

Pharmaceutical development of the finished product contains QbD elements.

The key physicochemical properties of lenacapavir sodium that are relevant to the development and performance of lenacapavir injection are ionization state, solubility, chemical stability (oxidative, photolytic, and hydrolytic stability), solid-state properties and physical stability.

During development of lenacapavir injection, formulations with amorphous lenacapavir free acid and crystalline lenacapavir sodium were evaluated. Crystalline lenacapavir sodium was selected for further development and was used in Phase 2 and 3 clinical and stability study batches. The formulation used during clinical studies is the same as that intended for marketing.

The primary packaging is a glass vial sealed with an elastomeric butyl rubber closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The components needed to administer the product are co-packed with the vials: two 3 mL polypropylene disposable syringes with Luer lock fitting, two 18G 1 ½ inch withdrawal needles with Luer lock fittings and two 22G ½ inch injection safety needles with Luer lock fitting. All the co-packed devices are CE-marked.

Manufacture of the product and process controls

Two finished product manufacturers are proposed for the solution for injection. Satisfactory GMP documentation of the sites has been provided.

The manufacturing process consists of 6 main steps: dissolution and mixing, bioburden reduction via filtration, filtration/filling/stoppering/sealing, moist heat terminal sterilization, visual inspection, and kitting.

The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV, LC), assay (LC), degradation products (LC), viscosity (rotating viscometer method), volume in container (in-house), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and container closure integrity (USP).

The proposed control parameters are in accordance with ICH Q6A specifications.

Recommendations in relevant pharmacopeia, ICH and EU regulatory guidelines, process capabilities and controls, development data, batch release data, and stability data of representative batches have been taken into consideration when establishing the acceptance criteria. A number of degradation products are controlled as specified degradation products in the specification for lenacapavir injection.

A reporting limit of 0.1%, an identification limit of 0.2% and a qualification limit of 0.2% calculated based on a maximum daily dose of 927 mg lenacapavir is accepted for the finished product, in accordance with ICH Q3B.

During the procedure, the justification for the endotoxin limit was not accepted considering that the patient population includes adults and adolescents weighing at least 35 kg, resulting in a major objection. The limit was tightened as requested and the issue considered resolved.

The shelf-life limits for degradation products have been confirmed as adequately qualified through toxicological studies.

Assessment of potential mutagenicity of actual and potential degradation products, that might be present in lenacapavir tablets arising from the manufacture and storage of the finished product has been performed. Some alerting structures were identified, which were also found in the active substance or compounds related to the active substance (i.e., intermediates and impurities) which have been tested and found non-mutagenic.

pH is not included in the specification as the quality of input materials effectively controls pH, variations in formulation composition have little impact on the apparent pH, the composition and manufacturing process do not require pH adjustment, lenacapavir injection is predominantly formulated in the organic solvent

macrogol 300, and pH measured is considered as "apparent pH" that does not reflect the actual proton concentration in solution.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Pd-based catalysts are used in the manufacture of the active substance but not in the manufacture of the finished product. Batch analysis data of lenacapavir solution for injection using a validated ICP-MS method was provided, demonstrating that Pd was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data on Pd, it can be concluded that it is not necessary to include any elemental impurity controls in the active substance and finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and non-pharmacopoeial methods appropriately validated in accordance with the ICH guidelines. The same reference standards used in the active substance are used for the lenacapavir solution for injection.

Batch analysis results are provided for 17 batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from eleven commercial scale batches of finished product stored for up to 36 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the specifications. The analytical procedures used are stability indicating. No significant changes or trends have been observed.

In addition, one commercial batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Lenacapavir solution for injection is photolabile. It was, however, shown that secondary packaging protects the finished product from photodegradation. A storage restriction regarding sensitivity to light is therefore justified.

Stress studies were conducted on one pilot batch of finished product at -20 °C, and 50 °C/ambient humidity in Type 1 borosilicate and aluminosilicate vials, as well as at 5 °C/ambient humidity in Type 1 borosilicate vials, stored in the inverted orientation.

Physical and chemical stability after five temperature cycles between -20 °C and 40 °C/75% RH, for up to one month at -20 °C, up to 12 months at 5 °C/ambient humidity, and two weeks at 50 °C/ambient humidity were confirmed.

In-use stability studies have demonstrated that the product is chemically and physically stable for 4 hours at 25 °C outside of the package.

Based on available stability data, the proposed shelf-life of 3 years with the following storage conditions: "Store below 30 °C. Store in the original outer carton in order to protect from light. Once the solution has been drawn into the syringes, the injections should be used immediately, from a microbiological point of view. Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C outside of the package. If not used immediately, in-use storage times and conditions are the responsibility of the user." as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

4.1.4. Finished medicinal product (film-coated tablets)

Description of the product and pharmaceutical development

Lenacapavir tablets are an immediate-release oral dosage form containing 300 mg of lenacapavir (equivalent to 306.8 mg of lenacapavir sodium). Lenacapavir tablets are beige, capsule-shaped, film-coated tablets, debossed with "GSI" on one side and "62L" on the other side. The tablet dimensions are approximately 10 x 21 mm.

Lenacapavir is a BCS Class 4 compound with low aqueous solubility and low apparent permeability. An immediate-release solid oral tablet with the active substance in an amorphous spray dried suspension was the dosage of choice based on the physicochemical properties and to improve the pharmacokinetic (PK) performance of lenacapavir; an immediate-release solid oral tablet also meets the requirements target dose, product performance, and desired product shelf-life.

Lenacapavir sodium is spray-dried with copovidone and poloxamer 407 to form lenacapavir SDD as a finished product intermediate. Lenacapavir SDD is dry granulated with microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate. The resulting granules are lubricated with magnesium stearate and compressed into lenacapavir tablets, 300 mg, which are then film-coated with Opadry II Green 85F110186.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, with the exception of the colourants which comply with Regulation EU 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Excipient compatibility was demonstrated through compatibility studies during development. The formulation is considered suitable for the intended patient population.

There are no overages in lenacapavir tablets.

Lenacapavir was originally isolated as an amorphous free acid and evaluated in a Phase 1 clinical study using a solution in capsule. Lenacapavir was then isolated as a crystalline sodium salt (lenacapavir sodium) that was subsequently formulated as lenacapavir SDD, incorporated in an immediate-release tablet, and evaluated in Phase 1, Phase 2, and Phase 2/3 clinical trials. The composition of the clinical trial formulation is identical to the proposed commercial formulation. No bioequivalence study was hence needed.

Lenacapavir contains two atropisomers due to the restricted rotation around the biaryl bond. Under ambient conditions in the solution state, interconversion of these two atropisomers is observed. NMR studies demonstrate that interconversion occurs rapidly in physiologically relevant media including simulated gastric, intestinal, and human serum solutions at 37 °C. Given that interconversion is expected to occur rapidly *in vivo*, at a rate significantly faster than elimination, consideration of atropisomerism is not needed. From a safety and efficacy perspective both atropisomers are acceptable.

Lenacapavir SDD is an amorphous solid with a single glass transition temperature that is approximately 100 °C above the temperatures experienced during downstream manufacturing processes, transportation/distribution, and storage. Lenacapavir SDD has shown no tendency for crystallization or phase transition in any development or clinical batches manufactured to date.

Lenacapavir SDD is hygroscopic, however, it is chemically stable at 40 °C/75% RH for up to 6 months under closed conditions with desiccant.

Pharmaceutical development of the finished product contains QbD elements.

The suitability of the tablet formulation was discussed during the procedure. The film-coated tablet is intended to be used for the adults and adolescents and is considered to be acceptable for these patient groups. The tablets are proposed to be swallowed whole; however, as substantiated during the procedure, for patients not able to swallow the tablets whole, the tablets can be also split into two halves and be taken one after the other. The PI has been updated accordingly.

Lenacapavir solubility, dissolution robustness, and discriminating capability in different media led to selection of the dissolution method.

The discriminatory power of the dissolution method has been demonstrated. The container closure system for lenacapavir tablets consists of a 45 mL, white, HDPE bottle and a PP, continuous-thread, child-resistant cap which is lined with an induction-sealed, aluminium foil liner. Each bottle contains four tablets, a canister or sachet containing three-gram silica gel desiccant, and polyester coil packing material.

The packaging materials comply with the Ph. Eur. and/or EU food regulation. Acceptable specifications have been provided. The bottle is child-resistant and evidence of its compliance has been demonstrated.

Manufacture of the product and process controls

Satisfactory GMP documentation of the sites of lenacapavir SDD and lenacapavir tablets has been provided.

The manufacturing process is a standard process consisting of spray drying (manufacture of lenacapavir SDD), blending, milling, granulation by roller compaction, milling, blending, tablet compression, film-coating and packaging.

The manufacturing process of the lenacapavir SDD consists of four main steps: feed solution preparation, spray drying, secondary drying and packaging. The manufacturing process of the lenacapavir tablets consists of four-unit processes: blending and milling, tableting, film coating and primary packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications includes appropriate tests for this kind of dosage form: appearance (visual), identification (UV, LC), water content (Ph. Eur.), assay (LC), degradation product content (LC), uniformity of dosage units (LC, Ph. Eur.) dissolution (Ph. Eur./in house), microbiological examination (Ph. Eur.).

The proposed control parameters are in accordance with ICH Q6A and the parameters suggested are considered as relevant for the dosage form.

Recommendations in relevant pharmacopoeia, ICH and EU regulatory guidelines, process capabilities and controls, development data, batch release data, and stability data of representative batches have been taken into considerations when establishing the acceptance criteria. The degradation products GS-833248, LENA-2078, GS-832077/GS-837509, GS-837322, GS-968750, and GS-1068699 are controlled as specified degradation products in the specification for lenacapavir tablets.

As explained under the active substance section, a reporting limit of 0.1%, an identification limit of 0.2% and a qualification limit of 0.2% calculated based on a maximum daily dose of 927 mg lenacapavir is accepted for the finished product, in accordance with ICH Q3B.

Assessment of potential mutagenicity for actual and potential degradation products, that might be present in lenacapavir tablets arising from the manufacture and storage of the finished product has been performed. Some alerting structures were identified, which were also found in the active substance or compounds related to the active substance (i.e. intermediates and impurities) which have been tested and found non-mutagenic.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Pd is used as a catalyst in the active substance process but has been shown to be routinely below 30% of the PDE threshold. Based on the risk assessment, and active substance data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and non-pharmacopoeial methods appropriately validated in accordance with the ICH guidelines. The same reference standards used for the active substance are used for lenacapavir tablets.

Acceptable batch analysis data for three pilot and seven production scale batches has been provided. All data complied with the specification limits confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from seven commercial scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines was provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the specifications reported in . The analytical procedures used are stability indicating. All results were within the specification limits, but small trends were seen with a decrease in water content and dissolution rate.

The stability program also includes lenacapavir tablets manufactured with lenacapavir SDD stored in bulk under not-controlled warehousing conditions for up to 36 months prior to tablet manufacturing. The long-term (12 months) and accelerated stability data (6 months) generated for these batches are comparable to the data from tablets manufactured with un-aged lenacapavir SDD.

Additional supporting data on tablets manufactured with aged lenacapavir SDD package in blisters supports the applicant´s approach to define the tablet date of manufacture as the date lenacapavir SDD is combined with excipients.

In addition, one commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. There was no difference observed in the test results for appearance, assay, degradation product content, and dissolution between the dark control and the test sample, apart from water content which was higher content on the test sample due to unprotected exposure, but still within specification. The data confirms that lenacapavir tablets are not photosensitive.

The tablets also complied with the specification after storage at – 20 °C for 1 month or at 50 °C for 2 weeks. There was no trend of loss in assay or increase in degradation product content for lenacapavir tablets in an open dish study at 30 °C/75% RH for 1 month.

Transportation of bulk tablets between manufacturing sites is proposed, and the impact of excursions outside of the defined storage conditions has been satisfactorily discussed and supported by stress stability studies.

Based on available stability data, the proposed shelf-life of 3 years with the following storage conditions: "Store below 30 °C. Store in the original package in order to protect from moisture." as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

4.1.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished products has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and the finished products and their manufacturing processes. Design spaces have been proposed for several steps in the manufacture of active substance. In view of the paediatric indication, the limit for endotoxins in the injectable formulation has been tightened during the procedure to address a MO raised by the CHMP. Additionally, during the procedure it was agreed that the proposed reporting, identification and qualification thresholds for the active substance and for each of the finished products can be accepted considering an MDD of 927 mg/day (i.e., the MDD of the subcutaneous injection). The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

4.1.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

4.1.7. Recommendations for future quality development

Not applicable.

5. Non-clinical aspects

5.1. Introduction

Lenacapavir (LEN, used in clinical drug formulations lenacapavir sodium) has been developed and approved for treatment of HIV-1 infected via subcutaneous depot (SC) and oral administration (Sunlenca). The present procedure concerns the use of LEN for the indication of pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg. The PrEP dosing schedule is similar to the Sunlenca setup where of the most noteworthy is that initiation and maintenance of treatment depends on SC injections every 6 months.

Non-clinical proof-of concept in-vivo studies for PrEP have been conducted and are assessed under the Pharmacology section. Pharmacological in-vitro studies have been assessed under the clinical sections. The non-clinical characterisation of the absorption, distribution, metabolism, and excretion (ADME) of LEN, using the intended clinical route of administration (oral and subcutaneous [SC]) in primarily rats, dogs, rabbits and monkeys is assessed under the (non-clinical) Pharmacokinetics section. Human toxicology (e.g., non-clinical safety studies) and Ecotoxicology (for environmental risk assessments) are discussed under the Toxicology section. All pivotal toxicology and ecotoxicology studies are of GLP status.

5.2. Analytical methods

For non-clinical pharmacokinetics and toxicokinetics purposes, LEN was quantified by HPLC-MS/MS in plasma from mouse, rat, dog, rabbit and monkey. Validation of the methods were performed in accordance with the guideline on bioanalytical method validation and the principles of GLP. Radioactivity in blood, plasma, urine, faeces, bile and tissues from ADME-studies of [14C]-lenacapavir in rats and dogs was assessed by liquid scintillation counting (LSC), quantitative whole-body autoradiography (QWBA) and/or profiling by LC-14C-HRMS. LEN in bile, faeces and urine from rats and dogs was quantified by a LC-MS/MS method. Viremic loads in the PrEP SHIV challenge models were measured using a PCR TaqMan method using primers specific to the gag gene of SIVmac251, ELISA, Intact proviral DNA assay (SHIV-IPDA, based on total genomic DNA being extracted from unfractionated PBMCs), and RT-PCR genotyping of capsid coding area of gag combined with population-level bulk sequencing.

5.3. Pharmacology

With regard to the pharmacological mechanisms of action for LEN, it is a selective multi-stage inhibitor of HIV-1 capsid functionality. The compound binds with high affinity to recombinant HIV-1 capsid proteins and increases both the rate and extent of in-vitro capsid assembly, resulting in the formation of poorly organized capsid polymers relative to assembly products formed in the absence of LEN.

5.3.1. Pharmacodynamics

5.3.1.1. Primary pharmacodynamics

For the purpose of supporting the PrEP indication (proof-of-concept), two in-vivo pharmacology studies have been conducted. Both studies used the Indian Rhesus macaque rectal SHIV challenge model (simian HIV infection via rectal route starting after dosing) but the first study used the LEN structural analogue GS-CA1 (at 150 mg/kg or 300 mg/kg SC, with repeated SHIV challenges starting 1-week post-dosing) – providing information on viral exposure levels for the second study - whereas the other was used LEN as test substance (single dose groups between 5 and 75 mg/kg SC, with a single SHIV challenge starting 7-week post-dosing). In the first study, after a total of n=15 SHIV challenges, 8/8 animals became infected in the placebo group, whereas 2/8 animals in the low dose group and 5/8 animals in the high dose group remained protected. The first study provided a basis for the viral exposure levels used in the second study. At least 50% infection rate per challenge corresponded to 77 TCID50.

For the LEN SHIV challenge model study, animals receiving doses between 5 to 20 mg/kg SC were only followed pharmacokinetically for a maximum of 14 weeks (as their LEN levels more rapidly fell below the paEC95 [8.8 nM] mark) while animals dosed at 50 and 75 mg/kg SC were followed for up to 25 weeks (see Pharmacokinetics section). After 7 weeks, 9 animals had LEN plasma levels below 2x paEC95 (the level, which is needed for inhibition of SHIV, based on GS-CA1 data). The remaining animals – n=3 or 4 from 20, 50 and 75 mg/kg SC groups - were assessed for prevention efficacy. No vehicle control group was used in this study, but data from SHIV-inoculated untreated animals was presented. Of the in total 11 animals challenged (at 100 TCID50 corresponding to 65.3% infection rate), 3 animals became viremic 2 weeks after challenge (2 in the 20 mg/kg group and 1 in the 75 mg/kg group). These animals had detectable SHIV RNA

as well as measurable antibodies and detectable intact proviral SHIV DNA in their plasma. LEN exposures among 11 challenged animals ranged from 18nM to 177nM. All infected animals had LEN levels below the rhesus adjusted clinical target C_{trough} concentration (<70 nM, statistically significantly lower in the infected group compared to the infected group, p = 0.005, unpaired t test with Welch's correction).

In-vitro primary pharmacodynamics studies are addressed in the Clinical section.

5.3.1.2. Secondary pharmacodynamics

Cytotoxicity of lenacapavir was investigated in various human cell types, including the MT-4 T-lymphoblastoid cell line, primary CD4+ T-lymphocytes, monocyte-derived macrophages, non-target cell lines and primary hepatocytes. The concentrations of LEN resulting in 50% cell death (CC50values) varied from 26 µM to more than the maximum concentrations tested, i.e. > 50 µM, and the corresponding selectivity indexes (CC50/EC50 for HIV-1) varied from 140 000 to >1 670 000. This indicates that the risk for cytotoxic effects at the human total and free C_{max} of 0.140 µM and 0.002 µM, respectively, after administration of the oral loading dose and a 927 mg subcutaneous dose is low. LEN (10 µM) was evaluated in an in vitro battery of 87 off-target assays. No significant responses (≥50% inhibition or induction) were observed for the tested receptors, ion channels, transporters or enzymes. The margin between the tested concentration of 10 µM and the human total and free C_{max} of 0.140 µM and 0.002 µM for lenacapavir, is approximately 70 and 5000-fold, respectively, which indicates a low potential for clinically significant off target effects.

5.3.1.3. Safety pharmacology

LEN was tested in a battery of safety pharmacology assays investigating effects on cardiovascular, central nervous system (CNS)/neurobehavior and respiratory function. Subcutaneous administration of lenacapavir to dogs in a 6-week GLP SC toxicity study showed no effects on blood pressure, heart rate or any of the ECG parameters including QT or QTC prolongation in conscious dogs up to a single dose of 100 mg/kg (free C_{max} of 39 ng/ml) and a repeated dose of 30 mg/kg. As LEN became a suspension at concentrations ≥ 0.1 µM in the DMSO/buffer vehicle used for the patch clamp technique no GLP hERG assay was performed. The applicant considers the cardiovascular evaluations in the dog toxicity study which showed no adverse effects on ECG or blood pressure at exposures 20-fold higher than the clinical free C_{max} of 1.98 ng/ml to be sufficient for assessment of the cardiovascular toxicity of LEN. Due to the low free plasma concentrations of LEN (free C_{max} of 0.002 µM) in the clinic, a hERG assay at ≤ 0.1 µM could have been useful. As no adverse cardiovascular effects were observed in dogs at exposures 20-fold the clinical free C_{max} and a human thorough QT study without significant effects at supratherapeutic doses of LEN is available, the lack of a hERG study is however considered acceptable. Taken together, LEN does not appear to have a potential for adverse cardiovascular effects.

SC-administration of LEN to rats in a 6-week GLP SC toxicity study showed effects on behavioural endpoints in a functional observation battery (FOB) and on locomotor activity at the lowest dose of 10 mg/kg. The NOEL of 100 mg/kg for CNS endpoints (see section for Non-clinical discussion). At a dose level of 100 and 10 mg/kg the free C_{max} was 2.70 and 0.54 ng/ml, respectively, which is 1.4 and 0.27-fold, respectively, the free C_{max} of 1.98 ng/ml obtained after the 6-months clinical oral and SC dosing regimen.

Single dose SC-administration of LEN to rats showed minor non-statistically significant increase in tidal volume and decrease in respiration rate at the highest dose of 100 mg/kg without affecting total ventilatory capacity. No LEN-related changes in tidal volume or respiration rate were noted at ≤ 30 mg/kg. Free C_{max} was estimated to 1.64 and 0.67 ng/ml at 100 and 30 mg/kg, respectively, which is 0.83-fold and 0.34-fold the clinical free C_{max} of 1.98 ng/ml, respectively.

It was noted that no safety concerns related to CNS, CV or respiratory function were found in the assessment of the clinical studies for LEN (see Clinical section below).

5.3.1.4. Pharmacodynamic drug interactions

See Clinical Pharmacology

5.3.2. Pharmacokinetics

5.3.2.1. Absorption

LEN showed low forward and high reverse permeability through monolayers of Caco-2 with evidence of efflux transport. Single dose pharmacokinetics of LEN in plasma following intravenous (IV), SC and oral administration were determined in male rats and dogs, the main toxicological species. Following IV administration of 1 mg/kg mean Vss (2.22 l/kg in rat and 1.96 l/kg in dog) was larger than that of total body water and mean plasma CL (0.045 l/h/kg in rat and 0.070 l/h/kg in dog) was low, 1 and 4% of hepatic blood flow in rat and dog, respectively, indicating wide distribution, low metabolism and a long t1/2. The mean plasma elimination half-life was estimated to 38 hours in rat and 30 hours in dog. As LEN has low aqueous solubility and low permeability across membranes various formulations (2% poloxamer 188 in normal saline [aqueous suspension], 77:10:13 w/w/w PEG200:ethanol:water [Solution Formulation A], 65:25.2:9.8 w/w/w PEG300:LEN:water [Solution Formulation B]) with various concentrations of LEN as free acid and sodium salt were tested for SC-administration. A sustained drug release with no prominent initial burst release, long T_{max} values and high relative bioavailability was observed both in rats and dogs. The mean t1/2 ranged from 219 to 403 hours in rats and from 66 to 525 hours in dogs, which are substantially longer than the mean t1/2 following IV administration, indicating flip-flop PK following SC-administration. As indicated by longer mean T_{max}-values (up to 672 and 448 hours in rat and dog, respectively), lower initial burst release (up to 1.3 and 1.6% of AUCinf on Day 3 in rat and dog, respectively) and lower F% (from 77 and 69% in rat and dog, respectively), the release and absorption of LEN from Solution Formulation A was somewhat more sustained than from the aqueous suspension. Administration of LEN sodium salt resulted in comparable mean AUCinf and mean %F relative to the free acid. Comparable exposure parameters were obtained for Solution Formulation A and Solution Formulation B in dogs indicating that the presence of ethanol did not have any significant impact on the release profile. Plasma exposure to LEN generally increased in an approximately dose proportional manner for rats (10-100 mg/kg) and less than dose proportional manner for dogs (6 to 100 mg/kg).

Following a single oral administration to rats (5 mg/kg) and dog (4 mg/kg) absorption was slow (mean T_{max} was 10 hours in rats and 11 hours in dogs) and absolute oral bioavailability was low (mean F% was estimated to approximately 15% in rats and 22% in dogs. Plasma pharmacokinetic parameters obtained from plasma sampled from portal and jugular veins of rats following an oral dose of 2 mg/kg were similar

and unaffected by pretreatment with ABT (a pan CYP p450 inhibitor) suggesting negligible hepatic extraction and negligible gastro-intestinal metabolism with a minor role for intestinal CYPs, i.e. that the low observed F% was related to limited absorption.

Repeated subcutaneous and oral administration to rats and dogs indicated no sex differences and a trend for accumulation following monthly subcutaneous administration to dogs and daily oral administration to rats and dogs. Following once daily oral administration the increase in exposure was less than dose proportional over the studied dose range in rats and between the mid and high dose in dogs.

In a Rhesus macaque rectal SHIV challenge model study, male animals were dosed with a single SC dose at 5, 10, 20, 50 or 75 mg/kg (n=4 males aged 3-5 years per group). LEN had a slow, sustained release and dose-proportional increase in exposure from 5 to 20 mg/kg and more than dose proportional increase from 50 to 75 mg/kg in macaque plasma. The 50 and 75 mg/kg doses had an C_{max} of 200 ng/mL and 530 ng/mL respectively. The corresponding AUC_{tlast} was 179 and 143 hxuM/mL, respectively, while the AUCinf was 284 and 367 hxuM/mL, respectively. The animals were followed only as long as their LEN plasma levels did not fall below the paEC95 mark of 8.8 nM. The 5, 10 and 20 mg/kg dose groups were therefore only monitored around 14 weeks. Only the 50 and 75 mg/kg dose animals were followed for the maximum of 25 weeks. The LEN half-life was in the range of 17-53 days following the single SC dose. The T_{max} was between 102 and 408h, showing an inverse dose relationship with the longest T_{max} at the lowest dose (5 mg/kg SC).

5.3.2.2. Distribution

Tissue distribution in albino and pigmented rats following a single IV administration of 3 mg/kg was evaluated by QWBA. The pattern of [14C]-LEN-derived radioactivity was similar in albino and pigmented rats with a rapid and wide distribution. Generally, the radioactivity was preferentially distributed into organs of elimination with the liver containing the highest concentration of radioactivity of the tissues sampled. Radioactivity was cleared from all tissues except liver by 672 hours (28 days) post-dose and from liver by 1344 hours (56 days) post-dose. No quantifiable or low levels of radioactivity were detected in brain and testes, respectively, suggesting that distribution of [14C]-LEN-derived radioactivity was restricted by the blood to brain and blood-to-testes barriers. No significant binding to melanin-containing tissues, e.g. pigmented uveal tract and pigmented skin, was observed. Binding of LEN to plasma proteins determined in vitro at a concentration of 2 µM was high with less than 1.5% unbound lenacapavir for all tested relevant species (human, mouse, rat, rabbit, dog and monkey). Whereas the reported plasma protein binding for the animal species were determined at a relevant concentration (2 µM) with respect to observed C_{max} values in the toxicity studies (0.5 to 6 µM), the in vitro plasma protein binding reported for humans with a C_{max} of approximately 0.1 µM was not. For humans the plasma protein binding of 99.8%, i.e., a free fraction of 0.2%, obtained in vivo is considered more appropriate. LEN (0.5 µM) blood to plasma ratio (B/R) was similar across species with mean values ranging from 0.59 for rat to 0.67 for dog and a human B/R of 0.64, showing minimal binding to blood cells.

In a PPND study in rats treated with a single SC-administration on gestational day 6 plasma concentrations were detected in pups. The mean maternal to mean pup plasma concentration ratio on lactation day 10 was up to 6-fold. This indicates that LEN distributed to the nursing pups either via milk or via placental transfer from maternal systemic circulation, which is reflected in SmPC section 4.6 for breast feeding. No specific

studies of placental transfer or excretion into milk were provided, i.e., the potential for LEN to pass the placenta or to be excreted into milk is not known. This is reflected in SmPC section 5.3.

5.3.2.3. Metabolism

The in-vitro metabolism of LEN was evaluated in liver microsomes and hepatocytes of rat, dog and human and in vivo in rat, dog and human.

In-vitro

LEN was present as 2 atropisomers (1 and 2). The LEN atropisomer pattern was shown to be stable over time with a ratio of LEN 1 to total LEN approximately 18-23% in plasma and not influenced by binding proteins or enzymes.

LEN was relatively stable in liver microsomes and hepatocytes across species with a predicted hepatic extraction ratio of 3% or less. Whereas no metabolism was observed in human microsomes, a total of 4 metabolites formed via oxidation (M19), reduction followed by glutathione conjugation (M9) or oxidation followed by glutathione conjugation (M8) were tentatively identified in rat and dog hepatic microsomes. After incubation with rat, dog and human hepatocytes a total of 7 metabolites formed via conjugation with glutathione (M9, M10 and M11; subsequent to reduction), pentose (M29), hexose (M35), glucuronic acid (M13) and cysteine (M33; subsequent to reduction) were tentatively identified. No oxidative metabolites were detected. No metabolites were detected in dog hepatocytes. One of the 3 metabolites identified in human hepatic co-cultures, the hexos conjugate (M35), was not detected in rat hepatocytes.

In-vivo

No major metabolites (>10% of total drug related materials in plasma) were identified in plasma of humans following a single IV administration of 20 mg [14C]-LEN and no metabolite at 1% or above of total radioactivity was identified in plasma of rats and dogs following a single IV-administration of 3 mg/kg and 1 mg/kg [14C]-LEN, respectively, or of dogs following a single oral administration of 2 mg/kg [14C]-LEN. Unchanged LEN (as atropisomers 1 and 2 combined) represented a predominant part (approximately 99%) of the total radioactivity in plasma of rats and dogs. LEN was metabolised via multiple metabolism pathways and eliminated as a combination of metabolites (a cysteine-glycine conjugate [M1] and other conjugates with glutathione and glucuronic acid [including M8, M9, M10, M11 and M13]) via bile and parent drug via faeces of rats and primarily as unchanged drug in bile and faeces in dogs.

5.3.2.4. Excretion

Mass balance data were obtained from intact and bile-duct cannulated rats and dogs. The excretion routes in intact animals were consistent across species, with a majority of the excreted [14C]-LEN dose in faeces (> 86% of dose) and minor amounts in urine (< 1.0% of dose). For rats, biliary excretion represented a major route of the elimination via faeces (42 and 35% of the dose via bile and faeces, respectively) whereas in dogs intestinal excretion represented the major route of elimination via faeces (32 and 63% via bile and faeces, respectively). In the rat a major part of the [14C]-LEN-derived radioactivity in bile was represented by metabolites whereas a major part of the radioactivity in bile of dogs was represented by unchanged drug.

Excretion and pharmacokinetic parameter obtained following concomitant oral administration with a Pgp and BCRP inhibitor to rats suggest that intestinal secretion of LEN by P-gp is the primary mechanism for faecal excretion and a significant overall clearance mechanism of unchanged drug in rats as well as in dogs.

5.3.2.5. Pharmacokinetic drug interactions

Not addressed in the non-clinical section.

5.3.2.6. Other pharmacokinetic studies

Not applicable

5.4. Toxicology

The toxicological programme is intended to represent a proposed PrEP regimen (SC depot and oral) for sexually acquired HIV-1 in adults and adolescents (with body weight at least 35 kg). The toxicological animal models used are primarily rat, dog (Beagle) and rabbit. Both animal models demonstrated difficulties to achieve systemic exposure levels that were comparable or higher than human exposure levels. In the case of the dog, the hepatobiliary toxicity was dose limiting. It should be noted that the toxicological programme has in most cases not been conducted with the exact clinical formulations especially the SC-formulation (lenacapavir sodium 26.46% [w/w], PEG300 50.13% [w/w] and water) where several variations have been used in the toxicological studies (containing variations of combinations of PEG200, PEG300, P188, ethanol and/or NaOH). This is considered a weakness but still acceptable as all SC-exposure independent of exact formulation has generated more or less the same toxicity findings. Oral exposure did not generate any toxicity (repeat-dose toxicity or in DART-EFD).

5.4.1. Single-dose & repeat-dose toxicity

Mortality:

No rats or dogs died prematurely after a single LEN IV-infusion or after oral exposure. No rats died/were terminated after SC-exposure whereas some dogs (n=3) died/were terminated prematurely after two to four once monthly SC-doses (411 mg/kg, 309 mg/mL, PEG300 formulation). The animals demonstrated among other things yellow colour of oral mucosa or conjunctiva – effects that are attributed to hepatobiliary degeneration. One of the three animals had thickened gallbladder and discoloured liver, lungs, and kidneys. All animals had strongly altered hepatobiliary biomarker levels.

Clinical signs, body weight changes and food consumption:

#Rat: Rat given two IM-injections within 7d (5-10 0mg/kg) demonstrated muscle twitching and vocalisation. No similar behaviour was seen with SC-injections.

#Dog: In an acute toxicity study, dogs vomited (transient effect) after exposure (single IV-infusion, 30 min) at 10 mg/kg and 30 mg/kg. Dogs that there were given daily oral gavage exposure (1 to 30 mg/kg) for 4w demonstrated struggling behaviour at all doses (most pronounced during the first week). Dogs exposed to 4 doses SC (once every 2w, 10-100 mg/kg), demonstrated vocalisation, struggling, and barrel rolls at the

time of injection at all dose levels (with no signs between injections or by control animals). Animals at 100 mg/kg were terminated prematurely while 10 mg/kg and 30 mg/kg/dose were completed following anesthetisation. In a second study with a once monthly SC-exposure (20-40 mg/kg) for a maximum of 10 doses (alternating injection sites), dogs showed atonia in some exposure group animals during the first ~3 months plus transient (~5 min) distress signs across both controls and exposure groups, corresponding to e.g., vocalisation and barrel rolling. No explanation has been provided/identified that would explain the high sensitivity and manner of response of dogs except that the differences between studies may depend on the use of different formulations (use of P188 alternatively PEG200 and ethanol) and/or their interaction with lenacapavir. Overall, there were generally little or no changes in body weight and food consumption (mainly in IV acute toxicity studies and IV EFD rabbit study). Clinical signs following LEN-exposure were primarily observed in dogs.

Organ toxicity:

Based on the repeat-dose toxicity (and local tolerance) studies, the main target organs of lenacapavir in rats and dogs (and rabbit for local tolerance) are the liver and the skin (at the injection sites).

 # Adrenals: There were some observations on adrenals effects in dogs. After four SC doses (once every 2w, 10-100 mg/kg), there was a trend of increased absolute and adjusted adrenal weight in males (≥10 mg/kg) and females (≥30 mg/kg) at d57. There was also vacuolation in adrenal cortex in 1/3 males (only) at 10mg/kg. The effect was reversible. In a once monthly SC exposure study (130 and 410 mg/kg) there was also a trend of absolute and adjusted weight increase (24%-34%).

 # Heart/cardiovascular: One dog study (four doses SC, once every 2w, 10-100 mg/kg) included telemetry measurements between d1 and d82. There were no irregular changes in PR interval, QRS-duration, QT interval, corrected QT (QTc) interval, or heart rate. Nor were there any abnormal ECG waveforms or arrhythmias or irregular changes in blood pressure. This gives a 'cardiac' NOAEL of 100 mg/kg. There were also no signs of cardiac adversity in the human clinical assessment. It can be noted that no hERG in-vitro test was conducted.

 # Kidney: After once monthly SC-exposure in dogs, there was reversible minimal tubular dilation and degeneration at 411 mg/kg after two to three doses. There are no indications of human renal adversity in the clinical assessment.

 # Liver and gall bladder: Transgenic RasH2 mice exposed to a single SC-dose (30-300 mg/kg) demonstrated a significant increase (11-17%) in mean liver weight values (unadjusted and adjusted) after 13w recovery.

In male and female rats exposed to single IV infusion (30 min), there was a statistically significant increase in absolute and adjusted liver weight at 30 mg/kg (+8-11%) after 14d. This was correlated in females with increases in ALT and AST biomarkers at 10 and 30 mg/kg. There were no signs of liver changes in rats after 4w daily oral exposure (3-30 mg/kg) except for possibly an ~2136% increase in cholesterol at all doses (mainly in females). After one single SC dose (100 mg/kg) in rat followed by 4w recovery, there was an increased globulin levels (~20-30%) and decreased albumin:globulin ratio (~20-27%). After 4 SC doses (once per 2w, 10-100 mg/kg), there were no hepatic/-associated changes except an increase in cholesterol levels (~30%) at 100 mg/kg at d57 with signs of recovery at d85. There were no changes in hepatic biotransformation proteins (i.e., total cytochrome P450 content, CYP1A activity, CYP2B activity, CYP3A activity CYP2E activity, CYP4A activity, or UDPGT activity).

In male and female dogs, there was a statistically non-significant trend of absolute and adjusted liver weight increase at d2 and reduction at 14d after a single 30 mg/kg IV-infusion. There was hepatocyte degeneration in males (up to moderate grade) and females (up to slight grade) on d2 between 10 mg/kg and 30 mg/kg (minimal signs also at 3mg/kg in males and necrosis at 10mg/kg in females and at 30 mg/kg in males). The degeneration was characterised by enlargement (swelling) of centrilobular hepatocytes, with cytoplasmic pallor and vacuolation suggestive of hydropic change, and discrete eosinophilic intracytoplasmic inclusions. The hepatic findings were supported by a clear increase of AST, ALT and ALP biomarkers in all dogs on d2 at 10 mg/kg and 30 mg/kg (females also showed increase in GGT at 30 mg/kg). ALT biomarkers remained elevated after 2w at 10 mg/kg and 30 mg/kg. After daily oral exposure for 4w (1-30 mg/kg), there were no clear hepatic/-associated changes except for a hepatic CYP2B activity (~2x) in females at 30 mg/kg and possibly a weak increase in ALP in some animals at 30 mg/kg. There was also a trend of increased cholesterol levels (36-55%) in mainly males at 30 mg/kg. Four SC-doses (once every 2w, 10-100 mg/kg) did not give any clear hepatic changes in dog. There was trend of reduced liver weight in males and increased liver weight in females at 30 mg/kg. There were no direct liver effects after once monthly SC-doses (10-20 mg/kg) for a maximum of 10 doses. After 2-4 doses once monthly (411 mg/kg SC), some animals (n=3) were terminated prematurely based on likely hepatobiliary toxicity (see Mortality section above). In surviving animals (exposed/observed to d268 at 130 mg/kg SC, to d143 at 411 mg/kg SC), there was minimal to slight bile ductule/oval cell hyperplasia and minimal fibrosis at both doses plus vacuolar degeneration in hepatocytes and bile duct epithelium at 411 mg/kg. The gallbladder demonstrated minimal epithelial hyperplasia and slightly to moderate increased secretion into lumen and minimal to slight mononuclear cell infiltrate at ≥130 mg/kg and minimal mucosal oedema at 411 mg/kg. There were increases in hepatobiliary biomarkers at ≥130 mg/kg such as ALP (32%-276% at 130 mg/kg, 173%-2018% at 410 mg/kg), ALT (59%-187% at 130 mg/kg, 118%-1076% at 410 mg/kg), GGT (25%-100% at 130 mg/kg, 67%-1067% at 410 mg/kg), bile acids (133%-1300% at 130mg/kg, 200%-7700% at 410 mg/kg) and possibly cholesterol (37%-56% at 410 mg/kg in males). This dog study – which uses the same formulation content as the clinical SC formulation - had the most clearly established hepatobiliary toxicity and the associated NOAEL<130 mg/kg gives an unadjusted-AUC 'hepatobiliary' safety margin to humans of roughly between ~1x (based on 20-40 mg/kg SC once monthly study without clear hepatotoxicity) and <11.5x (130-411 mg/kg once-monthly study with clear hepatotoxicity) (see also Toxicokinetics section below).

Overall, the toxicology studies indicate that LEN can generate hepatobiliary effects in rats, dogs and possibly mice if achieving sufficient systemic exposure. That being said, clear hepatotoxic effects beyond changes in organ weight or biomarker elevation were only seen in dogs after IV exposure (max 30 mg/kg IV) or after high dose SC exposures (410 mg/kg). The severity of the liver effects in dogs may be linked to the LEN inhibition of dog Bile Salt Export Pump (BSEP) protein transporter (IC50 0.12uM).

 # Reproductive organs: See DART discussion.

 # Skin/injection sites: See Local tolerance discussion.

 # Stomach: After once monthly SC-exposure in dogs, there was mucosal atrophy/degeneration at 411 mg/kg after two to three doses. The NOAEL<130 mg/kg gives an exposure margin to humans of roughly <11.5x (unadjusted AUC).

 # Behaviour: No dedicated neural safety pharmacology studies have been conducted. Nervous system endpoints (behaviour) were included in a repeat-dose toxicity study in rat (four SC doses between 10 mg/kg

and 100 mg/kg, once every 2w, n=10 males/group). The rats manifested a general (non-dose-response) trend of reduced elicited approach response (no sign in controls) at all doses until last observation on d81 and reduced locomotor activity most clearly at 10 0mg/kg (twice the extent than controls) until d81. The 10 mg/kg dose correlates an average AUC0-336h of 120000 ng x h/mL and a C_{max} of 419 ng/mL, which gives an exposure margin to humans of roughly 0.43x (unadjusted AUC), 5.6x (adjusted AUC) and 3x (C_{max}).

5.4.2. Genotoxicity

LEN did not generate any mutagenicity or clastogenicity signal in Ames test, In-Vitro Human Lymphocyte Chromosome Aberration Assay or after four doses (SC) once per two weeks in a rat in-vivo micronucleus test (measurement of polychromatic erythrocytes). The latter study used a max-dose of 100 mg/kg which corresponded to an average AUC0-336h of 583000 ng x h/mL. In a dedicated impurity qualification study using a single SC-dose of 100 mg/kg followed by 13w recovery, there was no increase in micronucleus levels 46-70h post-dose (corresponding to an average AUC0-672h 569000616000 ng x h/mL, AUC0-2184h 640000-987000 ng x h/mL, and C_{max} 1470-2350 ng/mL).

5.4.3. Carcinogenicity

There were no neoplastic outcomes in a 6-month rasH2 transgenic mouse study at LEN doses of up to 300 mg/kg/dose once every 13 weeks but a 104w rat carcinogenicity study with LEN (SC between 102 and 927 mg SC, injected in dorsal regions at different sites on different days, once per 13-weeks) found that primary sarcomas were generated in LEN-exposed animals. No systemic neoplasms were detected in the latter study. These neoplasms were not generated by vehicle. The details of the study results are described in the Sunlenca section SmPC 5.3 and also in the proposed SmPC section 5.3 text for the PrEP indication:

> *"In a 2-year rat carcinogenicity study, there were lenacapavir-treatment induced subcutaneous primary sarcomas associated with fibrosis and inflammation present at the injection sites in animals administered 927 mg/kg/dose once every 13 weeks. 11/110 animals manifested sarcomas at the high dose where each animal had up to 16 injection sites – corresponding to an incidence of <1% total injection sites across animals at the high dose. Drug concentrations in the injection depot sites are difficult to determine but systemically, the 927 mg/kg dose corresponds to 44 times the exposure in humans at the RHD. At the no-observed-adverse-effect level (NOAEL), the 309 mg/kg/dose corresponds to 25 times the exposure in humans at the RHD. Rats are prone to sarcoma formation at the subcutaneous injection site, but a clinical relevance cannot be excluded considering the long duration of the drug depot in humans. There were no neoplasms associated with systemic exposure to lenacapavir at any dose."*

5.4.4. Developmental and reproductive toxicity

A standard Developmental and Reproductive Toxicity (DART) test set was conducted for LEN. The fertility and early embryonic development (FEED, segment I) study assessed the effects from a single SC-administration (20 mg/kg or 100 mg/kg) in both male (6 weeks prior to mating) and female (4 weeks prior to mating) Sprague Dawley rats – generating a maternal exposure period that included the premating

period through conception and implantation. There were no adverse effects in female or male reproductive endpoints or on early embryogenesis, giving a NOAEL of 100 mg/kg (LOAEL > 100 mg/kg) corresponding to an average AUC0-672h of 231000 ng x h/mL an C_{max} of 587 ng/mL, and a human exposure margin of 0.83x (unadjusted AUC0-672h) and 5.4x (adjusted AUC0-672h).

The teratogenicity of lenacapavir was investigated for oral exposure in rats (daily oral gavage between gestational days [Gd] 6 and 17 at doses 3, 10 and 30 mg/kg) and for intravenous exposure in rabbits (daily IV-infusions between Gd7 and Gd19 at doses 5, 10 and 20 mg/kg). Oral exposure, representing clinical exposure on the first 2 days of treatment, did not generate any maternal or embryofoetal toxicity, giving an oral NOAEL of 30 mg/kg (and a LOAEL of >30 mg/kg) corresponding to an AUC0-24h of 22000 ng x h/mL, a C_{max} of 1210 ng/mL, and a human safety margin of 0.08x (unadjusted AUC0-24h) and 14.4x (adjusted AUC0-24h).

In rabbits, daily IV-infusions between Gd7 and Gd19 generate maternal toxicity at the low dose of 5 mg/kg (discoloration, bruising and scabbing, extensively reduced body weight and food intake; maternal NOAEL <5 mg/kg IV) but there were no clear embryofoetal toxicity findings (embryofoetal NOAEL 20 mg/kg and LOAEL >20 mg/kg IV). No toxicokinetics were assessed, but a similar nonpivotal rabbit study gave a 5 mg/kg AUC0-24h of 26600 ng x h/mL and C_{max} 7120 ng/mL (with unadjusted AUC0-24h margin of 0.1x and adjusted AUC0-24h margin 17.4x) and a 20 mg/kg AUC0-24h of 178000 ng x h/mL and C_{max} 45700 ng/mL (unadjusted AUC0-24h margin of 0.64x, adjusted AUC0-24h margin 182x).

For the assessment of long-term development toxicity effects from prenatal exposure, a prenatal and postnatal development (PPND) rat study was conducted. Exposure of single SC injection (30 or 300 mg/kg SC) occurred already in the F0 dams on Gd6. The F0 mothers were then followed to weaning (postnatal day [PND] 21) and the F1 offspring was assessed on PND21 and finally terminated on PND114-118 (males) alternatively on GD15 (females, after a successful mating event). There were some adverse effects in the F0 dams (swollen trunk, scabbing) at both tested doses, but no developmental or reproductive toxicity in the F1 offspring. This gives a F1 NOAEL of 300 mg/kg (LOAEL > 300 mg/kg SC) corresponding to an average AUC0-192h of 54800 ng x h/mL, an C_{max} of 412 ng/mL, and a human safety margin of 0.20x (unadjusted AUC0-192h) or 4.5x (adjusted AUC0-192h). The systemic exposure for 300 mg/kg between rat dams and PND10 offspring was ~5-6x more in mother compared to pups.

An oral gavage rat juvenile toxicity study (GLP) used doses at 3, 10 and 30 mg/kg for an exposure between PND7 and PND55 (plus 4-week recovery for control and 30 mg/kg groups until PND84). There were no clear signs of toxicity at any exposure dose – giving a NOAEL of high dose 30 mg/kg (combined male+female C_{max} 3080 ng/mL and 2440 ng/mL at PND7 and PND55 respectively, combined male+female AUC24h 60 600 ngxh/mL and 42 600 ngxh/mL at PND7 and PND55 respectively). Besides minimal increases in cholesterol on PND 56 in males at 30 mg/kg/day and females at ≥10 mg/kg/day, it can be noted that there were 15 unscheduled deaths (9 in main study, 6 in TK animals), of which 12 were probably related to gavage accident or gavage-related reflux. The cause of death in the other 3 animals was undetermined, making it – in absence of any other clear toxicological profile or indicators - unlikely of there is a LEN-based toxicity link. Systemic exposure to LEN increased with the increase in LEN dose level from 3 to 30 mg/kg/day. The increases in C_{max} and AUC0 24h were generally dose proportional from 3 to 30 mg/kg/day on PND 7 and 55 with the exception of AUC0-24h on PND 55 from 10 to 30 mg/kg/day which was less than dose proportional. After multiple doses of LEN in rats, less than 2-fold accumulation was observed at dose levels of 3 and 10 mg/kg/day while no accumulation was seen at 30 mg/kg/day.

With regard to reproductive organ toxicity in the acute toxicity and repeat-dose toxicity studies, there were some epididymis, prostate, and ovary findings in dogs. A single IV-infusion LEN-dose of 30 mg/kg in dogs generated a trend of reduced epididymis weight (unadjusted and adjusted) at 30 mg/kg. A once monthly exposure of dogs (SC, 130 mg/kg until/terminated at d268, 410mg/kg until/terminated at d143) generated a reduction in absolute and adjusted prostate weight (39%-41%) at 130mg/kg and cellular debris in epididymis lumen at 411 mg/kg. Ovary weight (adjusted) was also reduced (34%-46%) at 130 mg/kg. The relevance of these findings is unclear.

5.4.5. Toxicokinetics and exposure margins

For animal-to-human exposure margins, a clinical C_{max}d1-w26 is 136.2 ng/mL and AUC d1-w26 of 277902.9 ng x h/mL has been used. Both rat and dog studies indicated no consistent sex-differences in systemic exposure, dose accumulation over time, and that it is difficult to achieve higher levels of systemic exposure compared to humans.

#Rat: The NOAEL or LOAEL exposure (unadjusted AUC) margins were 0.12x (daily oral exposure for 4w at 30 mg/kg), 0.81x (single IV injection at 30 mg/kg), 0.43x-1.11x (single or two SC-injections at 10 or 100 mg/kg). Among studies, the lowest LOAEL was 10mg/kg (SC, NOAEL<10 mg/kg) after 4 doses, once every two weeks – corresponding to an average AUC0-336h of 120000 ng x h/mL and a C_{max} of 419 ng/mL and an exposure margin of 0.43x. The rat repeat-dose toxicity study most similar to the human dosing regimen used two SC injections at 100 mg/kg with 13w recovery after each injection. This gave a T_{max} of 728-1230h, an average AUC0-672h of 284000-307000 ng x h/mL and C_{max} 451-780 ng/mL on d92, and an exposure margin of ~1x (unadjusted AUC) or 6.64x-7.18x (adjusted AUC). A juvenile oral gavage rat study (3 to 30 mg/kg/d) between PND7 and PND55 gave a NOAEL of 30 mg/kg/d corresponding to a male+female combined AUC average of 60,600 h x ng/mL at PND7 and 42,600 h x ng/mL for AUC0-24h. T_{max} between 3h and 8h. The increases in C_{max} and AUC0 24h were generally dose proportional from 3 to 30 mg/kg/day (oral) on PND 7 and 55. Sex-based differences were less than 2-fold in LEN C_{max} and AUC0-24h values. After multiple doses of GS-6207 in rats, 1.8- and 1.3-fold accumulation was observed at dose levels of 3 and 10 mg/kg/day, while no accumulation was seen at 30 mg/kg/day (0.7-fold).

In a rat study for impurity qualification (single SC dose followed by 13w recovery), the NOAEL of 100 mg/kg corresponding to an average AUC0-672h 569000-616000 ngxh/mL, AUC0-2184h 640000-987000 ngxh/mL, and C_{max} 1470-2350 ng/mL. This gave an exposure margin to humans of roughly 2.05x-3.55x (unadjusted AUC0-672h) or 13.1x-14.4x (adjusted AUC0-672h).

#Dog: The NOAEL or LOAEL exposure (unadjusted AUC) margins were 0.27x (daily oral exposure for 4w at 30 mg/kg), 0.13x (single IV injection at 30 mg/kg), <0.43x (four SC-doses once every two weeks, NOAEL <10 mg/kg), <0.96x-1.27x (once monthly SC-doses, NOAEL <20 mg/kg), and <11.5x (once monthly SC doses, NOAEL <130 mg/kg). Among studies, the lowest repeat-dose toxicity dose was 10 mg/kg (four SC-doses once every two weeks, NOAEL <10 mg/kg) corresponding to an average AUC0-168.5h of 118000 ng x h/mL and a C_{max} of 641 ng/mL and an exposure margin of 0.43x (unadjusted AUC) or 10.19x (adjusted AUC). The T_{max} for the once per month SC exposures was 172541h (20 mg/kg) and 424-588h (130 mg/kg). For the study with the most serious toxicity (dog 37w exposure), the applicant calculates a margin of 51x, and it is not exactly clear how this number has been generated (3200 ugxh/mL x 6.5 / 278 ug/mL = 74.8x).

Either way, the safety margin for the hepatobiliary toxicity in dog has a large, adjusted safety margin and somewhere between ~1 and 11x for non-adjusted safety margins.

A time-adjusted AUC (human: 26w) is used for safety margin calculations (e.g., 13 x AUC0-336h or 6.5 x AUC0-672h). The exact relevance for such adjustment is somewhat uncertain considering the complexity of oral and SC-exposure plus depot dosing design and absence of steady-state in relation to the experimental designs of the tox-studies. Time-adjusted safety margins give a clearly greater safety margin compared to unadjusted. This issue may be relevant for the primary internal organ toxicity of concern (i.e., hepatobiliary toxicity in dogs where unadjusted exposure margins for hepatobiliary toxicity in dogs are somewhere between ~1 and 11x) and possibly developmental/reproductive toxicity.

Margins of exposure are based on the C_{max} and $AUC_{Day1\text{-}Week26}$ after 600 mg oral dosing and 927 mg SC administration on Day 1 and 600 mg oral dosing on Day 2 in the POP-PK study with lenacapavir.

The exposure (adjusted AUC) margins achieved in the SC and oral studies in rats are 31x (daily oral exposure for 4w at 30mg/kg) and 6.7x (2 SC doses, 26-week study at 100 mg/kg). For juvenile rats, the adjusted AUC margin is 38x.

The exposure (adjusted AUC) margins achieved in the SC and oral studies in dogs are 68x (daily oral exposure for 4w at 30mg/kg) and 8.2x (four s.c. doses once every two weeks, NOAEL<10mg/kg), <8.5-8.8x (once monthly SC doses, NOAEL <20mg/kg), and <102x (once monthly SC doses, NOAEL <130mg/kg). This is considered sufficient.

5.4.6. Local tolerance

One of the clinical outcomes from Sunlenca treatments is that some patients develop slow- or non-resolving SC-injection site nodules whose nature at present are not fully understood and which should be subject to clinical monitoring (noted in Sunlenca and proposed PrEP indication SmPC 4.4). The injection sites are also of interest in the carcinogenicity assessment (see above).

In-vivo studies - Rabbit:

Repeated IV-infusions in pregnant rabbits (5-20 mg/kg) generated skin discoloration, bruising and scabbing. Five dedicated local tolerance rabbit studies using single SC-injections were conducting (using different doses between 50 mg/kg to 400 mg/kg, formulations and durations of observation periods between 4w and 39w). Independent of formulation, all studies reported the LEN-dependent manifestation of varying degrees of erythema and oedema (up to severe grade), and mixed cell and/or granulomatous inflammation (up to marked grade). Several studies also reported the presence of subcutis necrosis (up to marked level). Generally, the oedema and necrosis signs were most pronounced 4d and/or ~1 month after injection. Moderate levels of granulomatous inflammation were still seen 13w to 39w after a single injection for doses between 100 mg/kg and 400 mg/kg (50 mg/kg not tested beyond 1 month), which is noteworthy considering that the proposed clinical time interval between SC-doses is 26w. Greater test substance concentrations (between 200 mg/mL and 400 mg/mL) were correlated with oedema findings. The presence of NaOH seemed also to generate a more potent effect. All studies are considered to show adverse effects in rabbits without a NOAEL (LOAEL between 50 and 300 mg/kg depending on study).

One study used a single dose intramuscular injection (IM) where the impacts of 400mg to 500 mg LEN in three different vehicles were explored (first vehicle: 68.17% (w/w) polyethylene glycol (PEG-300) and

31.83% (w/w) sterile water; second vehicle: 61.89% (w/w) PEG-300, 28.89% (w/w) sterile water, 9.22% (w/w) poloxamer 188; third vehicle 53.37% (w/w) PEG-300, 24.94% (w/w) sterile water, 13.09% (w/w) poloxamer 188, and 8.60% (w/w) ethanol). The second rabbit study used the clinically relevant SC (but also IM) slow bolus administration at 500 mg LEN together with the PEG-300/sterile water/poloxamer 188/ethanol vehicle. In both studies, the animals were their own controls, with the vehicle controls injected on the left side (dorsal lumbar) whereas the lenacapavir doses were injected on the right side (dorsal lumbar). Dose sites were assessed histologically. In the first (IM-only) study, all animals manifested (after 30d) some reaction at the LEN injection sites (raised areas in nearly all animals, discolouration in one animals) but only one animal had a similar reaction in the corresponding vehicle-only site. Histologically, the LEN injection sites manifested up to moderate levels of inflammation, mineralisation and even necrosis in subcutis and skeletal muscle at d31 but much less so at d91 – indicating some degree of recovery in rabbits. A lesser degree of pro-inflammatory injection site effects were also seen in the vehicle-only sites independent of vehicle composition. In the second (SC and IM) rabbit study, the LEN SC injection sites tended to have more frequent signs of various adverse local effects (atonia, desquamation, erythema, eschar, and oedema; but no necrosis) than the IM sites. These outcomes were also present to a lesser degree in the vehicle-only sites (around one third of the LEN-site notations). Together, these studies indicate that that vehicle components in themselves are pro-irritation/inflammatory but that the drug formulations require LEN to generate a more marked adverse effect. It is noted that there were no clear differences in impact between vehicles in the IM-only study but that the common denominator across vehicles is PEG-300. In both of the latter studies, lenacapavir doses up to 500 mg were considered locally tolerable, since observed effects were of mild severity and reversible.

In-vivo studies – Rat:

In a rat acute toxicity study (single exposure 3-30 mg/kg IV-infusion over 30 min, LEN formulation with NaOH), the injection site demonstrated congestion/haemorrhage or necrosis plus cell inflammation, thrombus, oedema, and fibrosis 14d post-dose. Two SC-doses within a week (5-100 mg/kg) generated minimal to marked necrosis, surrounded by mixed cellular infiltrates in sub-cutis (primarily neutrophils, lymphocytes, and macrophages) at ≥5 mg/kg with dose-dependent severity. In a study using four once per 2w SC injections (10-100 mg/kg), the injection sites were thickened at ≥10 mg/kg and contained minimal to marked granulomatous inflammation until end of study (including recovery, d85). Rats exposed to two SC doses (100 mg/kg) with 13w recovery periods after each dose demonstrated scabs and thickened regions, slight to moderate oedema after injections 72h post-dose, plus minimal to moderate granulomatous inflammation and macrophage infiltrate (and minimal to slight necrosis in some animals) on d92 (end of first recovery period) and d183 (end of second recovery period). The effects were most clear in formulations with NaOH or a high concentration of 400 mg/mL.

In-vivo studies – Dog:

Two dose injections (between 3 and 30 mg/kg SC) in dog over 7d generated swelling, thickening, mass, and haemorrhage at all doses at the injection sites plus abscess formation at 10 mg/kg and 30 mg/kg. Four (4) SC doses (once every 2w, 10-100 mg/kg) generated raised areas and scabs mainly at 100 mg/kg on d57 but also subcutaneous infiltrates of epithelioid macrophage and minimal to marked granulomatous inflammation at ≥10 mg/kg on d57 and d85. After a once monthly SC-dose (10 or 20 mg/kg) for a maximum of 10 doses, dogs manifested slight to severe oedema and very slight to well-defined erythema, minimal to marked granulomatous inflammation, slight to moderate mixed cell inflammation, minimal to

moderate necrosis across all doses (≥10 mg/kg) at d88, d172 and d256. The necrosis was characterised by variably large area(s) of subcutaneous adipose tissue with fragmentation, saponification, and/or pale staining. In a similar study with once monthly SC exposure (doses 130 mg/kg and 411 mg/kg), the injection sites were discoloured and manifested granulomatous inflammation (minimal to marked) and necrosis (minimal to moderate) and fibrosis (minimal to slight) at 130 mg/kg on d268 and at 411 mg/kg on d143 (termination day for that dose).

Overall, the injection exposure to LEN generally generated long-lasting local effects of oedema, granulomatous inflammation, and necrosis (the last mostly within one-month post-dose). This is seen more or less consistently in rats, dogs, and rabbits.

5.4.7. Other toxicity studies

Antigenicity:

A total set of four skin sensitisation tests were conducted. Out of those, LEN was considered to be weakly positive in the Direct Peptide Reactivity Assay and positive in the human Cell Line Activation Test. The other two tests (ARE-Nrf2 Luciferase Test Method and Local Lymph Node Assay, LLNA) were negative. It can be noted that the LLNA used a topical solution of 10, 25 and 50% v/v LEN in dimethylforamamide applied to mice.

Phototoxicity:

A phototoxicity assessment of LEN in a Neutral Red Uptake Phototoxicity Assay. The PIF value was 2>PIF>1 and the MPE value <0.15. Based on ICH S10 guidance, such PIF and MPE values are of questionable toxicological relevance for systemic drugs. The relevance for a SC-depot that is supposed to provide a dosing interval of 26w and is linked to long-term local inflammation is more uncertain but as only one of the parameters was very slightly over the limit (PIF 1.12 >1) and the other is below (MPE<0.15), LEN is unlikely to have a phototoxic potential.

Impurities:

A relatively large number of impurities have been found and based on ICH Q3A (drug substance) and ICH Q3B (drug product) recommendations identified. The clinical formulation/dose of most toxicological relevance is the 927 mg SC as there will be a relatively high local exposure level in the tissue surrounding the depot. Four impurities were assessed for genotoxicity whereof two impurities were found to be positive for mutagenicity in Ames test (Ames non-positive impurities were also assessed for clastogenicity but were found to be negative). Most of the impurities have been qualified in dedicated qualification rat studies using single SC injections (test substance formulation with spiked impurities) with post-dose/recovery periods of 4w and 13w. This gives a qualification for most impurities to a NOAEL of 100mg/kg.

5.4.8. Ecotoxicity/environmental risk assessment

The ERA for LEN under Sunlenca – based on the 2006 CHMP ERA GL framework - encompassed a full Phase IIB assessment and concluded that LEN (experiments conducted on the sodium salt of LEN) was unlikely to be an environmental risk (based on risk quotients, RQ < 1) or a PBT/vPvB substance. For the proposed PrEP indication, the ERA has been restructured to account for the 2024 CHMP ERA GL. This involved new refined

environmental exposure estimates (based on member state maximum European HIV1 prevalence using Joint United Nations Programme on HIV/AIDS partnership estimates from 2023 in combination with PrEP fraction of the member state population estimates). For the Phase I+ PECsw, a maximum daily dose of 9.19 mg/d is used together with a refined Fpen [0.009] that combines the maximum prevalence [0.008] with the PrEP fraction of the population estimate [0.001] –giving a refined PECsw of 0.041ug/d. The new PEC values did not shift the RQ conclusions and the PBT assessment conclusions remain the same as the Sunlenca ERA.

LEN has a molecular weight of 990.3 g/mol. Its water solubility is 3.79 ug/L (or 3.79ng/mL) which makes it a substance of low aqueous solubility. This is supported by OECD TG123-generated log Dow values of 5.9 (pH 5), 5.3 (pH 7) and 3.6 (pH 9).

It can be noted that LEN was found to be very persistent in soils (DT50 in soil > 180d) and toxic in aquatic organisms (NOEC/EC10 values < 10 ug/L, with fish being most sensitive at NOEC 2.1 ug/L) but the OECD TG305 study does not indicate that LEN bioaccumulates in fish (BCF <100 L/kg). As such, while LEN has a Log Dow > 3, it is not an PBT/vPvB substance and there is also no need to conduct a secondary poisoning assessment in line with the 2024 CHMP ERA GL.

Table 4. Summary of main study results: Phase I

Substance (INN/Invented Name):	Lenacapavir (GS-6207)		
CAS-number (if available):	2189684-45-3		
PBT/vPvB screening			
Study type	***Test protocol***	***Result***	***Conclusion***
Bioaccumulation potential-log Kow	OECD TG123	5.9 at pH 5 5.3 at pH 7 3.6 at pH 9	Potential PBT: Y
PBT/vPvB assessment			
Property	***Parameter***	***Result***	***Conclusion***
Bioaccumulation	log Kow	5.3 at pH 7	potentially B
	BCFKlg	53-73 L/kg ww	Not B
Persistence	Ready biodegradability	No	potentially P
	DT50,X at 12°C DT50,X at 20°C	X d 475 – 1470 d	vP (soil)
Toxicity	NOECaquatic	2.1 ug/L	T
PBT/vPvB statement:	Lenacapavir is considered to be not PBT, nor vPvB		

Phase I			
Parameter	***Value***	***Unit***	***Conclusion***
PEC_{sw}, refined	0.041	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 5. Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	***Test protocol***	***Result***	***Remarks***
Water solubility	OECD TG105	3.79 mg/L at 20 °C and pH7.5 to 7.7.	Column elution method
Dissociation in Water	OECD TG112	pKa, 1 = 5.46 pKb, 1 = 1.58 pKb, 2 = 3.73 pKb, 3 = 3.86	
Adsorption-Desorption Soil 1 = Speyer 2.2 (sandy loam)	OECD TG106	$K_{FOC, soil\ 1}$ = 137618 L/kg_{oc}	% OC was 0.65% to 1.78% for the soils and 33.6% to 35.6% for the sludges.
Soil 2 = Speyer 2.3 (sandy loam)		$K_{FOC, soil\ 2}$ = 236953 L/kg_{oc}	
Soil 3 = Speyer 6S (clay)		$K_{FOC, soil\ 3}$ = 125003 L/kg_{oc}	
Sludge 1 = Tilburg & Aa (municipal)		$K_{FOC, sludge\ 1}$ = 113277 L/kg_{oc}	
Sludge 2 = Maas (municipal)		$K_{FOC, sludge\ 2}$ = 128452 L/kg_{oc}	
Ready Biodegradability Test	OECD TG301B	8-10 % (28 d) Not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	NA	Not conducted. See instead OECD TG307.
Aerobic and anaerobic transformation in soil Soil 1 = CA Hanford (Loam)	OECD TG307	DT50, soil1 = 475d (1014d) CO2 = 0.84 % NERtotal = 16.8 % NERtype I = X %	at 20°C (and 12 °C) CO2 and NER values at test end
Soil 2 = DU-L-PF (Loam)		DT50,soil2 = 840d (1793d) CO2 = 0.41 % NERtotal = 11.5 % NERtype I = NA	at 20°C (and 12 °C) CO2 and NER values at test end
Soil 3 = Iowa Fayette (Silt loam)		DT50,soil3 = 693d (1479d) CO2 = 0.88 % NERtotal = 13.5 % NERtype I = NA	at 20°C (and 12 °C) CO2 and NER values at test end
Soil 4 = RMN-SL-PF (Sandy loam)		DT50,soil4 = 1470d (3138d) CO2 = 0.42 % NERtotal = 7.7 % NERtype I = NA	at 20°C (and 12 °C) CO2 and NER values at test end
Transformation products		>10% = N	

Phase II Aquatic effect studies					
Study type	***Test protocol***	***Endpoint***	***Value***	***Unit***	***Remarks***
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD TG201	NOEC	2.7	µg/L	Limit test. Growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD TG211	NOEC	3.1	µg/L	Max concentration for all endpoints.

Fish, Early Life Stage Toxicity Test/ Fathead minnows (*Pimephales promelas*)	OECD TG210	NOEC LOEC EC_{10}	2.1 3.8 3.4	µg/L	Growth (weight)
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	1000	mg/L	Respiration
Phase II Sediment effect studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD TG218	NOEC LOEC EC_{10}	108 225 456	mg/kg_{dw}	Developmental rate
Phase II Soil effect studies					
Soil Micro-organisms: Nitrogen Transformation Test	OECD TG216	NOEC LOEC	1000 >1000	mg/kg dw	at day 28 <10% reduction in NO3 formation rates.
Terrestrial Plants, Growth Test/ *Zea mays – corn* *Allium cepa – onion* *Brassica oleracea – cabbage* *Helianths annuus – sunflower* *Glycine max – soybean* *Lycopersicon esculentum – tomato*	OECD TG208	*Cabbage* NOEC LOEC EC25 -------- *Onion* NOEC LOEC EC25 -------- *Soybean* NOEC LOEC EC25	3.30 10 >10 10 >10 >10 500 >500 >500	mg/kg dw	After initial limit tests with all 6 species, pivotal studies were conducted for cabbage, onion and soybean. NOECs for the other species are 500 mg/kg dw. Affected endpoints: Emergence.
Earthworm, Chronic Toxicity Test/*Eisenia fetida*	OECD TG222	NOEC LOEC	1000 >1000	mg/kg_{dw}	Limit test. Survival & reproduction endpoints.
Collembola, Reproduction Test/ Springtails (*Folsomia candida)*	OECD TG232	NOEC LOEC EC50	1000 >1000 >1000	mg/kg_{dw}	Survival & reproduction
Phase II Secondary poisoning					
Bioaccumulation Test/Carp (Cyprinus carpio) Test 1 = 0.21 µg/L Test 2 = 2.1 µg/L	OECD TG305	BCF_k BCF_{kl} BCF_{klg}	23-27 49-62 53-73	L/kg_{ww}	Max %lipids: 3.4%
Mammal or Bird Test/	NA	NOAEL	NA	NA	NA

Species					
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	0.41 µg/L	100 mg/L	4.14×10^{-6}		No risk
Surface water	0.041 µg/L	0.21 µg/L	0.20		No risk
Groundwater	NA	NA	NA		NA
Sediment	980 ug/kg dw	20.22 mg/kg dw	0.05		No risk
Soil	10.8 ug/kg dw	0.33 mg/kg dw	3.27×10^{-2}		No risk
Secondary Poisoning	NA	NA	NA		NA

Considering the above data from Phase I and Phase II, Lenacapavir is not expected to pose a risk to the environment. Lenacapavir is not a PBT substance (although it can be noted that it is likely to be applied to agricultural soils via sludge and is very persistent in soils).

Based on available data the following statement is considered appropriate and proposed for the Summary of Product Characteristics (SmPC) and Package (Patient) Leaflet of the medicinal product.

> SmPC Section 6.6: *'Any unused product or waste material should be disposed of in accordance with local requirements.'*
>
> Package Leaflet: *'Do not throw any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.'*

This is supported by the rapporteurs (i.e., that based on the evidence presented, no specific environmental precautionary and safety measures are required).

5.5. Overall discussion and conclusions on non-clinical aspects

5.5.1. Discussion

Pharmacological aspects

A SHIV challenge study in Rhesus macaque provides proof-of-concept that LEN can prevent SHIV infection. That being said, the measured LEN plasma levels in the study do not provide a simple infection determinator as several non-infected animals also had LEN levels that where similar to those of the infected animals (at or below 70 nM). As n=2 infected animals came from the 20 mg/kg LEN group and n=1 from the 75 mg/kg LEN group, there was also no simple external dose-response (prevention of infection) correlation. Other pharmacological aspects are addressed in the Clinical section.

Pharmacokinetic aspects

The clinical dosing regimen for PrEP is similar to that of Sunlenca (the Sunlenca indication includes an additional 300 mg oral dose during the initiation of treatment compared to the proposed PrEP indication), so the ncPK-conclusions below, which are derived from the Sunlenca assessment and also considering the poor oral bioavailability of lenacapavir in humans, remain relevant.

Non-clinically, following oral administration of LEN, the PK curves were comparable for rat and dog and showed slow absorption with a C_{max} at 8 – 12 hrs, followed by a very slow elimination as indicated by the almost flat PK profiles (from 12h to T_{last} (72h). The oral bioavailability (Fpo) originally listed as about 22% based on calculations using AUCinf was not considered accurately determined given the incomplete curves with respect to the long elimination time of the drug (>30 h) and a T_{last} of 72 h. Oral bioavailability of about 15% in rats and 22% in dogs estimated based on AUC_{last}, i.e. AUC0-72h, were higher than the ~6% – 10% in human.

Whereas the reported plasma protein binding for the mouse, rat, rabbit and dog were determined at a relevant concentration (2 µM) with respect to observed C_{max} values at relevant NOAELs in the toxicity studies (e.g., 0.4 to 6 µM in rats and dogs, 7 to 47 µM in rabbits), the in-vitro plasma protein binding at 2 µM reported for humans with a C_{max} of approximately 0.1 µM was not. For humans the plasma protein binding of 99.8%, i.e., a free fraction of 0.2%, obtained in vivo is considered more appropriate. As the free fraction of lenacapavir in plasma of the toxicological species is comparable to or higher (0.13 to 0.83%) than the free fraction in humans (0.2%) the exposure margins calculated based on total plasma concentrations are considered adequate and do not need to be adjusted for plasma protein binding.

Toxicological aspects

The toxicological dossier (i.e., repeat-dose toxicity and local tolerance) identified the liver and the skin (at the injection sites) as the main target organs for lenacapavir. Severe hepatobiliary toxicity was only seen in dogs at higher systemic exposure levels (from intravenous or multiple high dose SC-exposures) but rats also displayed some liver-associated effects (mainly biomarkers). After 2-4 doses once monthly (411mg/kg SC), several dogs (n=3) were terminated prematurely based on likely hepatobiliary toxicity. The severity of the liver effects in dogs may be linked to the lenacapavir inhibition of dog Bile Salt Export Pump (BSEP) protein transporter (in-vitro IC50 0.12uM). Liver effects were indeed seen at doses that resulted in C_{max} and Cave values above the dog IC50 value. However, at doses that did not result in liver toxicity, for example 40 mg/kg for 9mo SC dosing and 30 mg/kg for 4w oral dosing, C_{max} values were also above the IC50 value. In fact, in the oral study similar C_{max} values were achieved as with SC dosing resulting in toxicity. The data may indicate that other mechanisms besides BSEP inhibition may be involved. It can also be noted that lenacapavir inhibition of the human BSEP is 10x less potent compared to the dog BSEP. The affinity for rat BSEP is unknown. It can be noted that there have been some findings on elevated cholesterol levels (in rats), but no such effects have been detected in human (see Clinical section). In humans, there were some infrequent transient biomarker signs indicating hepatobiliary effects but no clear hepatobiliary toxicity that would identify it as a serious adverse worth to consider. Overall, and considering that there seems to be limited dose accumulation in humans (leading to lower C_{max} levels), the risk for significant exposure-linked increases in bilirubin and total bile acid concentrations is deemed low and therefore not included in SmPC 5.3.

Regarding skin-effects and local tolerance, injection exposure to LEN generally generated long-lasting local effects of oedema, granulomatous inflammation, and necrosis in all animal models (rat, dog and rabbit, manifesting mostly within one-month post-dose). In Rabbit, which was used in the longest duration studies,

there were moderate signs of inflammation 39w after a single SC depot/injection. It can be noted that local tolerance effects similar to those from SC were also seen with IM administrations in rabbit. The studies in rabbits used clinically relevant concentrations and suspension formulations to screen prior to clinical use. Some of these studies demonstrated signs of reversibility. The studies used polyethylene glycol-based vehicles (PEG-300) and it can be noted that vehicle-only injections also generated pro-inflammatory conditions (although not as severe as with LEN). In humans, observations of injection site effects are considered an adverse drug reaction (e.g., site swelling, erythema, nodule, pain, induration, pruritus, discomfort, granuloma, extravasation, haematoma, oedema, and ulcer) but the magnitude/extent of the clinical side effects seem to be much milder than in the animal models. The nodules are slow- or non-resolving whose nature at present are not fully understood and which should be subject to clinical monitoring (noted in Sunlenca and proposed PrEP indication SmPC 4.4).

The Safety pharmacology assessment for nervous system toxicity was included in rat repeat-dose toxicity assessment. In this study, which the applicant has set the NOAEL to the max-dose of 100mg/kg, there was a clearly reduced elicited approach response (no sign in controls) at all doses until last observation on d81 and reduced locomotor activity most clearly at 100mg/kg (twice the extent than controls) until d81. There is some uncertainty around these findings but overall, they are considered to reflect an irregular control group rather than a toxicological effect. The response was not a clear monotonic one, the overall novelty seeking behaviour was uncommon, and some control animals behaved inconsistently. There was also an absence of other findings that would support neural changes (in the safety pharmacology assessment or in other studies).

LEN has not demonstrated any genotoxicity signals. While LEN was negative in a 6-month rasH2 transgenic mouse study, it generated neoplasms in a 104w rat carcinogenicity study (for all doses between 102 and 927 mg SC, injected in dorsal regions at different sites on different days, given once per 13-weeks). Primary sarcomas were found at the injection sites in LEN-exposed animals (no systemic neoplasms were detected) but not in vehicle-controls. Rats are historically/experimentally known to manifest sarcoma formation at SC-injection sites (with different agents, although there have been cases where there has been no sarcoma formation as well, indicating that there are agent specific criteria involved), so the extrapolation of the LEN findings to the human condition is not clear (i.e., while not an clear or obvious risk considering the rat tendencies for sarcoma formation, a risk can also not be fully dismissed/excluded at this stage of non-clinical/clinical knowledge). The details of the study results are described in the Sunlenca SmPC 5.3 and also in the proposed SmPC 5.3 text for the PrEP indication.

Two of the impurities were found to be mutagenic in an S9-dependent manner. An impurity induced mutation in three histidine-requiring strains (TA98, TA100 and TA1537), and one tryptophan-requiring E. coli strain (WP2 uvrA). Another impurity induced mutations only in histidine-requiring strain Salmonella typhimurium TA100. The clinical SC depot dose of 927 mg was considered the dose used as the premise for the maximum dose for impurity calculations for lenacapavir.

With regard to the DART studies, the choice of conducting repeated oral exposure in rat (which has low bioavailability) and IV exposure in rabbit means that, in practice, a setup where only one animal model has achieved a higher systemic exposure (i.e., rabbit). No teratogenic or clear embryotoxic effects were found although there was a slight reduction in foetal weight (<8%) which likely correlates to a body-weight gain reduction seen in maternal rabbits. The segment III study in rat with SC exposure from Gd6 achieved some higher systemic exposure and there no indications of prenatal toxicity. There is no information on the extent

of placenta passage, but the segment III study indicates that rat offspring (at PND10) are exposed to lenacapavir. An oral gavage juvenile toxicity study in rat (PND7-PND55 exposure window) did not find any clear toxicity. There were some sporadic enlarged liver findings among exposed males (1 per 9 or 10 animals/group), which may relate to the presence of liver biomarkers in rat repeat dose toxicity studies, and increased cholesterol levels (also seen in repeat-dose toxicity studies) but these outcomes were not considered sufficient to assign a LOAEL. The juvenile rat NOAEL AUC is 42 600 ngxh/mL. This gives a margin of 38x – based on that rat AUC0-24h × 28 × 6 (to adjust 24 hours to 168 days/6 months).

SmPC

Regarding non-clinical SmPC texts, it is acceptable that the proposed a SmPC 4.6 text describe that animal studies do not indicate direct or indirect harmful effects with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. The inclusion of the details (i.e., LEN-induced primary sarcomas at the injection sites) from the 104w carcinogenicity study in rats is also supported.

Environmental risk assessment

LEN was assessed in line with the 2024 CHMP ERA GL and found to be very persistent in soils (DT50 in soil > 180d), toxic in aquatic organisms (NOEC/EC10 values < 10 ug/L, with fish being most sensitive at NOEC 2.1 ug/L) but not an environmental risk (RQ<1) or a PBT/vPvB substance. A secondary poisoning assessment was not triggered.

5.5.2. Conclusions

There are no objections to an approval of Lenacapavir Gilead from a non-clinical perspective.

6. Clinical aspects

6.1. Introduction

6.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In both PURPOSE 1 and 2 there were participants who were found to be not eligible for inclusion in the randomised blinded phase of the study after screening, but who were randomised.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 3.4.3).

6.1.2. Tabular overview of clinical trials

Table 6. Tabular overview of main clinical studies

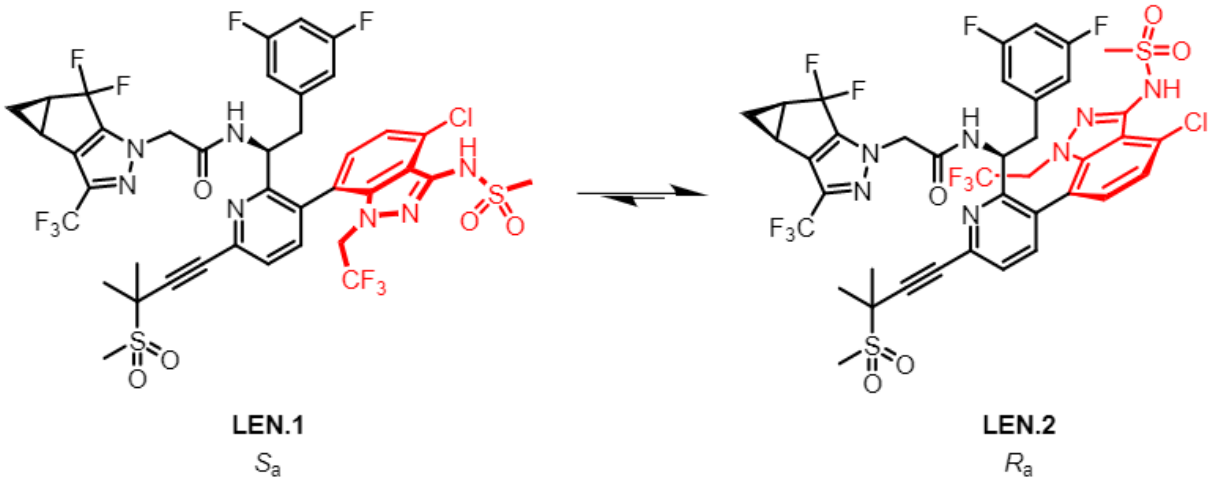
Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
GS-US-412-5624 (PURPOSE 1)	Randomized: 5368 LEN group: 2148 DVY group: 2147 TVD group: 1073 30 August 2021 (first participant screened) 08 May 2024 (last participant last visit for this report)	Phase 3, randomized, double-blind, multicenter study	LEN group: Oral LEN 600 mg on Day 1/Injection 1 and Day 2 (loading dose) SC LEN 927 mg every 26 weeks + PTM oral TVD or PTM oral DVY once daily starting on Day 1/Injection 1 DVY group: PTM oral LEN on Day 1/Injection 1 and Day 2 (loading dose) Oral DVY (F/TAF 200/25 mg) once daily + placebo SC LEN every 26 weeks starting on Day 1/Injection 1 TVD group: PTM oral LEN on Day 1/Injection 1 and Day 2 (loading dose) Oral TVD (F/TDF 200/300 mg) once daily + placebo SC LEN every 26 weeks	Cisgender adolescent girls and young women ≥ 16 to ≤ 25 years of age who have sex with cisgender males. <u>Incidence Phase:</u> HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months. Prior use of HIV PrEP (including TVD) or HIV postexposure prophylaxis [PEP] in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir) was not allowed. Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) were not eligible. <u>Randomisation Blinded Phase:</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 test (NAAT).

			starting on Day 1/Injection 1 Randomized Blinded Phase: planned minimum duration of 52 weeks LEN OLE Phase: planned duration of up to 65 weeks PK Tail Phase: up to 78 weeks	
GS-US-528-9023 (PURPOSE 2)	Randomized: 3292 LEN group: 2195 TVD group: 1097 28 June 2021 (first participant screened) 05 August 2024 (last participant last visit for this report)	Phase 3, randomized, double-blind, multicenter study	LEN group: Oral LEN 600 mg on Day 1/Injection 1 and Day 2 (loading dose) SC LEN 927 mg every 26 weeks + PTM oral TVD once daily starting on Day 1/Injection 1 TVD group: PTM oral LEN on Day 1/Injection 1 and Day 2 (loading dose) Oral TVD (F/TDF 200/300 mg) once daily + placebo SC LEN every 26 weeks starting on Day 1/Injection 1 Randomized Blinded Phase: planned minimum duration of 52 weeks LEN OLE Phase: planned duration of up to 65 weeks PK Tail Phase: up to 78 weeks	Cisgender men, transgender women, transgender men, and gender nonbinary ≥ 16 years of age who have sex with partners assigned male at birth. <u>Incidence phase:</u> HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months. Prior use of HIV PrEP (including TVD or DVY) or HIV postexposure prophylaxis in the past 12 weeks or any prior use of long-acting systemic PrEP (including cabotegravir or islatravir) was not allowed. Participants who previously received an HIV vaccine or HIV broadly neutralizing antibody (bNAb) were not eligible <u>Randomisation blinded phase:</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 test (NAAT).

6.2. Clinical pharmacology

Lenacapavir (LEN; GS-6207) is a first-in-class, multistage, selective inhibitor of HIV-1 capsid function. Lenacapavir is present as two atropisomers, LEN-1 and 2 (also named GS-6207-1 and 2) **Figure 2**.



LEN.1 and LEN.2 are assigned as S_a and R_a, respectively, according to the Cahn-Ingold-Prelog system.

Figure 2. Two atropisomers of lenacapavir

Two commercial formulations of lenacapavir are available: LEN tablets, 300 mg and LEN injection, 309 mg/mL. Lenacapavir tablets, 300 mg, were developed for oral administration, and are administered as a PK loading dose combined with the initial subcutaneous (SC) administration of LEN injection, 309 mg/mL. The intended commercial formulations were used in the phase 3 studies.

On treatment Day 1, the proposed recommended dose of LEN is 600 mg taken orally and 927 mg administered by subcutaneous injection. On treatment Day 2, the proposed recommended dose is 600 mg taken orally. Thereafter, the proposed recommended dose is 927 mg administered by subcutaneous injection once every 6 months from the date of the last injection.

6.2.1. Methods

Plasma and urine concentrations of lenacapavir (GS-6207) were determined with validated LC-MS/MS methods using deuterated lenacapavir (GS-833737) as internal standard. For lenacapavir in plasma, 2 analytical methods were applied with a different calibration curve range. Cross validation between the 2 methods showed comparable results.

6.2.2. Pharmacokinetics

6.2.2.1. Introduction

Lenacapavir is a known chemical substance, previously approved in combination with other antiretrovirals(s) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with multidrug resistant HIV-1 infection, under the Tradename Sunlenca®. This is a complete application for lenacapavir in a new population; people who would benefit from pre-exposure prophylaxis (PrEP), but in large the same clinical pharmacology documentation as for Sunlenca is submitted.

The proposed recommended dose for lenacapavir (simplified dosing regimen) differs during the first weeks of treatment compared with the recommended dose for Sunlenca. The simplified dosing regimen was investigated in a phase I study, GS-US-200-5709, and used in the two pivotal phase III studies (PURPOSE 1 and PURPOSE 2).

The primary roles of pharmacokinetics in this submission were to support efficacious and safe exposure in the indicated population (adults and adolescents ≥35 kg), during pregnancy, after administration at alternative injection sites, and during oral bridging. In addition, popPK and PBPK models are submitted to support dose adjustment when co-administrated with rifampicin and rifabutin.

The available data on alternative injection sites (thigh, upper arm and gluteal region vs abdomen) are limited (parallel single dose study in 40 healthy volunteers), displaying high variability. The lower 90% CI of the mean concentrations at week 26 (C_{trough}) crossed the target exposure (IQ4) of 15.5 ng/ml. The Applicant has committed to provide additional PK data for the alternative injection sites buttocks and upper arm post approval to support use of these injection sites (**REC**).

6.2.2.2. Evaluation and qualification of models

6.2.2.2.1. Population Pharmacokinetics

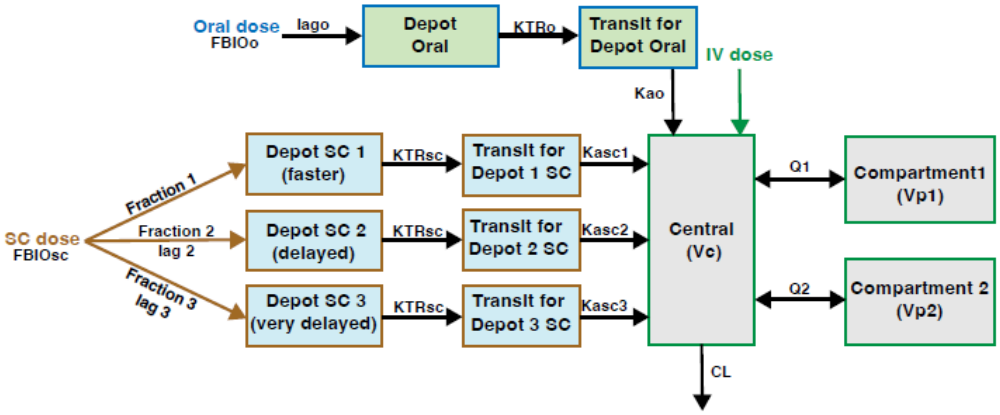
The population PK model for lenacapavir was fitted to pooled data from 9 Phase I studies in healthy participants, 2 Phase II/III studies in subjects with HIV-1, and 2 Phase III studies (PURPOSE 1, with data cut-off 28 February 2024; PURPOSE 2, with data cut-off 9 February 2024) in participants who would benefit from PrEP (PWBP). Only subjects that were administered 300 mg oral doses, 600 mg oral doses, and/or 927 mg SC doses, as well as subjects that received IV administration of lenacapavir, were included in the analysis. In total, 1337 participants contributed 14861 plasma samples, of which 213 samples (1.4%) were below the limit of quantification and were excluded from the analysis.

In PURPOSE 1, sparse PK sampling was conducted in a subset of the participants. The population PK analysis included 408 participants from PURPOSE 1, contributing 2002 quantifiable plasma concentrations. The participants in PURPOSE 1 consisted exclusively of females at birth — specifically adolescent girls and young women who have sex with partners assigned male sex at birth — aged 16 to 25 years (median age 21; 55 of 408 (13.5%) were < 18 years of age) and weighing between 37.9 and 161 kg (median body weight 60.2).

In PURPOSE 2, sparse PK sampling was conducted in a subset of the participants. The population PK

analysis included 534 participants from PURPOSE 2, contributing 2021 quantifiable plasma concentrations. The participants in PURPOSE 2 were predominately assigned male sex at birth (496, 92.9%), aged 17 to 74 years (median age 29; 3 of 534 (< 1%) were < 18 years of age) and weighing between 44.0 and 195 kg (median body weight 77.6).

A previously developed population PK model (QP-2023-1078 LEN PopPK) served as the base model in the analysis. Previously identified covariate effects were reassessed, and additional covariate effects were evaluated. The final model was a 3-compartment model with linear disposition and elimination, a transit compartment model for oral absorption, and three parallel absorption phases with increasing delays for SC absorption (). Model parameters were estimated using the stochastic approximation expectation maximization (SAEM) algorithm followed by importance sampling (IMP) in NONMEM. To enable estimation of systemic clearance (CL), an informative prior was incorporated, obtained by fitting only IV data to the model.



Abbreviations: CL = clearance; FBIOsc = subcutaneous bioavailability; FBIOo = oral bioavailability; IV = intravenous; Kao = oral absorption rate constant; Kasc1 = subcutaneous absorption rate constant from faster depot 1; Kasc2 = subcutaneous absorption rate constant from delayed depot 2; Kasc3 = subcutaneous absorption rate constant from very delayed depot 3; KTRo = oral transit compartment rate; KTRsc = subcutaneous transit compartment rate; lag2 = ALAGsc2 = subcutaneous lag time into absorption delayed depot 2; lag3 = ALAGsc3 = subcutaneous lag time into absorption very delayed depot 3; lago = ALAGo = oral lag time; Q1 = intercompartmental clearance to compartment 1; Q2 = intercompartmental clearance to compartment 2; SC = subcutaneous; Vc = central volume of distribution; Vp1 = volume of distribution of compartment 1; Vp2 = volume of distribution of compartment 2;

Figure 3. Structural model for disposition, oral absorption, and subcutaneous absorption of lenacapavir

The final model incorporated: fixed allometric scaling of body weight on all clearance and volume of distribution terms with exponents of 0.75 and 1, respectively; effects of cobicistat and ritonavir (pharmaco-enhancers/boosters) on systemic clearance (CL); effects of sex, ritonavir, of being highly treatment experienced, and of being treatment naïve on the second peripheral volume of distribution (Vp2); effects of dose and of being heavily treatment experienced on oral bioavailability (FBIOo); an effect

of food on oral absorption lag-time; and study effects on the residual error. The only covariate effects relevant for PWBP are the effects of body weight, sex, food, and dose (the effect of dose is only relevant during a potential oral bridging), as well as the study specific residual error. The parameter estimates for the final model are presented in **Table 7, Table 8, Table 9, Table 10, Table 11**, and **Table 12**.

Table 7. Fixed effect disposition parameter estimates for the final lenacapavir model

			Final model	Non-parametric bootstrap
			Estimate (% RSE)	Median (95% CI)
Structural Parameters				
CL (L/h)	θ_1	Clearance	3.44 (1.38)	3.44 (3.33, 3.53)
Vp2 (L)	θ_2	Volume of distribution of compartment 2	1621 (5.55)	1638 (1519, 1767)
Q2 (L/h)	θ_3	Intercompartmental clearance to compartment 2	47.1 (2.05)	47.7 (44.6, 51.7)
Vc (L)	θ_4	Volume of distribution of central compartment	4.31 (7.55)	4.24 (4.08, 4.46)
Vp1 (L)	θ_5	Volume of distribution of compartment 1	31.9 (3.58)	31.8 (30.4, 34.2)
Q1 (L/h)	θ_6	Intercompartmental clearance to compartment 1	63.2 (5.99)	65.3 (61.7, 71.3)

Table 8. Fixed effect oral absorption parameter estimates for the final lenacapavir model

			Final model	Non-parametric bootstrap
			Estimate (% RSE)	Median (95% CI)
Absorption Parameters				
KTRo (1/h)	θ_7	Oral transit compartment rate	0.0471 (4.36)	0.0479 (0.0428, 0.0548)
ALAGo_fasted (h)	θ_8	Oral lag time fasted	0.00100 (Fixed)	0.00100 (Fixed)
ALAGo_fed (h)	θ_9	Oral lag time fed	1.12 (0.832)	1.11 (0.954, 1.22)
Kao (1/h)	θ_{10}	Oral absorption rate constant	1.25 (3.66)	1.21 (1.12, 1.31)
FBIOo_600	θ_{17}	Oral bioavailability for 600 mg dose	0.0441 (5.10)	0.0444 (0.0396, 0.0495)
FBIOo_300	θ_{23}	Oral bioavailability for 300 mg dose	0.0699 (5.96)	0.0700 (0.0649, 0.0750)

Table 9. Fixed effect subcutaneous absorption parameter estimates for the final lenacapavir model

			Final model	Non-parametric bootstrap
			Estimate (% RSE)	Median (95% CI)
Absorption Parameters				
Kasc1 (1/h)	θ_{11}/1000	Subcutaneous absorption rate constant from depot 1 (faster)	0.00143 (4.45)	0.00147 (0.00136, 0.00163)
Kasc2 (1/h)	θ_{13}/1000	Subcutaneous absorption rate constant from depot 2 (delayed)	0.000386 (5.04)	0.000404 (0.000368, 0.000436)
Kasc3 (1/h)	θ_{12}/1000	Subcutaneous absorption rate constant from depot 3 (very delayed)	0.000437 (4.78)	0.000409 (0.000346, 0.000468)
KTRsc (1/h)	θ_{14}	Subcutaneous transit compartment rate	0.411 (4.26)	0.411 (0.383, 0.439)
ALAGsc2 (h)	θ_{16}	Subcutaneous lag time for depot 2 (delayed)	631 (1.38)	635 (608, 663)
ALAGsc3 (h)	θ_{15}	Subcutaneous lag time for depot 3 (very delayed)	1416 (1.53)	1444 (1358, 1523)
FBIOsc	θ_{18}	Subcutaneous bioavailability	0.909 (0.682)	0.909 (0.905, 0.912)
Fr1	$\theta_{19}/(1+\theta_{19}+\theta_{20})$	Subcutaneous fraction on depot 1 (faster)	0.116 (6.10)	0.113 (0.101, 0.125)
Fr3	$\theta_{20}/(1+\theta_{19}+\theta_{20})$	Subcutaneous fraction on depot 3 (very delayed)	0.371 (3.97)	0.369 (0.334, 0.406)

Table 10. Covariate fixed effect parameter estimates for the final lenacapavir model

			Final model	Non-parametric bootstrap
			Estimate (% RSE)	Median (95% CI)
Covariate Effect Parameters				
HTE on FBIOo	θ_{25}	Effect of highly treatment experienced status on bioavailability (proportional)	1.25 (8.72)	1.24 (1.10, 1.41)
Cobicistat on CL	θ_{27}	Effect of cobicistat on CL (proportional)	0.677 (9.31)	0.677 (0.593, 0.761)
Ritonavir on CL	θ_{28}	Effect of ritonavir on CL (proportional)	0.579 (9.75)	0.574 (0.514, 0.640)
Ritonavir on Vp2	θ_{43}	Effect of ritonavir on Vp2 (proportional)	0.384 (19.6)	0.388 (0.270, 0.591)
Female on Vp2	θ_{42}	Effect of female on Vp2 (proportional)	1.47 (5.56)	1.43 (1.30, 1.58)
HTE on Vp2	θ_{44}	Effect of highly treatment experienced status on Vp2 (proportional)	0.488 (13.4)	0.490 (0.376, 0.603)
TN on Vp2	θ_{45}	Effect of treatment naive status on Vp2 (proportional)	0.516 (9.21)	0.512 (0.435, 0.589)

Table 11. Interindividual variance parameter estimates for the final lenacapavir model

		Final model		Non-parametric bootstrap
		Estimate (% RSE)	Shrinkage (%)	Median (95% CI)
Variance Parameters				
IIV on CL	$\Omega_{(1,1)}$	0.105 [CV%=33.3] (5.56)	18.5	0.104 (0.0927, 0.116)
IIV on Vp2	$\Omega_{(2,2)}$	0.337 [CV%=63.3] (8.86)	36.3	0.328 (0.254, 0.425)
IIV on Q2	$\Omega_{(3,3)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Vc	$\Omega_{(4,4)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Vp1	$\Omega_{(5,5)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Q1	$\Omega_{(6,6)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on KTRo	$\Omega_{(7,7)}$	0.355 [CV%=65.3] (9.96)	54.3	0.362 (0.289, 0.449)
IIV on ALAGo	$\Omega_{(8,8)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Kao	$\Omega_{(9,9)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Kasc1	$\Omega_{(10,10)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on Kasc2	$\Omega_{(12,12)}$	0.706 [CV%=101] (10.1)	24.8	0.672 (0.568, 0.832)
IIV on Kasc3	$\Omega_{(11,11)}$	0.373 [CV%=67.2] (6.53)	45.0	0.403 (0.192, 0.724)
IIV on KTRsc	$\Omega_{(13,13)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on ALAGsc2	$\Omega_{(15,15)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on ALAGsc3	$\Omega_{(14,14)}$	0.0250 [CV%=15.9] (Fixed)	-	0.0250 (Fixed)
IIV on FBIOo (600 mg dose)	$\Omega_{(16,16)}$	0.290 [SD=0.0255] (9.53)	46.1	0.273 (0.224, 0.320)
IIV on FBIOo (300 mg dose)	$\Omega_{(16,16)}$	0.290 [SD=0.0375] (9.53)	46.1	0.273 (0.224, 0.320)
IIV on FBIOsc	$\Omega_{(17,17)}$	0.0250 [SD=0.0392] (Fixed)	-	0.0250 (Fixed)

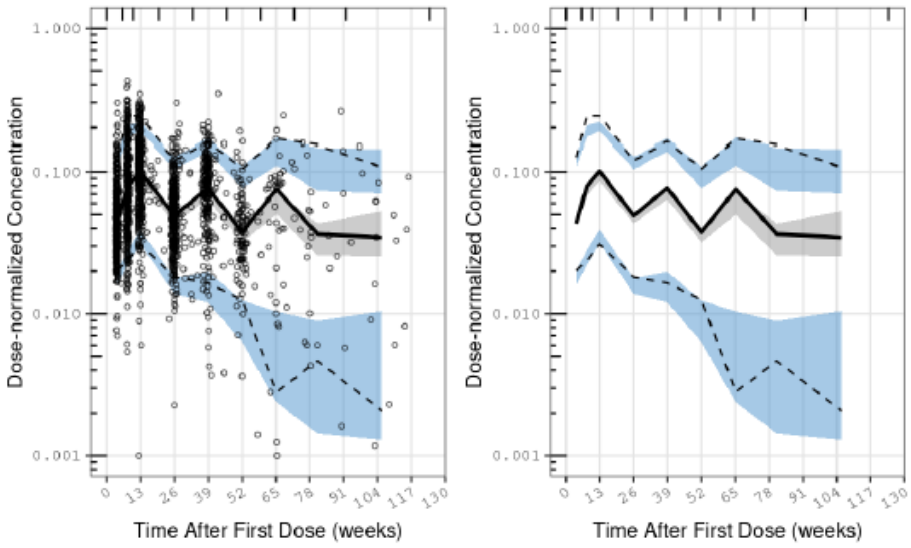
Abbreviations: CV = coefficient of variation; exp = exponential; IIV = interindividual variability; prop.=proportional; RSE = relative standard error; sqrt = square root; SD = standard deviation
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100

Table 12. Residual variance parameter estimates for the final lenacapavir model

		Final model		Non-parametric bootstrap
		Estimate (% RSE)	Shrinkage (%)	Median (95% CI)
Residual Variance				
Proportional error (Study GS-US-200-4329)	θ_{21}	0.151 (5.86)	-	0.152 (0.128, 0.180)
Additive error	θ_{22}	0.00100 (Fixed)	-	0.00100 (Fixed)
Effect of GS-US-200-4071 on prop. error	θ_{29}	1.58 (8.94)	-	1.57 (1.29, 1.94)
Effect of GS-US-563-6148 on prop. error	θ_{31}	1.43 (8.09)	-	1.42 (1.08, 1.76)
Effect of GS-US-200-4333 on prop. error	θ_{32}	1.15 (6.76)	-	1.14 (0.939, 1.38)
Effect of GS-US-200-4330 on prop. error	θ_{33}	1.50 (11.1)	-	1.50 (1.17, 1.91)
Effect of GS-US-200-4331 on prop. error	θ_{34}	1.57 (11.8)	-	1.55 (1.27, 1.94)
Effect of GS-US-200-5709 on prop. error	θ_{35}	1.19 (7.22)	-	1.18 (0.992, 1.43)
Effect of GS-US-200-4334 on prop. error	θ_{36}	1.92 (6.81)	-	1.89 (1.59, 2.28)
Effect of GS-US-200-4625 on prop. error	θ_{37}	2.50 (7.38)	-	2.45 (2.08, 2.92)
Effect of GS-US-200-4538 on prop. error	θ_{38}	0.913 (13.2)	-	0.899 (0.739, 1.08)
Effect of GS-US-200-4540 on prop. error	θ_{39}	1.01 (9.27)	-	0.972 (0.762, 1.23)
Effect of GS-US-412-5624 on prop. error	θ_{40}	1.67 (6.57)	-	1.66 (1.39, 1.98)
Effect of GS-US-528-9023 on prop. error	θ_{41}	1.48 (6.72)	-	1.47 (1.24, 1.75)
IIV on proportional error	$\Omega_{(18,18)}$	0.0518 [CV%=23.1] (11.5)	48.5	0.0495 (0.0390, 0.0606)

Abbreviations: CV = coefficient of variation; exp = exponential; IIV = interindividual variability; prop.=proportional; RSE = relative standard error; sqrt = square root; SD = standard deviation
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100
PURPOSE 1 = GS-US-412-5624 and PURPOSE 2 = GS-US-528-9023

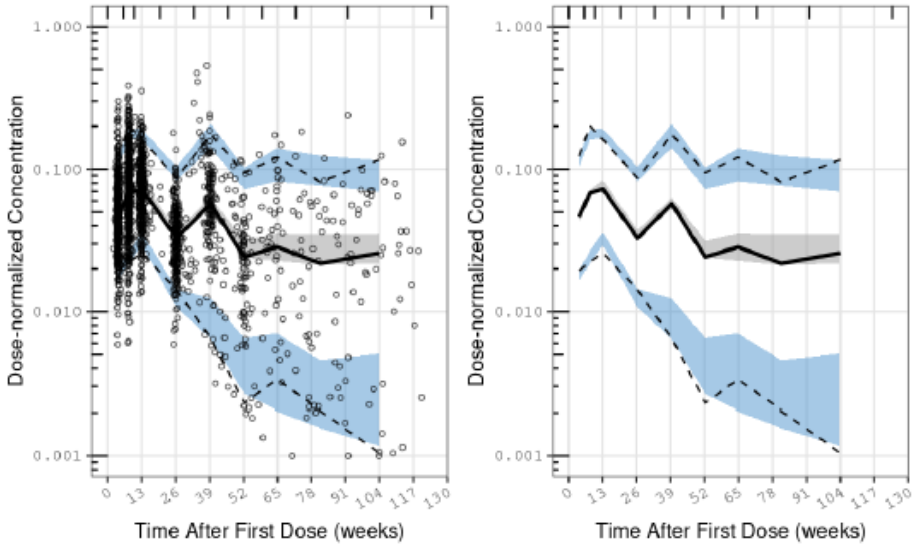
Dose-normalised visual predictive checks (VPCs) for participants in PURPOSE 1 and PURPOSE 2 are provided in **Figure 4** and **Figure 5**, respectively.



Source code: vpc-script-finalmodel.R
Source graphic: deliv/figures/report/vpcs/final/80/80-4125624-vpc.png

Abbreviations: VPC = visual predictive check
PURPOSE 1 = GS-US-412-5624
Each VPC shows the median (solid line) and 5th and 95th percentiles (dashed lines) of observed data and 90% confidence intervals of the median (grey) and 5th (blue) and 95th (blue) percentiles of model predicted simulations (shaded areas). Left shows the VPCs with observed data overlaid (each circle) and right shows the VPCs without observed data overlaid. All available data from PURPOSE 1 was included, including data collected during oral bridging and the PK tail phase.

Figure 4. Dose-normalised visual predictive check for the final lenacapavir model stratified on study PURPOSE 1



Source code: vpc-script-finalmodel.R
Source graphic: deliv/figures/report/vpcs/final/80/80-5289023-vpc.png

Abbreviations: VPC = visual predictive check
PURPOSE 2 = GS-US-528-9023
Each VPC shows the median (solid line) and 5th and 95th percentiles (dashed lines) of observed data and 90% confidence intervals of the median (grey) and 5th (blue) and 95th (blue) percentiles of model predicted simulations (shaded areas). Left shows the VPCs with observed data overlaid (each circle) and right shows the VPCs without observed data overlaid. All available data from PURPOSE 2 was included, including data collected during oral bridging and the PK tail phase.

Figure 5. Dose-normalised visual predictive check for the final lenacapavir model stratified on study PURPOSE 2.

6.2.2.3. Absorption

Lenacapavir is a Biopharmaceutics Classification System (BCS) Class 4 compound with low aqueous solubility and low apparent permeability with respect to dose. Lenacapavir is a substrate for P-gp.

The median t_{max} was 4 hours after administration of a single oral dose of LEN 50, 300 and 900 mg tablets to healthy participants (fasting conditions) (Study GS-US-200-4071).

Due to slow redissolution from the site of administration, the absorption profile of s.c. administered lenacapavir is complex, involving a combination of delayed and first-order absorption kinetics. The plasma concentrations increased slowly following a single subcutaneous dose of 927 mg LEN 309 mg/mL (NaS, injection volume 2 x 1.5 mL) to healthy participants, with a median (range) t_{max} of 84 days (70-109 days) (study GS-US-200-4538).

Bioavailability

No absolute bioavailability studies have been conducted with lenacapavir tablets or injection. The bioavailability was estimated based on the observed exposure of LEN in healthy participants following oral

(studies GS-US-200-4329 and GS-US-200-4071) and subcutaneous administration (study GS-US-200-4538) as compared to IV administration (study GS-US-200-4329). The observed oral bioavailability was approximately 10% following administration of LEN 300 mg.

Based on population PK modelling, the oral bioavailability for LEN 300 mg tablets was estimated to 7.0%, the oral bioavailability for LEN 600 mg tablets (2 x 300 mg) was estimated to 4.4%, whereas the SC bioavailability was estimated to 91%.

No comparative BA or BE studies have been conducted. The majority of the studies were carried out with the final 300 mg tablet formulation.

Simplified dosing regimen

Study GS-US-200-5709 evaluated the pharmacokinetics of lenacapavir after administration of the approved dosing regimen for Sunlenca (cohort 1) or a simplified dosing regimen as proposed for lenacapavir for PrEP (cohort 2). Both dosing regimens achieved concentrations above IQ4 within day 2. The time to maximum concentration (T_{max}) was slightly shorter for the simplified regimen (10 weeks, vs 12 weeks). The C_{max} was similar between the approved and the simplified dosing regimens. The total exposure (AUC0-inf) was 7.7% lower for the simplified regimen compared with the approved regimen, and the AUC over the period from sc injection to week 26 was 4.2% lower for the simplified regimen compared with the approved regimen. Mean plasma concentrations of lenacapavir were maintained above IQ4 (15.5 ng/ml including lower bound of 90% CI: 15.6 ng/ml) during the dosing interval of 26 weeks.

Alternative injection sites

A study (GS-US-200-4540) on alternative sc injection sites on the pharmacokinetics of lenacapavir was conducted in 40 healthy volunteers. The PK after single injections of 927 mg into thigh (n=10), upper arm (n=10) or gluteal region (n=9) was compared with PK after single injection into the abdomen (n=8; reference region). The C_{max} was similar for thigh and abdomen, but higher for upper arm and gluteal region (52.1 ng/mL, 56.7 ng/mL, and 75.6 ng/mL, and 71.2 ng/mL, respectively). Lenacapavir AUClast and AUCinf were 12% lower and 20% higher, respectively, for the thigh compared to the abdomen; 4% higher and 7% lower for the upper arm compared to the abdomen; and 18% and 11% higher for the gluteal region compared to the abdomen. The mean concentration at 6 months (C_{6mo}) was 22.6 (90% CI: 13.9-36.7) ng/mL, 18.7 (90% CI: 12.6, 27.8) ng/mL, and 25.2 (90% CI: 15.7, 40.4) ng/mL for the thigh, upper arm, and gluteal region, respectively, compared to 28.6 (90% CI: 17.9-45.6) ng/mL for the abdomen. The lower CI 90% bound of the mean concentration at 6 months was below the efficacy target IQ4 of 15.5 ng/ml at 6 months in the thigh cohort (13.9 ng/ml) and upper arm cohort (12.6 ng/ml).

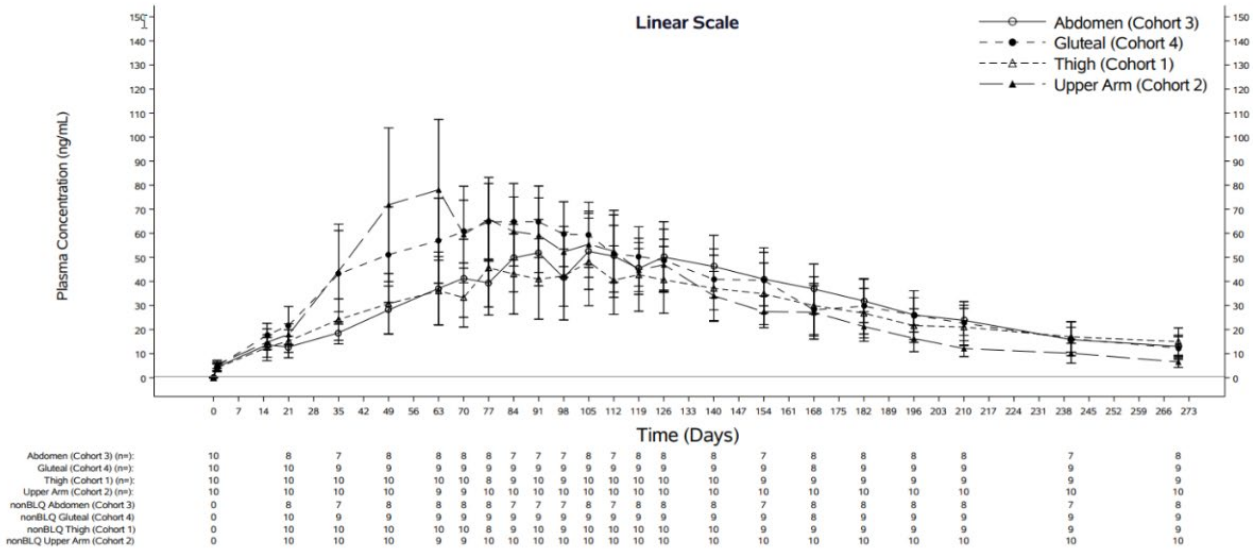


Figure 6. Mean (90% CI) plasma concentrations (ng/ml) of lenacapavir after sc administration at different injection sites (abdomen, gluteal region, thigh and upper arm)

In addition to the phase I study, sparse PK data was available from patients in PURPOSE 1, 3 and 4, who had received LEN via alternative injection sites. In general, the trough concentrations after the first LEN dose when administered in the thigh, upper arm or buttocks were within the range of those observed after injection in the abdomen. The amount of PK-data was however very limited after injection in arm or buttock.

Figure 7. Plasma LEN concentration following SC administration at alternative injection sites (upper arm, buttock, thigh) compared with abdomen as reference site (randomised blinded phase up to week 52 of PURPOSE 1 and 2)

Influence of food

The effect of food on oral LEN was evaluated in healthy volunteers with a high- or low-fat meal relative to fasted conditions using the 300 mg tablet formulation (intended commercial formulation, study GS-US-200-4071). The geometric least squared mean (GLSM) (90% CI) ratio for AUC_{inf} values were 115% (72 to 184%) and 99% (58 to 167%) for high-fat and light meals relative to fasting, respectively, whereas corresponding C_{max} GLSM ratios were 145% (78 to 270%) and 116% (55 to 242%), respectively, with similar range of t_{max} values compared to fasting.

In the population PK analysis, the absorption was estimated to be slightly delayed when oral LEN was administered together with food relative to fasting. The delay was not predicted to have any clinically relevant impact on the exposure.

Food effect was not evaluated for the solution formulation, as this is administered s.c. and no food effect is expected.

6.2.2.4. Distribution

The binding of LEN to plasma proteins was high with a fraction unbound (fu) of 1.46 ± 0.23% at 2 µM lenacapavir. Lenacapavir demonstrated very high binding to human serum albumin (HSA) with 0.01 ± 0.0% free and it bound moderately to α1-acid glycoprotein (AAG) with mean of 7.0% free at a typical level of 0.8 mg/mL AAG and 1.8 ± 0.1% free at a more pathological level of 4.0 mg/mL AAG. In pooled human plasma with AAG concentration of 0.86 mg/mL, fu was 0.70 ± 0.1%.

Binding to blood cells was minimal at 0.5 µM lenacapavir. The blood to plasma ratio was 0.64 ± 0.05 in human blood. Cell to plasma concentration ratio in human was 0.31 ± 0.11.

Unbound fractions of LEN were similar in the severe renal impairment group (0.246%, CV 35.3%) relative to their matched healthy controls (0.206%, CV 27.2%) (study GS-US-200-4330). In the hepatic impairment study GS-US-200-4331, LEN mean fu was 0.366% (53% CV) and 0.214% (68% CV) in the moderate hepatic impairment and the normal hepatic function groups, respectively. Thus, in vivo data from healthy volunteers on plasma binding suggest that lenacapavir is highly protein bound (99.8%).

Lenacapavir is a substrate of PgP, no data is available regarding its distribution to the human brain.

In healthy participants, at single oral doses of 300 and 900 mg, the mean (%CV) values for the apparent volume of distribution during the terminal phase (V_z/F) were 19 240 L (65%) and 51 077 L (65%), respectively (study GS-US-200-4071).

The mean (CV%) V_z/F was 11 675 L (49%) following a single SC dose of 927 mg (309 mg/mL, NaS, 2 x 1,5 ml) in healthy participants (study GS-US-200-4538). After i.v. administration of 10 or 20 mg lenacapavir to healthy participants, a high volume of distribution is observed of 1793 – 1986 L, indicating extensive tissue distribution (study GS-US-200-4329).

In the population PK analysis, the distribution was described by a 3-compartment disposition model. The estimated volume of distribution at steady state (V_{ss}) was 1657 L.

6.2.2.5. Metabolism

The predominant chemical species circulating in plasma was unchanged lenacapavir (68.8%); no single circulating metabolite accounted for >10% of plasma drug-related exposure. The only other peaks (P9 and P11, corresponding to 8.74% and 9.28% of the total $AUC_{0\text{-}1176h}$, respectively) were likely photolysis and/or radiolysis degradant products, as they were also present in controls.

The chemical structure of lenacapavir has several chiral centres. The potential for changes in the proportions of the two atropisomers was assessed following incubation of lenacapavir (0.1 or 1.0 µM) for 24h in phosphate buffer or in human plasma at 37°C. There was no detectable change in the relative distribution between the two lenacapavir atropisomers, at either lenacapavir concentration, in any of the matrices, at 0 or 24 hr. This indicated that the balance between the two atropisomers is stable with time and is unaffected by binding proteins or enzymes in plasma. Formation of an additional new chiral centre due to metabolism would generate diastereomers or lead to metabolism mediated cleavage of LEN that would be expected to show up in the LC-^{14}C-high-resolution mass spectrometry method used for metabolite profiling; no unaccounted peaks were observed.

In vitro turnover of lenacapavir was low, with only traces of metabolism by CYP3A5 and UGT1A1.

Adjusting for the 75.9% mean cumulative faecal recovery of the administered radioactive dose, LEN and the LEN-hexose conjugate metabolite (rotamers M42 and M35) were the 2 most abundant components recovered in the faeces and accounted for a mean abundance of 43.4% (32.9% of dose, 5.2% unadjusted for recovery) and 8.7% (6.6% of dose, 1.2% unadjusted for recovery), respectively. Other metabolites identified in faeces were the rotamer pair LEN-glucuronide-1 and -2 (M13A, M13B), LEN-C9H9NO3 adduct (M16), hydroxyl-LEN-2 (M19), N-[des-trifluoroethyl]-LEN (M20), rotamer pair LEN-pentose conjugate-1 and -2 (M43, M29), rotamer pair dihydro-LEN-cysteine conjugate-1 and -2 (M41, M33), dihydro-dioxy-LEN (M44), dihydro-oxy-LEN (M45), and LEN-CO2 adduct (M46), each of which accounted for < 2% of the dose. The proposed biotransformation pathways are summarised in **Figure 8**.

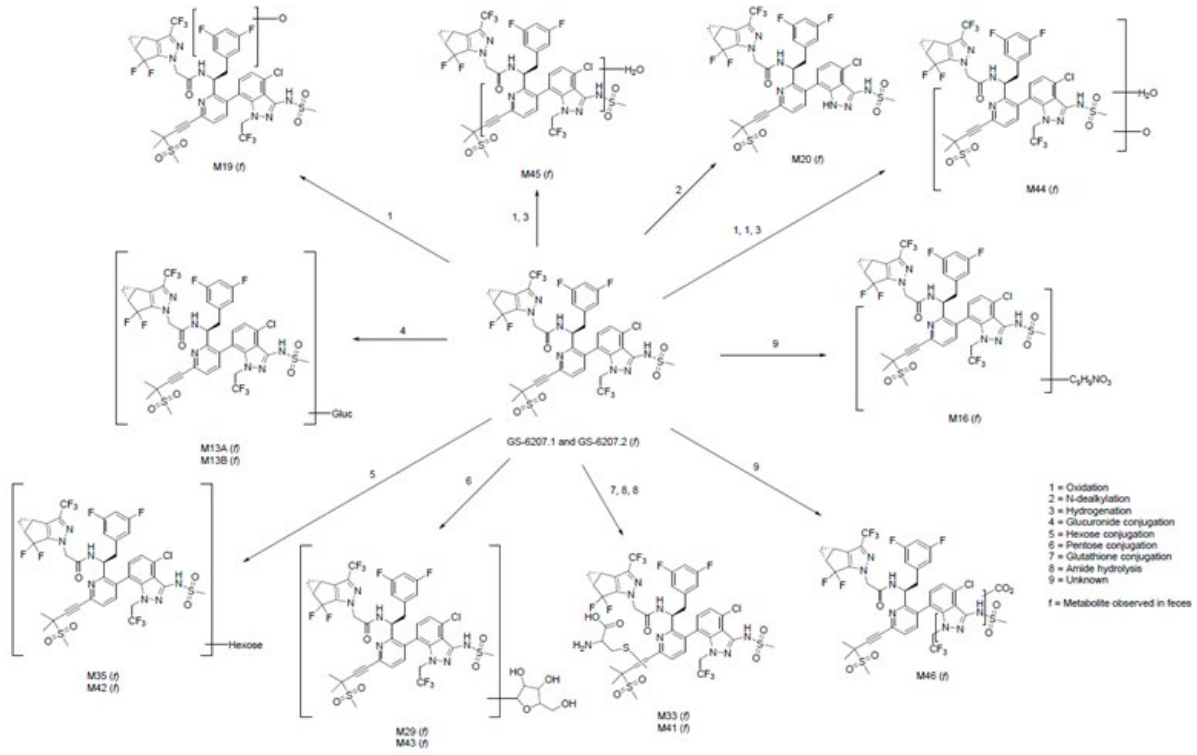


Figure 8. Proposed major biotransformation and excretion pathway for lenacapavir in humans (Source: GS US 200-4329 CSR)

6.2.2.6. Elimination

In study GS-US-200-4329, CL of lenacapavir was 4.4 and 4.9 L/h in healthy subjects given a single intravenous dose of 10 mg lenacapavir, and 20 mg ^{14}C-lenacapavir as 1h iv infusion, respectively. $T_{1/2}$ was 274 and 268h (11 days), and V_z 1793 and 1986 L.

The median $t_{½}$ ranged from approximately 10 to 12 days after single oral administration of 300 and 900 mg LEN tablets to healthy participants (fasted state) (study GS-US-200-4071). At the same doses the mean (SD) apparent oral CL was 54.8 (33.3) L/h and 112 (53.8) L/h, respectively.

Following single SC administration of 927 mg LEN to healthy participants, the median $t_{½}$ was 81 days (study GS-US-200-4538) and 59 days (study GS-US-200-5709).

Based on population PK analysis, the systemic CL was estimated to 3.4 L/h for a typical 70-kg subject. The model derived median apparent half-life following oral (600 mg) and subcutaneous (927 mg) administration was 15.7 days and 10.5 weeks, respectively.

In the mass balance study GS US 200 4329, lenacapavir was primarily eliminated in the faeces via biliary excretion mediated by P-gP (75.9%, 81.8% excluding early withdrawal), renal excretion being a minor pathway (0.237%, 0.245% excluding early withdrawal). Thus 76.1% (82% excluding early withdrawal) of the administered radioactive dose was recovered. 74.7% of the administered radioactive dose was recovered in the first 1608 hours post-dose, with levels of radioactivity being below the limit of

quantitation by 576 – 600 h in urine and 2784 – 2808 h in faeces.

6.2.2.7. Dose proportionality and time dependency

After a single oral dose of LEN 50 mg, 300 mg, 900 mg (3 x 300 mg), and 1800 mg (6 x 300 mg) as oral tablets to healthy volunteers (study GS-US-200-4071), C_{max} and AUC increased in a less than dose proportional manner across the dose range of 50 to 1800 mg, with a slope of approximately 0.5 for AUC_{inf}, AUC_{last} and C_{max}.

Following twice daily oral administration of 600 mg LEN (2 x 300 mg) to healthy volunteers, a large accumulation in exposures, in terms of C_{max} and AUC, were observed over time (>53-fold; study GS-US-200-5709). In a limited number of subjects (<40), the mean accumulation observed in the oral bridging regimen over 10 weeks in GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2) was 1.4 and 2.3, respectively.

LEN exposures were generally dose proportional at single SC doses of 309 mg (1 x 1 mL) and 927 mg (3 x 1 mL) in healthy volunteers (study GS-US-200-4538). Dose proportionality has not been studied after repeated sc administration.

From week 26 (including the oral loading phase) to week 52, the observed mean C_{trough} increased 1.3-fold in the PURPOSE 1 study and 1.2-fold in the PURPOSE 2 study, indicating a small degree of accumulation. Based on simulations from the population PK model, the proposed dosing regimen in PWBP results in a median accumulation ratio of AUC_{tau} at steady state of 1.3.

6.2.2.8. Pharmacokinetics in the target population

The intended population for the proposed indication is people who would benefit from pre-exposure prophylaxis (PWBP), i.e. in large healthy adults and adolescents. Pharmacokinetics is therefore not expected to differ substantially between the general population and the intended target population.

Two phase III studies were conducted in the target population, PURPOSE 1 (adolescent girls and young women at risk of HIV infection) and PURPOSE 2 (cisgender men, transgender women, transgender men, and gender nonbinary people ≥ 16 years of age who have sex with male partners, at risk of HIV infection).

Week 52 interim-analyses for PURPOSE 1 and PURPOSE 2 have been submitted, including sparse PK sampling. Lenacapavir PK was analysed in a preselected random subset of 10% of the adult participants and in additional subpopulations of interest.

The mean (and 90% CI) C_{trough} at week 26 and week 52 (second and third sc injection of lenacapavir) for the main 10% PK subset, was above the efficacy target IQ4 (15.5 ng/ml), see **Table 13**.

Table 13. Mean observed C_{trough} and 90% CI at week 26 and 52 in the phase III studies PURPOSE 1 and PURPOSE 2

	PURPOSE 1 Week 26 (n=156)	PURPOSE 1 Week 52 (n=73)	PURPOSE 2 Week 26 (n=267)	PURPOSE 2 Week 52 (n=111)

Mean C_{trough} (ng/ml)	34.1	44.7	22.8	27.8
Lower 90% CI (ng/ml)	31.5	39.8	21.6	25.2
Upper 90% CI (ng/ml)	36.6	49.7	24.1	30.4
%CV	55.95%	56.29%	55.67%	55.54%

Exposure relevant for safety evaluation

At steady state, based on the population PK model, simulated mean (%CV) lenacapavir exposures following administration of the simplified regimen in PWBP was: AUC_{tau} 257334 ng*h/mL (38.7%), C_{max} 82.4 ng/mL (40.4%) and C_{trough} 36.9 ng/mL (53.5%).

Oral bridging

In PURPOSE 1 and 2, if lenacapavir sc injections could not be administered within the injection window, participants received 300 mg oral lenacapavir once-weekly, for up to 10 weeks.

For PURPOSE 1, the mean lenacapavir concentration was 28.2 (n=8, 90% CI: 19.0 to 37.4) ng/mL before the first oral bridging dose and 40.3 ng/mL (n=10, 90% CI: 32.6 to 48.0) before resuming sc injections. For PURPOSE 2, mean LEN concentration was 22.9 ng/mL (n=31, 90% CI: 19.4 to 26.5) before oral bridging, and 53.8 ng/mL (n=24, 90% CI: 39.9 to 67.7) before resuming sc injections. Thus, mean LEN concentration and the lower bound 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.

Observed data on lenacapavir oral bridging in HIV-1 treated patients from study GS-US-200-4625 and GS-US-200-4334 have also been submitted. Sparse PK samples were collected at the start, and approximately every 10 to 12 weeks during the oral regimen of 300 mg lenacapavir per week. The oral bridging period lasted for up to 30 weeks. Overall, mean LEN concentration and the lower bound 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 (see **Figure 9**).

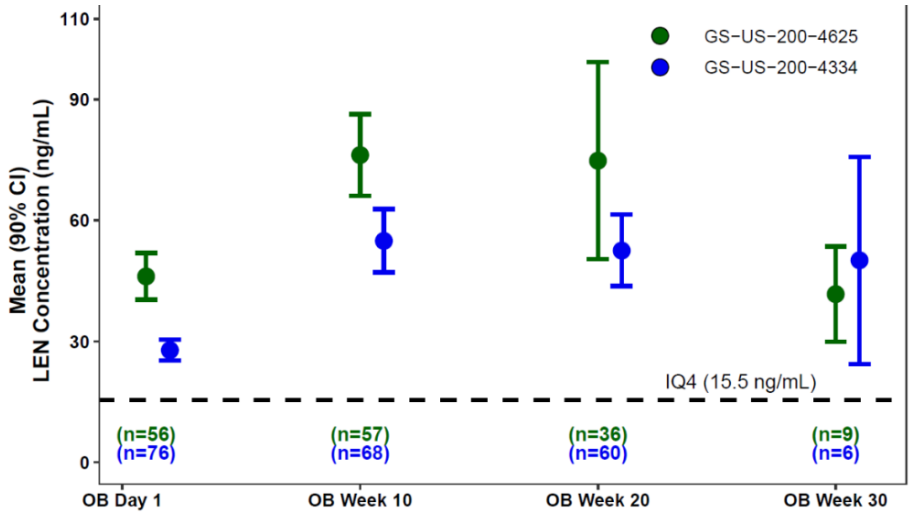
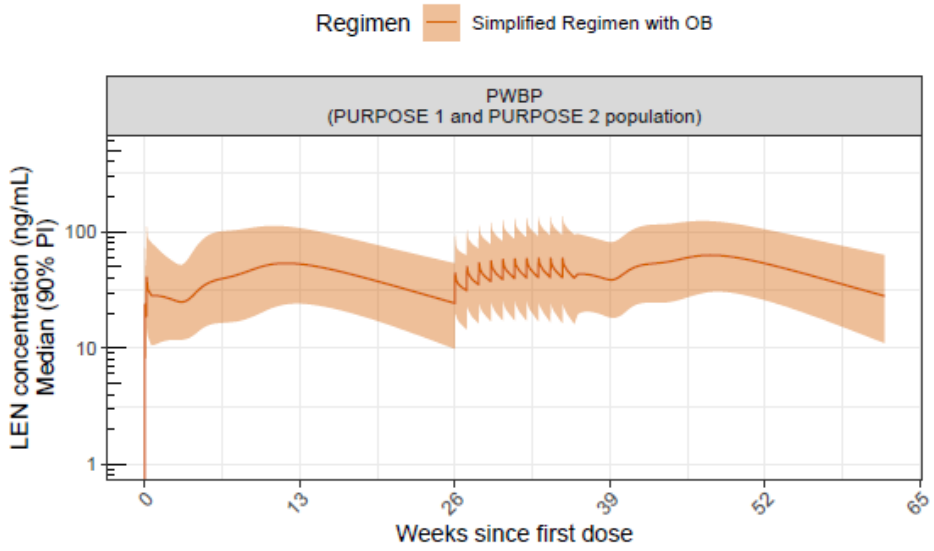


Figure 9. mean (90% CI) lenacapavir concentrations (ng/ml) at different time points in oral bridging regimen. OB = oral bridging

Simulations, using the population PK model, support that the lenacapavir concentration does not decrease over time when applying the proposed oral bridging regimen in PWBP (**Figure 10**).



Source code: plot–sims–simplified–withOB–PWBP–PURPOSEcombined.R
Source graphic: deliv/figures/report/simulations/simplifiedOB–med90PI–PURPOSE.pdf page: 2

Abbreviations: IQ4 = inhibitory quotient 4; PI = prediction interval; PrEP = pre-exposure prophylaxis; PWBP = people who would benefit from PrEP; SC=subcutaneous
Oral bridging (300 mg oral LEN once weekly) began at Week 26 of the Simplified (600 mg oral LEN on Day 1 and Day 2, and 927 mg SC LEN on Day 1). Oral bridging continued for a duration of 10 weeks, after which a subcutaneous dose was administered. Solid line is the median concentrations and shaded areas are the 90% PI. Dashed horizontal line is the IQ4 threshold of 15.5 ng/mL. 100 replicates of PWBP in PURPOSE 1 and PUROSE 2 (N = 942) combined were simulated.

Figure 10. Simulated median (90% prediction interval) lenacapavir concentrations versus time profiles following 10 weeks of the QW oral bridging regimen in PWBP

Dosing window

The dosing window for a missed SC dose were evaluated with simulations of lenacapavir concentrations from 22 to 32 weeks following the first 927 mg SC dose of the proposed dosing regimen for PWBP, without a second SC dose at Week 26, using the population PK model. The 90% CI of mean lenacapavir concentrations consistently remained above the IQ4 (15.5 ng/mL). If the maintenance SC dose is delayed by 2 weeks (i.e., Week 28), mean (90% CI) lenacapavir concentrations are predicted to be 23.8 (23.2, 24.5) ng/mL.

6.2.2.9. Special populations

Renal impairment

Lenacapavir C_{max} and AUC_{inf} increased by 162% and 84%, respectively, in participants with severe renal impairment compared with their matched healthy controls (study GS-US-200-4330). Unbound fractions of LEN were similar in the severe renal impairment group (0.246%, CV 35.3%) relative to their matched healthy controls (0.206%, CV 27.2%). Unbound PK parameters were not presented. As lenacapavir is

greater than 98.5% protein bound, dialysis is not expected to alter exposures of lenacapavir.

Hepatic impairment

Lenacapavir AUC_{inf} and C_{max} were approximately 47% and 161% higher, respectively, in participants with moderate hepatic impairment relative to their matched healthy controls with normal hepatic function (study GS-US-200-4331). Lenacapavir mean fu was 0.366% (53% CV) and 0.214% (68% CV) in the moderate hepatic impairment and the normal hepatic function groups, respectively. Unbound lenacapavir C_{max} and AUC_{inf} increased by 406% and 184%, respectively, in participants with moderate hepatic impairment compared with their matched healthy controls.

Age

There is limited data in elderly for lenacapavir in PWBP.

In the population PK analysis, no effect of age was identified. However, although subjects aged 16 to 78 years old were included in the analysis, the age distribution was skewed towards younger participants (**Table 14**).

Table 14. Number of participants 65 years and older included in the popPK analysis dataset

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PopPK Analysis Dataset	18/1337	1/1337	0/1337

Source: QP-2024-1082-LEN-PopPK

Sex and gender identity

In the population PK analysis, sex was identified as a statistically significant covariate. In total, 797 subjects assigned male sex at birth, and 540 subjects assigned female sex at birth, were included in the analysis. The impact of sex on the exposure of lenacapavir is minor (< 10%) and not considered clinically relevant. No effect of gender identity (transgender women, N=182; transgender men, N=29; gender nonbinary, N=93) was identified in the analysis.

Race

In the population PK analysis, no effect of race was identified. In total, 450 white, 755 black, 53 Asian were included in the analysis; 7 participants were defined as 'other' race.

Body weight

In the population PK analysis, body weight was included as covariate on all disposition parameters. Participants weighing 37.9 to 195 kg were included in the analysis. The model predicts a 31% higher C_{trough} in participants with a body weight of 49 kg (5^{th} percentile), and a 25% lower C_{trough} in participants with a body weight of 110 kg (95^{th} percentile), compared with participants with a body weight of 72 kg (median). The impact of body weight on the exposure of lenacapavir is not considered clinically relevant.

Paediatrics

Adolescent participants, ≥16 to <18 years of age and weighing ≥35 kg, were included in the PURPOSE 1 (55 participants < 18 years of age at the PK cut-off date) and PURPOSE 2 (3 participants < 18 years of age at the PK cut-off date) studies. Efficacy and safety of lenacapavir are to be extrapolated from adults to the adolescent population based on similar exposure. The mean lenacapavir concentration at week 26 in adolescents in the PURPOSE 1 study was 31.4 ng/mL (lower bound of 90% CI of 27.7 ng/mL). This was similar to the mean concentration found in adults, which was 34.1 ng/mL (lower bound of 90 % CI of 31.5 ng/mL). Additionally, in PURPOSE 2, the two adolescents who had pharmacokinetic samples showed trough concentrations of 30.8 and 50.6 ng/mL at week 26. Observed exposures in adolescent participants were within the range observed in adult participants. Based on the population PK model, the exposure is expected to increase with decreasing body weight, but simulated exposures are generally within the range observed in adult participants.

The use of lenacapavir in paediatric participants weighing <35 kg has not been evaluated in clinical studies at this time.

Pregnancy

There is no dedicated study in pregnant women with lenacapavir treatment. Pregnant individuals were excluded from entering the PURPOSE studies, but those who became pregnant during the studies were given the choice to continue study drug. Trough PK samples were available from 74 patients in first trimester, 64 patients in second trimester and 51 patients in third trimester. There were no apparent trends of changes in exposure in the trimesters and post-partum, when compared side-to-side with non-pregnant cohorts (see **Figure 11**).

Figure 11. Observed lenacapavir concentrations up to 104 weeks after dose, stratified by pregnancy group

Lactation

The ratio of lenacapavir concentration in breast milk to that in maternal plasma (M:P ratio) was calculated using matched pairs of breast milk and maternal plasma samples, regardless of the time since the last injection. The median M:P ratio for LEN was 0.52, with an intraquartile range of 0.38-0.77, based on 102 matched pairs of samples. The median infant-to-mother plasma ratio in infants (n=98) who were breastfed was 0.02 (intraquartile range: 0.01-0.05), the median infant plasma concentration was 1.63 ng/ml (range: 0.0-92 ng/ml; **Table 15**).

Table 15. Summary statistics of infant and maternal plasma LEN concentrations (ng/mL)

	Infant[a]	Mother[b]
N[c]	98	96
Mean	3.00	72.97
SD	9.298	38.276
Median	1.63	65.65
Min	BLQ	14.40
Max	92.30	227.00
Q1	0.87	46.00
Q3	2.85	91.10

6.2.2.10. Pharmacokinetic interaction studies

There are no new in vitro or dedicated in vivo studies on drug-drug interactions (DDI) for the current application in PrEP. Therefore, results from the MAA of Sunlenca are presented. Of note, all clinical drug interaction data with lenacapavir as victim comes from studies with oral lenacapavir, there is no clinical drug interaction data with sc lenacapavir as victim. Sparse PK data on concomitant hormone treatments were collected in the phase III studies.

In vitro interaction studies were performed with lenacapavir and signals for potential interactions were further investigated in the in vivo study GS-US-200-4333, which was a single- and multiple-dose, multiple-cohort study to evaluate transporter and CYP-mediated DDIs between oral lenacapavir (single or multiple doses) and probe drugs in healthy participants. The probe drugs were the following: cobicistat (COBI), darunavir (DRV), voriconazole (VORI), atazanavir (ATV), rifampicin (RIF), efavirenz (EFV), famotidine (FAM), pitavastatin (PIT), rosuvastatin (ROS), tenofovir (TFV), tenofovir alafenamide (TAF), and midazolam (MDZ).

6.2.2.10.1. Effect of other medicines on lenacapavir

Lenacapavir was shown to be a substrate for P-gp but not BCRP, OATP1B1 or OATP1B3. In vitro turnover of lenacapavir was low, with only traces of metabolism by CYP3A5 and UGT1A1.

Coadministration of single-dose LEN with strong CYP3A4/P-gp/UGT inhibitor ATV/COBI resulted in a 321% increase in AUC_{inf} and a 560% increase in C_{max}.

Coadministration of single-dose LEN with a strong CYP3A4/P-gp inhibitor (COBI) and a mixed CYP3A4/P-gp inhibitor and inducer (DRV/COBI) under fed conditions resulted in 128% and 94% increases in AUC_{inf}, respectively, and 110% and 130% increases in C_{max}, respectively.

Coadministration of a single-dose LEN with the potent CYP3A4 inhibitor (VORI) under fasting conditions resulted in a 41% increase in AUC_{inf}, with no change in C_{max}.

Coadministration of single-dose LEN with strong inducer (RIF) under fasting conditions resulted in an 84% decrease in AUC_{inf} and a 55% decrease in C_{max}.

Coadministration of single-dose LEN with a moderate inducer (EFV) under fasting conditions resulted in a 56% decrease in AUC_{inf} and a 36% decrease in C_{max}.

Administration of single-dose LEN 2 hours after a gastric acid reducer (FAM) under fasting conditions resulted in a 28% increase in AUC_{inf}, whereas C_{max} was unchanged.

6.2.2.10.2. Effect of lenacapavir on other medicines

All dedicated clinical drug interaction data with lenacapavir as perpetrator comes from studies with oral lenacapavir. Some sparse PK data on concomitantly used longacting contraceptives and gender-affirming hormones were however collected in the PURPOSE 1 and PURPOSE 2 study. These data did not indicate clinically relevant changes in the concentrations of these hormones when co-administered with s c lenacapavir.

There was little or no evidence of direct or time-dependant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6 by lenacapavir and the IC_{50} values were reported as greater than 25 µM for direct inhibition and the lowest IC_{50} was 1.8 µM for time-dependant inhibition (CYP2C8). Lenacapavir inhibited UGT1A1 with an IC_{50} of 3.2 µM.

Lenacapavir directly inhibited CYP3A (for midazolam 1´-hydroxylation) with an IC_{50} of 5.4 µM and was shown to be a mechanism-based inhibitor of midazolam hydroxylase. Characterization of CYP3A inactivation kinetics revealed the rate of enzyme inactivation (k_{inact}) of 0.021 min^{-1} and the inhibition constant (K_I) of 1.14 µM. These findings were followed up in vivo.

Lenacapavir did not inhibit OAT1-, OAT3-, OCT1-, OCT2-, and (MATE)2-K-mediated transport when tested up to 10 µM. Lenacapavir showed concentration-dependent inhibition of MATE1 and BSEP mediated transport with IC_{50} values of 2.39 and 1.21 µM, respectively.

Lenacapavir showed dose-dependent inhibition of OATP1B1 and OATP1B3 mediated uptake with IC_{50} values of 0.021 and 0.049 µM, respectively. Inhibition of intestinal efflux transporters (P-gp and BCRP) following oral dosing of LEN cannot be ruled out from in vitro data as concentrations above 1 µM were not evaluated.

Lenacapavir did not induce CYP1A2 (AhR), CYP2B6 (CAR), PgP. Increases in the CYP3A4, CYP2C9 and UGT1A1 mRNA content were observed in only one of the three donors, increasing to >2-fold at the 3 and 10 µM (cytotoxic) dose concentrations (maximum FOC 2.38-fold and 2.48-fold, respectively). CYP3A

activity was reduced in all three donors in a concentration-dependent manner, likely reflecting an inhibitory effect of lenacapavir on CYP3A enzymes.

Coadministration of single-dose PIT (an OATP substrate) both simultaneously with LEN and staggered from LEN did not result in changes in PIT AUC_{inf} and C_{max}.

Coadministration of single-dose ROS (a BCRP substrate) simultaneously with LEN resulted in a 31% increase in AUC_{inf} and a 57% increase in C_{max} for ROS.

Coadministration of single-dose TAF (a P-gp substrate) simultaneously with LEN resulted in a 32% increase in AUC_{last} with a smaller effect on C_{max} (approximately 24% increase) for TAF and a 47% increase in AUC_{inf} with a smaller increase in C_{max} (approximately 23% increase) for TFV.

Coadministration of single-dose MDZ simultaneous with LEN resulted in 259% and 94% increases in AUC_{inf} and C_{max} of MDZ, respectively. Coadministration of single-dose MDZ staggered from LEN resulted in 308% and 116% increases in AUC_{inf} and C_{max} of MDZ, respectively. For 1-OH-MDZ, AUC_{inf} and C_{max} values were reduced by 16% to 24% and 48%, respectively.

6.2.3. Pharmacodynamics

6.2.3.1. Mechanism of action

Lenacapavir is a multistage inhibitor of HIV-1 capsid (CA) with high potency and selectivity in antiviral assays. Protein X-ray crystallography and biochemical assays indicate that LEN binds at the intermolecular interface between 2 adjacent CA monomers within a CA hexamer, such that up to six molecules of LEN can bind to each CA hexamer. This binding site is shared by capsid-binding host nuclear import factors such as NUP358, NUP153, CPSF6.

Surface plasmon resonance (SPR) experiments demonstrated that LEN binds with high affinity to cross-linked CA hexamer (KD = 1.4 ± 0.6 nM). Consistent with an on-target interaction, the capsid M66I resistance mutation attenuated LEN binding to recombinant CA protein (KD = 110 ± 40 nM).

Lenacapavir increased both the rate and extent of in vitro CA assembly, resulting in short, misshaped and heterogeneous polymers that differed from the uniformly long and well-organized CA tubes assembled in the absence of LEN. Lenacapavir interferes with late-stage virus production and CA core formation events. Lenacapavir also interferes with an early-stage process occurring after reverse transcription but before the integration of viral DNA.

The effect of LEN on virus production was assessed in HEK293T cells following transient transfection with plasmids encoding single-cycle HIV-1 reporter virus. Virus-producing HEK293T cells showed a dose-dependent reduction in the amount of mature HIV-1 released into the cell culture supernatant over a period of two days in the presence of LEN, with an EC50 of 0.305 nM as measured by p24 ELISA. Lenacapavir showed no cytotoxicity in HEK293T cells up to the highest concentration tested (10 μM) and did not inhibit the production of a drug-resistant HIV-1 variant with the capsid M66I mutation (EC50 > 2 μM), indicating that this late-stage effect is both virus-specific and requires the WT capsid domain.

6.2.3.2. Primary and secondary pharmacology

Activity of LEN in the MT-4 T-cell line

The antiviral activity of LEN was evaluated using a 5-day cytopathic assay in the MT-4 T-cell line acutely infected with HIV-1 (IIIB strain). Lenacapavir displayed antiviral activity in MT-4 cells, with an effective concentration to achieve 50% inhibition (EC50) value of 0.19 nM. In addition, the effective concentration to achieve 95% inhibition (EC95) of LEN in MT-4 cells was calculated from the EC50 and Hill slope values that were determined from a high resolution 40-point dose response curve. Lenacapavir showed a Hill slope of 3.5 in MT-4 cells, yielding an EC95 value of 0.23 nM.

The in vitro activity of LEN was reduced in the presence of human serum due to protein binding. The 95% effective concentration (EC95) calculated from a high resolution antiviral dose response in MT-4 cells was used in conjunction with the human serum shift determined by equilibrium dialysis to calculate a paEC95 value of 4 nM. This value which was used for the estimation of clinical inhibitory quotient (IQ) for the projected trough concentration of LEN in humans.

Table 16. EC50, Hill Slope and EC95 of LEN in MT-4 Cells

	MT-4 T-Cell Line					
	Standard Resolution	High Resolution				
Compound[1]	EC_{50} (nM)[2]	EC_{50} (nM)[3]	Hill Slope[3]	EC_{95} (nM)	EQD Shift (Fold Change)[4]	$paEC_{95}$ (nM)
LEN	0.19 ± 0.05	0.10 ± 0.01	3.51 ± 0.31	0.23 ± 0.02	17.4	4.0 ± 0.4
EFV	1.38 ± 0.64	0.79 ± 0.06	3.25 ± 0.59	2.0 ± 0.15	22.4	44 ± 3
DTG	1.92 ± 0.90	1.34 ± 0.14	2.14 ± 0.28	5.3 ± 0.55	29.5 ± 11.2	156 ± 16
ATV	10.7 ± 3.4	7.23 ± 0.50	3.13 ± 0.15	18.5 ± 1.3	8.1	150 ± 11

1 EFV = efavirenz; DTG = dolutegravir; ATV = atazanavir
2 Standard resolution EC_{50} values represent the geomean (± SD) from at least 19 independent experiments (Data from PC-200-2018).
3 High resolution EC_{50} and Hill Slope values represent the mean (± SD) from at least 2 experiments (Data from PC-200-2018).
4 Equilibrium dialysis (EQD) shift values were obtained from a single run for EFV, or represent the mean values obtained from 5 runs for DTG and 2 runs for LEN and ATV (Data from AD-200-2020).

Activity of LEN in Primary Human CD4+ T-Lymphocytes and Macrophages

The antiviral activity of LEN was determined in human primary CD4+ T-lymphocytes and monocyte-derived macrophages acutely infected with HIV-1 (BaL strain) using 7-day and 12-day virus production assays, respectively. Lenacapavir displayed anti-HIV-1 activity in each of these physiological target cells for HIV-1 replication, with EC50 values of 0.06 nM and 0.03 nM for CD4+ T-lymphocytes and monocyte-derived macrophages, respectively.

Activity of LEN Against HIV Clinical Isolates in Human PBMCs

The antiretroviral activity of LEN was tested against 23 clinical isolates of HIV-1 and two isolates of HIV-2 in freshly isolated human PBMCs. Lenacapavir displayed antiviral activity against all tested HIV-1 clinical

isolates representing all major subtypes with a mean EC50 value of 0.05 nM. Lenacapavir also showed antiviral activity against two HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1 isolates.

Activity of LEN Against Diverse HIV-1 Clinical Isolates in HEK293T Cells

The antiretroviral activity of LEN was tested in vitro against 40 clinical isolates of HIV-1 representing diverse subtypes and including 3 isolates harboring HIV protease inhibitor (PI) resistance mutations. For the 37 WT se results in table below. Overall, LEN showed antiviral activity against all HIV-1 isolates evaluated, regardless of subtype or presence of drug resistance mutations.

Table 17. Antiviral Potency of LEN and Control Compounds Against Wild-Type HIV-1 Clinical Isolates in HEK293T Cells

	IC_{50}, nM (n = 37)	
Compound	**Mean***	**Range**
LEN	0.238	0.148 - 0.357
ATV	7.87	2.47 - 14.5
DRV	0.947	0.209 - 2.74
LPV	11.4	2.60 - 35.1

ATV = atazanavir; DRV = darunavir; LEN = lenacapavir; LPV = lopinavir; (*) geometric mean (Data from PC-200-2041)

When tested against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, A1, AE, AG, B, BF, C, D, E, F, G, and H, LEN displayed similar antiviral activity against all isolates, with mean EC50 values of 0.05 nM (ranging from 0.02 to 0.16 nM) and 0.24 nM (ranging from 0.15 to 0.36 nM) in PBMCs and the HEK293T cell line, respectively. Consistent with these findings, the CA protein sequence is highly conserved across 8 major HIV-1 subtypes, including the majority of residues within the LEN binding site.

Most CA polymorphisms near the LEN binding site displayed WT susceptibility to LEN. Lenacapavir showed potent antiviral activity against 2 HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1.

LEN Cross-Resistance

Lenacapavir maintains potent antiviral activity against HIV-1 mutants and HIV-1 clinical isolates resistant to currently approved ARVs from the nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), INSTI and protease inhibitor (PI) classes.

The in vitro antiviral activity of LEN was determined in MT-2 cells against a broad spectrum of HIV-1 site-directed mutants (SDMs) and patient-derived HIV-1 isolates resistant to NRTIs, NNRTIs, INSTIs or PIs. Lenacapavir remained fully active against all 18 HIV-1 variants tested (Table below), while representative control compounds from each of the four antiviral drug classes showed significant loss of antiviral activity when tested against viruses with mutations within their respective viral target protein.

In addition, 40 HIV-1 clinical isolates with resistance against NRTIs, NNRTIs, INSTIs, and PIs (10 in each category) were tested. These results demonstrate a non-overlapping resistance profile for LEN.

Table 18. Activity of LEN Against NRTI-, NNRTI-, INSTI-, and PI-Resistant HIV-1 Site-Directed Mutants

Antiretroviral Inhibitor Class	Drug-Resistant HIV-1 Mutant[1]	LEN	Positive Control	
		Fold-resistance[2]	Compound[3]	Fold-resistance[2]
NRTI	K65R	0.6	FTC	12.8
	M184V	0.5		>42
	6TAMs	0.4		4.1
NNRTI	K103N	0.3	EFV	14.4
	Y181C	1.7		3.3
	Y188L	0.5		>23
	L100I/K103N	0.5		>23
	K103N/Y181C	0.5		>23
INSTI	Y143R	0.5	RAL	10.2
	E138K/Q148K	0.8	EVG	>53
	G140S/Q148R	0.9		>53
	E92Q/N155H	0.9		>53
	N155H/Q148R	1.3		>53
	M50I/R263K	0.9		5.1
PI	I50V	0.6	DRV	31.8
	I84V/L90M	0.3	ATV	32.9
	I54V/V82S	0.4		32.4
	G48V/V82A/L90M	0.4		15.2

1 The antiviral activity of WT HIV-1 and HIV-1 encoding RT mutations (NRTI/NNRTIs), IN mutations (INSTIs), or PR mutations (PIs) was measured. 6TAMs: M41L, D67N, K70R, L210W, T215F, K219Q.
2 Mean fold-resistance values (mutant EC_{50}/WT EC_{50}) obtained from 3 independent experiments (Data from m2.6.3, Section 1, PC-200-2027).
> 2-fold, > 10-fold, > 50-fold
3 ATV = atazanavir; DRV = darunavir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; RAL = raltegravir

Activity of LEN Against Clinical Isolates with Entry Inhibitor Resistant HIV-1

In Study GS-US-200-4625 in patients with multi-resistant HIV-1 baseline resistance analysis were performed. Phenotypic resistance to at least one of the entry inhibitor drugs (fostemsavir, maraviroc, enfuvirtide, and ibalizumab) was found in 67.2% of participants at baseline. Viral samples from all enrolled participants were also phenotypically evaluated against LEN. Notably, viruses with resistance to entry inhibitors fostemsavir, maraviroc, enfuvirtide, and ibalizumab showed no cross resistance to LEN, with a mean FC from WT of 0.97, 0.97, 0.92, and 1.0, respectively.

Activity of LEN in Clinical Isolates Containing Gag Cleavage Site Mutations

The antiviral potency of LEN was tested against a panel HIV-1 clinical isolates from treatment-experienced people with HIV (PWH) (TE; n=24) containing gag cleavage site mutations (GCSMs) with or without protease inhibitor resistance. These SDMs included some combination of the Gag mutations L363F/M, A364V, Q430R, A431V, K436E/S, I437T/V, L449H/V/F, and P453L cloned into pXXLAI. Drug susceptibilities to LEN, protease inhibitors (DRV, ATV), and maturation inhibitors (BVM, GSK-3532795) were measured in a multicycle HIV-1 assay in MT- 2 cells. Lenacapavir displayed WT antiviral potency across this panel of clinical isolates (TE: 1.0-fold). Overall high-level resistance (mean fold-change >22) to both PIs and MIs was observed in TE isolates containing GCSMs. Overall, these data indicate that LEN susceptibility was not affected by the presence of GCSMs TE isolates tested.

In Vitro Selection for LEN Resistant HIV-1 Variants

In vitro dose escalation resistance selections with LEN, EFV, and EVG were performed in MT-2 cells infected with clonal HIV-1 strain HXB2D. The in vitro rates of viral resistance emergence were similar for all three compounds under conditions of low drug pressure but were considerably slower for LEN relative to EFV and EVG at higher drug concentrations (> 10-fold EC50). At low LEN concentrations, the compound selected for virus encoding the capsid N74D variant, whereas at higher drug concentrations, LEN selected for virus encoding the capsid Q67H+N74D double mutant. Results from phenotypic profiling of selected viral passages (P3-P10) are presented in table below where the N74D and Q67H+N74D variants conferred an increased fold change for LEN, with no change in susceptibility to any of the control inhibitors from other antiretroviral classes (EFV, EVG, and ATV).

Table 19. Genotypic and Phenotypic Profiles of Selected Viral Passages

Selected Virus	Duration of Selection (days)	Drug Conc. Reached, nM (Fold EC_{50})	Mutation(s) [1]	EC_{50} (nM) (Fold-Change Relative to WT)[2]			
				LEN	EFV	EVG	ATV
HXB2D	—	—	None	0.26 ± 0.15 (1.0)	1.67 ± 0.47 (1.0)	1.72 ± 0.41 (1.0)	6.40 ± 1.43 (1.0)
LEN P3	12	0.28 (4)	None	0.13 ± 0.1 (0.5)	1.33 ± 0.49 (0.8)	1.50 ± 0.57 (0.9)	6.70 ± 0.82 (1.1)
LEN P4	19	0.56 (8)	N74D	1.42 ± 0.71 (5.5)	0.63 ± 0.12 (0.4)	1.72 ± 1.53 (1.0)	4.30 ± 0.35 (0.7)
LEN P5	36	1.12 (16)	N74D	1.31 ± 0.54 (5.0)	0.63 ± 0.12 (0.4)	1.25 ± 0.21 (0.7)	3.17 ± 0.51 (0.5)

Selected Virus	Duration of Selection (days)	Drug Conc. Reached, nM (Fold EC_{50})	Mutation(s) [1]	EC_{50} (nM) (Fold-Change Relative to WT)[2]			
				LEN	EFV	EVG	ATV
LEN P6	54	2.24 (32)	N74D, T107N/T	1.79 ± 0.67 (6.9)	0.67 ± 0.06 (0.4)	0.93 ± 0.32 (0.5)	4.30 ± 0.17 (0.7)
LEN P7	80	4.48 (64)	Q67H, N74D	11.1 ± 5.6 (43)	0.52 ± 0.32 (0.3)	0.32 ± 0.05 (0.2)	3.10 ± 0.62 (0.5)
LEN P8	89	8.96 (128)	Q67H, N74D	19.8 ± 22.9 (76)	0.46 ± 0.23 (0.3)	0.28 ± 0.16 (0.2)	1.98 ± 0.95 (0.3)
LEN P9	96	17.9 (256)	Q67H, N74D	53.9 ± 28.6 (207)	0.58 ± 0.21 (0.4)	0.29 ± 0.06 (0.2)	2.34 ± 0.32 (0.4)
LEN P10	103	35.8 (512)	Q67H, N74D	39.3 ± 6.5 (151)	0.57 ± 0.17 (0.4)	0.32 ± 0.01 (0.2)	2.15 ± 0.23 (0.3)
EFV P12	81	1,843 (2,048)	L100I, K103N, T165I/T	0.24 ± 0.08 (0.9)	>500 (>299)	3.99 ± 0.46 (2.3)	3.90 ± 0.45 (0.6)
EVG P10	101	512 (512)	T66I, E92Q	0.15 ± 0.03 (0.6)	0.91 ± 0.12 (0.6)	186 ± 48 (108)	3.33 ± 0.25 (0.5)

EFV = efavirenz; EVG = elvitegravir; ATV = atazanavir

1 Relative to HIV-1 HXB2D sequence.

2 Fold-change values are calculated from the ratio of EC_{50} of the selected virus over the EC_{50} of HIV-1 HXB2D. The values represent the mean (± SD) obtained from 3 independent experiments (Data from PC-200-2025).

Table 20. Viral Breakthrough Frequency at Fixed Concentrations of LEN in PBMCs Infected with Patient-derived HIV-1 Isolates

Drug[1]	Fixed Drug Exposure[2]	No. Breakthrough Samples From 36 Total Independent Selections Spanning 6 HIV-1 Isolates (Frequency)[2]	Mutation(s)[3] (No. of Breakthrough Samples with Each Genotype)
LEN	IQ = 4	17 (47%)	Q67H (10), N74D (4), L56I (1) Q67H+T107N (1) Q67H+N74S (1)
	IQ = 8	3 (8%)	N74D (3)
	IQ = 16	4 (11%)	N74D (2), M66I (1), K70N (1)
	IQ = 24	2 (6%)	L56 (1), M66I+Q67H (1)
FTC	C_{min}	29 (81%)	M184V (16), M184I (13)
RPV	C_{min}	12 (33%)	E138K (5), Y181C (2) E138K+M230I (2), L100I (1) E138K+V106A (1) Y181C+F227C (1)
EFV	C_{min}	3 (8%)	K103N (2), L100I+K103N (1)
DTG	C_{min}	0 (0%)	NA

1 FTC = emtricitabine; RPV = rilpivirine; EFV = efavirenz; DTG = dolutegravir
2 LEN test concentrations were 0.92, 1.9, 3.7, and 5.5 nM, corresponding to tissue culture equivalent fold EC_{95} values (IQs) of 4, 8, 16, and 24. Antiretroviral controls were tested at their respective tissue culture equivalent C_{min}: FTC (364 nM), RPV (8 nM), EFV (250 nM), DTG (73 nM). After 35 days in culture, samples were tested for breakthrough variants by assessing infectivity and genotype.
3 Relative to the sequence of each input patient-derived HIV-1 isolate (Data from m2.6.3, Section 1, PC-200-2025).

Activity of LEN Against LEN-Resistant Site-Directed HIV-1 Capsid Mutants in MT-2 Single Cycle Antiviral Assay

Lenacapavir was tested for antiviral activity against a panel of clonal site-directed HIV-1 variants encoding LEN resistance associated mutations identified in our in vitro selection experiments.

Relative to the WT virus, T107N and Q67H capsid variants conferred low level resistance to LEN (4- to 6.3-fold), K70N, N74D and the double mutant Q67H+N74S conferred moderate LEN resistance (22- to 32-fold), and L56I and M66I, as well as four additional double mutant viruses (M66I+Q67H, Q67H+N74D, Q67H+T107N, N74D+T107N), all conferred high level LEN resistance (58- to >3,226-fold).

Lenacapavir also showed 8.8-fold and 21-fold reduced activity relative to WT HIV-1, respectively, against the A105E and Q67Y variants identified during in vitro drug selection with structurally similar analogues of LEN but not with LEN itself. The control antiretroviral EFV remained fully active against all of the capsid HIV-1 variants tested, with mean fold-resistance values ranging from 0.6 to 1.9. All tested LEN-resistant HIV-1 variants except Q67H showed significantly reduced infectivity in MT-2 cells (4-50% of WT virus), suggesting that the majority of the identified LEN resistance associated mutations severely compromise virus fitness in the in vitro system.

Table 21. Single-Cycle Infectivity of LEN Resistant Mutants of HIV-1 and Susceptibility to LEN in MT-2 Cells

HIV-1 Capsid Genotype	Single-Cycle Infectivity (% of WT)[1]	LEN	
		EC_{50} (nM)[1]	Fold-resistance[2]
WT	100	0.031 ± 0.003	-
L56I	8 ± 1	7.40 ± 0.67	239
M66I	4 ± 2	> 100	> 3,226
Q67H	121 ± 16	0.196 ± 0.028	6.3
Q67Y	39 ± 5	0.635 ± 0.040	21
K70N	7 ± 1	0.741 ± 0.214	24
N74D	50 ± 11	0.682 ± 0.106	22
A105E	9 ± 3	0.272 ± 0.044	8.8
T107N	44 ± 4	0.124 ± 0.006	4.0
M66I + Q67H	8 ± 2	> 100	> 3,226
Q67H + N74D	29 ± 6	34.1 ± 2.6	1,099
Q67H + N74S	33 ± 5	0.996 ± 0.176	32
Q67H + T107N	41 ± 7	1.91 ± 0.12	62

1 Infectivity and EC_{50} values represent the mean (± SD) obtained from 3 independent experiments.
2 Mean fold-resistance values (mutant EC_{50}/WT EC_{50}) obtained from 3 independent experiments (Data from PC-200-2026).
> 2-fold, > 10-fold, > 50-fold, > 100-fold, > 1000-fold

Antiviral Activity and Selectivity of LEN Against Non-HIV Viruses

To assess whether LEN has any activity against viruses other than HIV, LEN was tested against hepatitis B and C viruses, human rhinovirus serotype 16 (HRV-16), and respiratory syncytial virus strain A2 (RSV A2) in cell-based assays. Lenacapavir did not display selective in vitro antiviral activity against HCV or HRV up to the highest concentration tested (EC50 > 29 – 50 µM). Lenacapavir demonstrated low micromolar antiviral activity against HBV and RSV, with EC50 values and corresponding CC50/EC50 ratios of 1.5 µM and >34, and 8.2 µM and >6.1, respectively. These data indicate that LEN is approximately 29,000-fold more active against HIV-1 compared to HBV and therefore should not exert any clinical activity against HBV at drug exposures relevant for the inhibition of HIV.

Cytotoxicity and Selectivity of LEN in Primary Human CD4+ T-Lymphocytes and Monocyte-Derived Macrophages

To assess the cytotoxicity of LEN in the natural target cells for HIV-1 infection, cytotoxicity assays were performed in uninfected primary human CD4+ T-lymphocytes and monocyte-derived macrophages following 7-day and 12-day incubations, respectively.

Table 22. Cytotoxicity and Selectivity of LEN in Primary Human Target Cells

	$CD4^+$ T-Lymphocytes		Monocyte-Derived Macrophages	
Compound[1]	CC_{50} (µM)[2]	Selectivity[3]	CC_{50} (µM)[2]	Selectivity[3]
LEN	> 50	> 833,330	> 50	> 1,670,000
EFV	17.4 ± 6.8	14,150	22.2 ± 14.1	76,200
DTG	15.8 ± 3.9	16,460	34.7 ± 21.6	18,560
ATV	29.8 ± 16.7	4,330	36.6 ± 23.1	4,400

1 EFV = efavirenz; DTG = dolutegravir; ATV = atazanavir
2 CC_{50} values represent the mean (± SD) obtained from 3 independent donors (Data from PC-200-2019).
3 CC_{50}/EC_{50} ratio. Corresponding EC_{50} values are presented in Table 2.

Cytotoxicity and Selectivity of LEN in Human PBMCs

The cytotoxicity of LEN was also measured in human PBMCs in the resting state and upon mitogen activation. The cytotoxicity of LEN in unstimulated and stimulated PBMCs from three independent donors was similar to that observed in primary CD4+ T-lymphocytes and macrophages

Table 23. Cytotoxicity and Selectivity of LEN in Human PBMCs

	Resting PBMCs		Activated PBMCs	
Compound	CC_{50} (µM)[1]	Selectivity[2]	CC_{50} (µM)[1]	Selectivity[2]
LEN	> 44.4	> 888,000	> 50	> 1,000,000
Puromycin	0.6 ± 1.5	-	0.2 ± 0.1	-

1 CC_{50} values represent the mean (± SD) obtained from 3 independent donors (Data from m2.6.3, Section 2, PC-200-2019).
2 CC_{50}/EC_{50} ratio. Corresponding mean EC_{50} value against 23 HIV-1 isolates in PBMCs (0.05 nM) is presented in Table 3.

Cytotoxicity and Selectivity of LEN in Non-Target Human Cell Lines and Primary Cells

The cytotoxicity of LEN was assessed in four non-target human cell lines, including two hepatoma cell lines (Huh7 and Gal-HepG2), a prostate cancer cell line (Gal-PC-3), a normal embryonic lung fibroblast line (MRC-5), and in primary human hepatocytes. Lenacapavir did not display any significant cytotoxicity in the four tested cell lines or in primary human hepatocytes from three independent donors, with CC50 values in each cell line > 44 µM and >50 µM in primary human hepatocytes. When the mean anti-HIV-1 activity of LEN in human PBMCs is taken into account, these data indicate that LEN has a selectivity index (CC50/EC50) of >730,000 in each of the non-target human cell lines and primary human hepatocytes tested.

In Vitro Receptor Binding Potencies

A Lead Profiling Safety Screen was conducted to evaluate the activity of LEN against a panel of 87 targets. A single concentration of 10 µM was assessed to evaluate significant responses (>50% inhibition or induction). There were no significant responses for any of the targets evaluated. With an observed human therapeutic C_{max} of 136 ng/mL (0.140 µM) (free C_{max} of 1.98 ng/mL [0.002 µM]), after administration of the oral loading dose and a 927 mg subcutaneous (SC) dose, there is > 4,000-fold margin, and thus no clinically significant target inhibition or induction is likely.

6.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Exposure–safety

QT

A thorough QT study (GS-US-200-4332) with twice-daily administration of oral LEN 600 mg for 8 days was performed in parallel design due to the PK characteristics of lenacapavir. Assay sensitivity was established with moxifloxacin and placebo controls. Following twice-daily oral administration of LEN 600 mg for 8 days (from study Days 5 to 12), LEN C_{max} (GLSM) was 967.55 ng/mL on Day 12, 16-fold higher than the expected therapeutic exposure estimates from the Phase 3 studies of LEN in PWBP (GS-US-412-5624 and GS-US-528-9023; expected exposures derived using the population PK model).

A large and unexpected imbalance in baseline QTcF between LEN and placebo treatment arms was noted, with a mean difference in the averaged baseline QTcF (LEN – placebo) of 6.5 msec. To appropriately adjust for this imbalance, additional post hoc analyses were conducted along with the prespecified analysis. The covariate of time-matched baseline QTcF was replaced with the participant-level averaged baseline QTcF in the prespecified mixed-effect model for the noninferiority evaluation. The estimated treatment effects were less than or equal to 5 msec and the upper bounds of ΔΔQTcF were below 10 msec for all time points. On Study Day 12 at the supratherapeutic dose, the maximum mean (upper bound of the 2-sided 90% CIs) increase in QTcF using participant level average-baseline adjustment was 5.0 (8.0) msec.

A further post hoc analysis was the C-QTc analysis using a linear mixed-effects model, as specified in the recommendations of "Scientific white paper on concentration-QTc modeling" {Garnett 2018}. At the mean LEN C_{max} of approximately 1070 ng/mL following twice-daily oral administration of LEN 600 mg for 8 days (Study Day 12), mean ΔΔQTcF is predicted to be approximately 2.63 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF is below 10 msec (4.81 msec).

Safety in PWBP

Exposure-safety relationships for LEN were evaluated in participants in the Phase 3 studies PURPOSE 1 (N = 2140) and PURPOSE 2 (N = 2183) who were in the randomized blinded phase safety analysis set. Exposure-safety evaluations used predicted steady state LEN exposures (AUC_{tau}, C_{max}, and C_{trough}) for the simplified regimen, either from post-hoc PK parameters (when PK data were available) or from participant characteristics, such as body weight and sex at birth, as derived from population PK analysis (QP-2024-1082 LEN PopPK). LEN exposures were evaluated in relation to presence/absence of 5 common treatment-emergent AEs (headache, nausea, dizziness, vomiting, diarrhoea) and injection site nodules in these 2 studies combined and each separately. Furthermore, LEN exposures were also evaluated in relation to presence/absence of treatment-emergent liver-related laboratory abnormalities, defined as an increase of at least one toxicity grade in levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and direct bilirubin from baseline at any postbaseline visit. Participants were excluded from treatment-emergent laboratory abnormality analysis if baseline assessment was missing or if no postbaseline data were available for the respective assessment.

Box plots of LEN AUC_{tau} in participants receiving LEN in studies PURPOSE 1 and PURPOSE 2 in relation to the presence or absence of common AEs are presented in **Figure 12**, and box plots of LEN AUC_{tau} in the relation to the presence or absence of laboratory abnormalities are presented in **Figure 13**. Regardless of the presence or absence of each AE or laboratory abnormality evaluated, LEN exposures were similar. Corresponding box plots of LEN C_{max} and C_{trough} showed the same lack of trend and are not shown. As with the analysis of the combined studies, LEN exposures (AUC_{tau}, C_{max}, and C_{trough}) within each study were similar regardless of the presence or absence of each AE or laboratory abnormality evaluated (box plots

not shown).

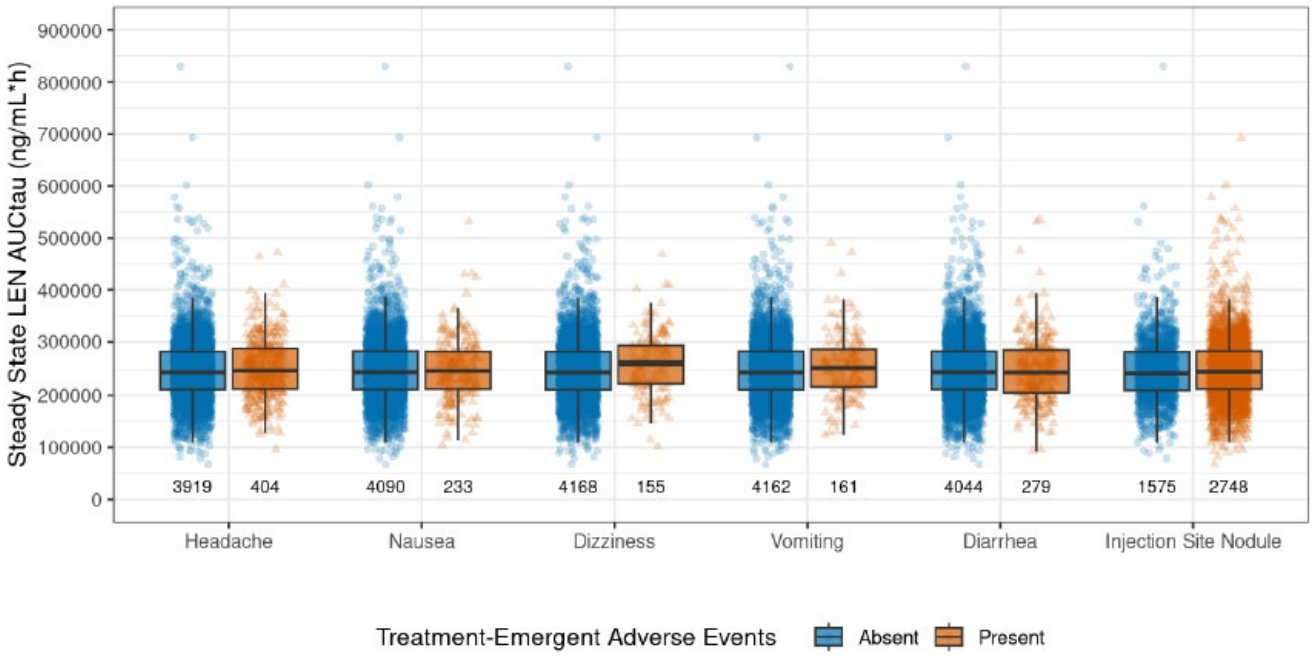


Figure 12. Box plots of steady state Lenacapavir AUC_{tau} by presence or absence of selected any grade treatment-emergent adverse events in participants in PURPOSE 1 and PURPOSE 2

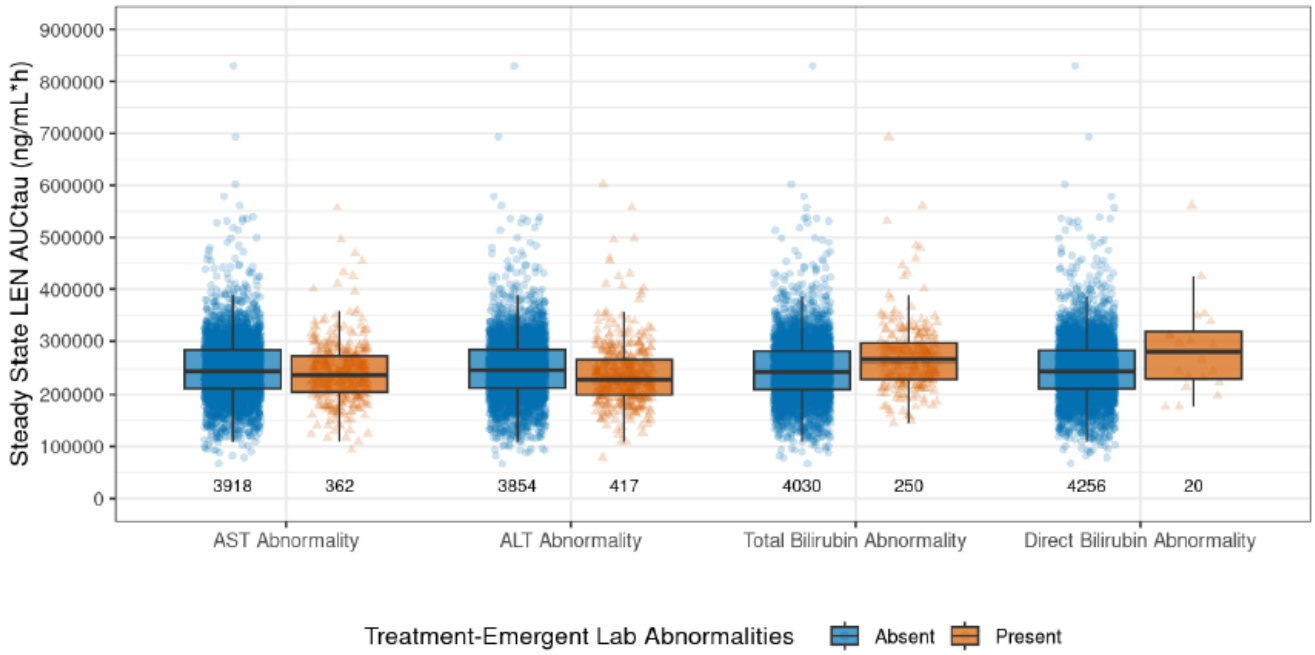


Figure 13. Box plots of steady state Lenacapavir AUC_{tau} by presence or absence of selected any

grade treatment-emergent laboratory abnormalities in participants in PURPOSE 1 and PURPOSE 2

6.2.5. Dose selection and therapeutic window

Lenacapavir dosing regimen proposed for people who would benefit from pre-exposure prophylaxis (PWBP) is SC LEN 927 mg (309 mg/mL, 2 x 1.5 mL) administered on Day 1 along with required oral doses of LEN 600 mg (2 x 300 mg tablet) administered on Day 1 and Day 2. This will be followed by SC doses of LEN 927 mg administered every 6 months (26 ± 2 weeks). This dose for PrEP was guided by the in vitro inhibitory quotient (IQ), the measure of drug concentration needed for inhibition of viral replication. Protein binding-adjusted 95% effective concentration (paEC95) is an IQ metric used to define the drug concentration at which viral replication is inhibited by 95% in serum (as determined in MT-4 cells).

The rationale for dose selection for LEN in PWBP is supported by antiviral activity, PK and safety data from the Phase 1b proof-of-concept study (Study GS-US-200-4072) in treatment naive and treatment-experienced (but CAI-naive) people with HIV-1, as well as PK and safety data from the 3 Phase 1 studies in healthy volunteers (Study GS-US-200-4538, Study GS-US-200-4071, and GS-US-200-5709). In the Phase 1b proof-of-concept study (Study GS-US-200-4072), 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 log10 copies/mL. All treated participants achieved at least 1 log10 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 (e.g., IQ 1.1 – 9.9) than the paEC95 for WT HIV-1 (paEC95 = 3.87 ng/mL in MT-4 cells). Based on these data, a plasma concentration of 15.5 ng/mL (corresponding to an IQ of 4 based on paEC95 from MT-4 cells) is anticipated to provide near maximal antiviral activity for HIV-1 treatment.

As with the Phase 2/3 clinical studies in people with HIV-1 and ongoing Phase 3 studies in PWBP, the proposed dosing regimen targets an exposure whereby the lower bound of the 90% CI of mean LEN concentration is 4-fold higher than the paEC95 (i.e., IQ4) within a few days of dosing initiation through the end of the SC dosing interval (every 6 months) (**Figure 14**).

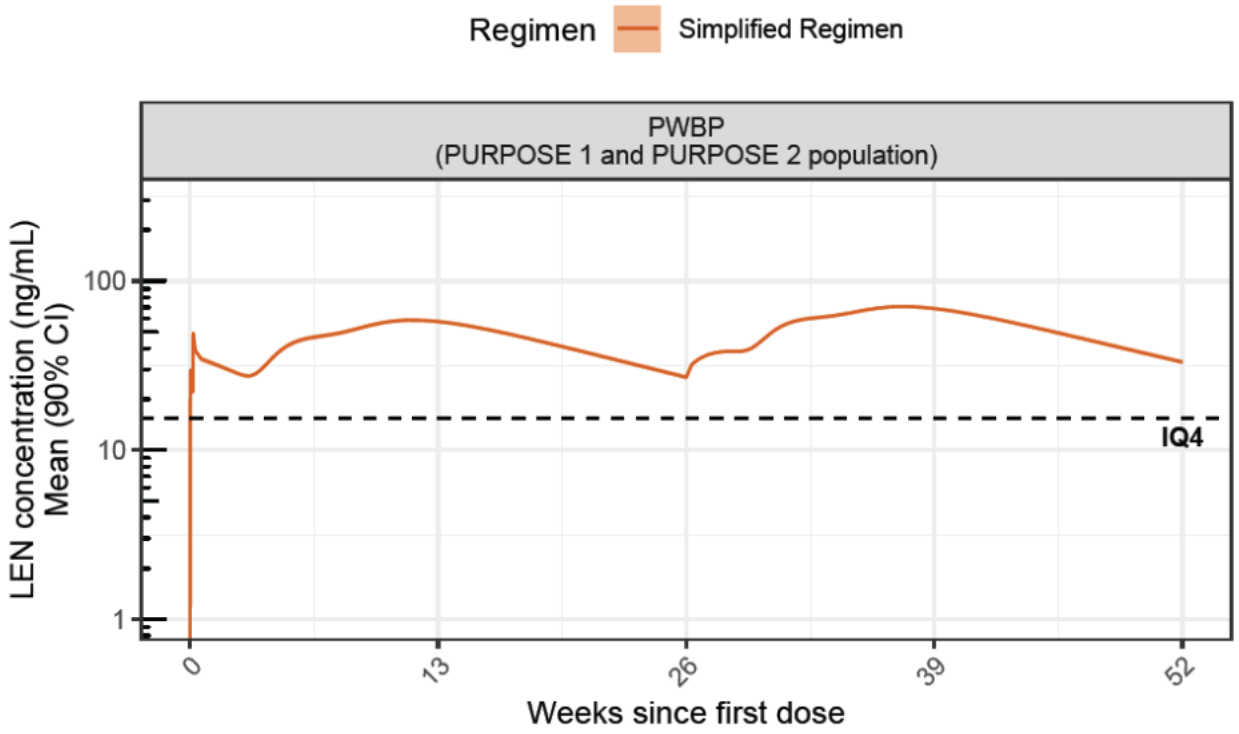


Figure 14. Simulated Mean (90% CI) LEN Concentrations Versus Time Profiles for the Simplified Q6M Regimen in PWBP

6.2.6. Overall discussion and conclusions on clinical pharmacology

6.2.6.1. Discussion

Pharmacokinetics

Lenacapavir is a known chemical substance, previously approved in combination with other antiretrovirals(s) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with multidrug resistant HIV-1 infection, under the Tradename Sunlenca®.

A new posology is introduced compared to that recommended for the HIV-1 indication (Sunlenca). An oral loading regimen is proposed, with 600 mg administered on Day 1 and Day 2, while a SC dose of 927 mg is administered on Day 1, and every 6 months thereafter. This simplified dosing regimen was applied in the pivotal pre-exposure prophylaxis (PrEP) studies PURPOSE 1 and PURPOSE 2.

The primary roles of pharmacokinetics in this submission were to support efficacious and safe exposure in the indicated population PWBP (in adults and adolescents ≥35 kg), during pregnancy, after administration at alternative injection sites, and during oral bridging.

Two SmPCs are provided, one for the SC and one for the oral formulation. With regards to their PK content, these are identical apart from section 4.2 (posology & administration).

The upper limit of the therapeutic window was previously concluded from the interaction potential of lenacapavir with the strong P-gP, CYP3A and UGT1A1 inhibitor atazanavir/cobicistat, which is not recommended by the Applicant, due to an increase in AUC of 4.2-fold and C_{max} of 6.6-fold. Thus, this was considered above the upper limit of the therapeutic window in human.

The lower limit of the therapeutic window is based on the in vitro inhibitory quotient (IQ), which is defined as the protein binding–adjusted 95% effective concentration at which viral replication is inhibited by 95% in serum. The proposed dosing regimen targets an exposure whereby the lower bound of the 90% CI of mean LEN concentration is 4-fold higher than the paEC95 (i.e., IQ4 = 15.5 ng/ml) within a few days of dosing initiation through the end of the SC dosing interval (every 6 months).

Methods

Bioanalysis
The performance of the bioanalytical methods for assessment of lenacapavir was satisfactory.

Lenacapavir is a mixture of atropisomers. In metabolism studies, bioanalysis separated these, but in the remaining clinical studies, chromatographic conditions were selected to generate a single peak for both atropisomers, which is acceptable.

Population PK analysis
A previously developed population PK model (QP-2023-1078 LEN PopPK) served as the base model in the current analysis (QP-2024-1082 LEN PopPK). The previously developed model was originally submitted in a Type II variation application for Sunlenca (EMEA/H/C/005638/II/0022/G). In that procedure, the model was of limited importance and was therefore not further assessed. In this procedure, the final model supports extrapolation of efficacy and safety from adult participants to adolescents weighing ≥35 kg, the proposed forgiveness window for missed dose (±2 weeks), the proposed oral bridging during planned missed injections, and PK parameter values reported in the SmPC. None of these claims are based solely on model simulations but are also supported by observed lenacapavir concentrations. However, only sparse PK sampling was conducted in PWBP and hence the only reliably observed exposure metric in the target population is C_{trough}.

In the final model, 43 THETA parameters and 8 OMEGA parameters were estimated, all with unexpectedly low relative standard errors (RSEs), and all OMEGA parameters with high η-shrinkage. The condition number was only 338, while the condition number for the base model (excluding 4 of the identified covariate effects) was 1523; the output file from NONMEM indicates negative eigenvalues. In total, these findings suggest that the model is over-parameterised. It doesn't seem like the Applicant has tried to reduce the model at any stage during model development. An easy way to simplify the model would be to fix all disposition parameters to the estimates received when the model was fitted to only IV data, and to reduce the number of study effects on the residual error. However, given that the VPCs stratified on study indicate that the model can predict the observed data from PURPOSE 1 and PURPOSE 2 adequately and given that none of the claims that the model is supporting requires an extrapolation outside observed PK data, no model updates are requested.

To support the current application, the Applicant submitted two additional population PK analyses: a model of lenacapavir when administered SC at different injection sites (QP-2024-1091 LEN PopPK), and a model of lenacapavir when dosed concomitantly with rifampicin or efavirenz (as a substitute for rifabutin) (QP-2024-1097 DDI LEN PopPK). The model for SC administration at different injection sites is highly over-parameterised, given the limited data that it is based on. The model for concomitant administration with rifampicin or efavirenz is based on data for the interactions when lenacapavir is orally administered, while it attempts to also predict the interaction when lenacapavir is subcutaneously administered, hence the predictions rely on untestable assumptions. Therefore, these models are not considered adequate for their purpose, and they are not presented further in the Overview.

Physiologically based PK analysis

The Applicant submitted a PBPK analysis to support dose-adjustments when lenacapavir is administered concomitantly with rifampicin or rifabutin. Due to lack of data on the parenteral interaction potential, the model relies on untestable assumptions. The model is hence not considered adequate for its purpose, and it is therefore not presented further here.

Absorption

The data on absorption for lenacapavir is acceptable.

The pharmacokinetics following SC administration at different injection sites was investigated in study GS-US-200-4540. The geometric mean values of C_{6mo} in this study (the concentration 6 months after injection) was somewhat lower for the alternative SC injection sites, compared to SC injection into the abdomen.

The Applicant submitted further data from available plasma lenacapavir concentrations collected from participants from PURPOSE 1, 3 and 4 clinical studies who chose to receive the subcutaneous (sc) injections via alternative injection sites (thigh, upper arm or buttocks). For thigh injections, the clinical data from PURPOSE 1, with 45 individuals with C_{trough} (week 26) data, indicates that the lenacapavir concentration at the second injection is within the same range as after injection in the abdomen, which has shown clinical efficacy. This is considered sufficient to accept thigh as an alternative injection site for sc of lenacapavir.

For upper arm and buttocks, data from PURPOSE 1 and PURPOSE 2 is not yet available, as these injection sites were only allowed in the later Open Label Extension Phase of the studies. The clinical studies PURPOSE 3 and PURPOSE 4 have very limited available data for upper arm, buttocks (and thigh) injections. While the concentrations after upper arm or buttock injection at Week 26 appear comparable to abdomen injection, the data generated so far is too limited. The Applicant has committed to provide additional PK data for the alternative injection sites buttocks and upper arm post approval to support use of these injection sites (**REC**).

In healthy subjects, C_{max} and AUC_{inf} of lenacapavir were up to 45 and 15% higher, respectively, after administration of LEN 300 mg tablets with a high- or low-fat meal as compared to fasted condition. The confidence interval included 100%, but the interindividual variability was large. The food effect was only studied at a dose of 300 mg. Due to the less than dose proportional increase in exposure the food effect should have been studied at the intended oral dose of 2 x 300 mg. Since no food restrictions have been

used in the pivotal clinical studies and the oral doses are only administered as an initiation treatment, this issue will not be further pursued.

At oral bridging regimen, the dose is 300 mg, which was the studied dose for food effect. The food effect at oral bridging is not likely to be of clinical significance.

Distribution

Lenacapavir is highly protein bound, with an in vitro free fraction of 0.70-1.46% in human plasma and binds primarily to albumin. The fu of 1.46% is however not deemed reliable due to low recovery and a determination at a single supratherapeutic concentration.

In vivo protein binding is high, 99.8% in healthy subjects (fu 0.2%), the in vivo data is stated in the SmPC.

Elimination

The total recovery of radioactivity in faeces and urine is low (76.1%), considering it should preferably exceed 90% of the dose, and 80% of the recovered radioactivity should be identified. Even when excluding subjects that withdrew early, the recovery does not reach 90 % (82%). Even though recovery of total radioactivity is incomplete, it seems unlikely that any major metabolite would arise or that it would change conclusions on excretion pathways. The overall conclusion that the extent of metabolism of lenacapavir is low is agreed. Lenacapavir is primarily eliminated unchanged via biliary excretion. Renal elimination is a minor pathway. Similar conclusions are reached in non-clinical data, however with a slightly higher extent of metabolism.

The effect of inhibitors on incubations of recombinant CYP3A5 or UGT1A1 and lenacapavir was not assessed in vitro. However in vivo data to confirm these findings are available with voriconazole (strong CYP3A inhibitor) and atanazavir/cobicistat (strong CYP3A/P-gp/UGT1A1 inhibitor) and rifampicin (strong inducer of multiple enzymes and transporters), respectively.

88% of the recovered radioactivity in plasma was identified. 68.8% of the $AUC_{0\text{-}1176h}$ can be attributed to the lenacapavir atropisomers. Several peaks were identified and were attributed to photo- or radiolysis, as they were also present in controls. This is endorsed. Thus, only lenacapavir was identified in plasma.

The rotation half-lives between LEN.1 and LEN.2 are in the hour range (up to 2h in hour serum, up to 14h in in FaSSGF, FaSSIF, FeSSIF), which is significantly shorter than the half-life in vivo. Thus, any interconversion of the atropisomers is not expected to be clinically relevant, as confirmed by similar ratios of LEN.1 and LEN.2 in the stability studies and in the mass balance study.

Lenacapavir has further chiral centres, which were not shown to epimerise in non-clinical and clinical studies with ^{14}C-lenacapavir. It is thus agreed that interconversion is not an issue for lenacapavir.

Genetic polymorphism is not likely to significantly affect the PK of lenacapavir as it has a low extent of metabolism.

Dose proportionality and time dependencies

Dose proportionality has not been studied at steady state, which is acceptable since the proposed posology only includes one subcutaneous (927 mg) dose level.

Extensive accumulation is observed following twice daily oral administration of 600 mg of LEN tablets. This is not unexpected due to the long oral terminal half-life (approximately 10-12 days). The dosing is considerably lower (300 mg/week) for the oral bridging regimen and limited to 6 months according to the SmPC. Given the wide therapeutic window and that observed data (mean plasma concentrations) do not indicate exposures of concern at oral bridging, this is acceptable.

The measured accumulation ratio after multiple s.c. doses in the two phase 3 studies included the oral loading phase, thus, not fully representative of accumulation of sc lenacapavir at steady state. However, this is acceptable as the degree of accumulation was small (1.2-1.3-fold).

Target population

The target population includes adults and adolescents who would benefit from pre-exposure prophylaxis (PrEP). Two Phase III studies, PURPOSE 1 and PURPOSE 2, were conducted in this population. The pharmacokinetics of lenacapavir is not expected to differ significantly between the general population and the target population.

Sparse PK samples have been collected in the target population, thus observed pharmacokinetic data only include plasma concentrations at a few predefined timepoints, including C_{trough}. This is acceptable, as the main role for PK was to support that therapeutically effective concentrations were maintained. The week 52 interim analyses from both studies were submitted. Lenacapavir PK was analysed in a random subset of 10% of adult participants and in additional subpopulations of interest. The mean (and 90% CI) trough concentration (C_{trough}) of lenacapavir at weeks 26 and 52 was above the efficacy target of 15.5 ng/mL, for the main PK subset, indicating effective drug levels.

Oral bridging
The Applicant proposed an oral bridging regimen of 300 mg lenacapavir per week, to maintain effective concentrations in case of missed sc injections. The mean lenacapavir concentrations before and after oral bridging were evaluated in PURPOSE 1 and PURPOSE 2, in a limited number of individuals (<40). The results showed that the mean lenacapavir concentrations were maintained above the efficacy target of 15.5 ng/mL throughout the oral bridging period in both studies. Additional data from studies GS-US-200-4625 and GS-US-200-4334, which involved HIV-1 treated patients receiving oral bridging of lenacapavir, also demonstrated that the mean lenacapavir concentration and its lower bound 90% confidence interval remained above the efficacy target throughout the oral bridging period, although data was limited at 30 weeks (n=15). The proposed oral bridging regimen is further supported by simulations from the population PK model. Overall, these results support the use of oral weekly lenacapavir as a bridging measure in case of missed injections.

Dosing window
The Applicant proposes a dosing window of 2 weeks for the sc administrations of lenacapavir. Based on simulations, the mean lenacapavir concentrations are predicted to be above target of 15.5 ng/mL, even if the dose is delayed by 2 weeks (lower limit of 90% CI: 23.0 ng/mL). If more than 28 weeks have elapsed

since the last injection, individuals must be retested for HIV-1 infection, and if clinically appropriate to continue PrEP with lenacapavir, the initiation regimen should be restarted. This recommendation can be agreed with.

Special populations

No dose adjustment is recommended for patients with severe renal impairment (nor mild or moderate), this is agreed, as it falls within the therapeutic window (< 2-fold increased exposure).

For hepatic impairment, the applicant presented unbound PK parameters, where increases in C_{max} and AUC were 5.06 and 2.84-fold, respectively, which the applicant considers lying within the therapeutic window, thus not requiring a dose adjustment. This is agreed.

No effect of age on the PK parameters of lenacapavir was identified in the population PK analysis. However, there is limited data in elderly for lenacapavir, both in the PURPOSE studies and in the previously submitted studies in HIV-1 infected subjects (studies GS-US-200-4625 and GS-US-200-4334). Eighteen subjects in the age span of 65-74 years and 1 subject in the age span of 75-84 years were included in the popPK analysis dataset.

Sex was identified as a statistically significant covariate in the population PK analysis. However, the impact of sex on the exposure is minor and clinically insignificant.

Body weight was included as a covariate on all disposition parameters in the population PK model, using fixed allometric scaling with standard exponents. The statistical significances of the effects were hence not formally tested. Given the physiological rational behind allometric scaling with standard exponents, this is considered acceptable. The impact of body weight on lenacapavir exposure is not considered clinically relevant and no dose adjustments are proposed, which is agreed.

Paediatrics
Efficacy and safety of lenacapavir are to be extrapolated to the adolescent population based on similar exposure. A limited number of adolescent participants in the pivotal studies contributed to the PK analysis (at week 26 n=41 in PURPOSE 1 and n=2 in PURPOSE 2). The observed exposure in adolescent participants were within the range observed in adult participants. Simulations from the population PK model indicate that the exposure is slightly increased in subjects with a low body weight (age was not a statistically significant covariate in the model). However, given the therapeutic window, this expected increase in exposure is not considered clinically relevant. Efficacy and safety can thus be extrapolated from adults to adolescents weighing ≥35 kg.

Pregnancy
No dedicated study has been conducted to evaluate the use of lenacapavir in pregnant women. Pregnant individuals were excluded from entering the PURPOSE studies, but those who became pregnant during the studies were given the choice to continue study drug. Observed concentrations at C_{trough}, is currently available from week 26, week 52, week 78 and week 104 for pregnant and post-partum participants. The pooled average C_{trough} for these timepoints (≥ 24 to ≤ 28 weeks after last injection) included more than 50 individuals for all trimesters of pregnancy, and N=39 post-partum, and indicates maintained efficacious concentrations in pregnancy and post-partum at these time points. Patients pregnant in the second and

third trimester have comparable LEN C_{trough}, to participants that did not become pregnant, in pre-pregnancy or post-partum. The Applicant has also submitted literature to support that the activity of Pgp as well as CYP3A4 in the intestine does not appear to be altered in pregnancy. The information that no clinically relevant changes in lenacapavir exposure during pregnancy and postpartum were observed compared to lenacapavir exposures in non-pregnant participants is included in the SmPC section 5.2.

Lactation
There was no dedicated lactation study, but data from around 100 breastfeeding women are available from the PURPOSE 1 study. Lenacapavir is present in breast milk, with a median milk-to-plasma ratio of 0.52. The median infant-to-mother plasma concentration ratio was 0.02, which indicates that lenacapavir is transferred to in the infant circulation to a relatively low degree, likely due to the low bioavailability of lenacapavir. However, the absolute concentrations in infant plasma were still not negligible, with a median of 1.63 ng/ml. Available data are presented in the SmPC.

For safety in pregnancy and lactation, see Clinical Safety section/SmPC section 4.6.

Pharmacokinetic interaction studies

There are no new in vitro or in vivo studies on the interaction potential for lenacapavir for the indication PrEP.

C_{max} for lenacapavir for PrEP at week 26 and at steady state was estimated to 81.4 ng/ml and 90.1 ng/ml. Since this is lower than what was estimated for Sunlenca, the earlier conclusions are still valid.

The design of in vitro studies and in vivo Study GS-US-200-4333 was overall acceptable with appropriate dosing and treatment lengths.

Effect of other medicines on lenacapavir
In vitro studies showed that lenacapavir is a substrate of CYP3A, P-gp and UGT1A1.

The in vivo study GS-US-200-4333 evaluated the drug-drug interaction with CYP3A4/P-gp/UGT1A1 inhibitors and CYP3A4/P-gp inducers.

The strong CYP3A4/P-gp/UGT1A1 inhibitors ATV/COBI (atazanavir/cobicistat) increased lenacapavir AUCinf 4.2-fold. This is reflected in sections 4.4 and 4.5 in the SmPC and co-administration of lenacapavir and atazanavir/cobicistat is not recommended, which is acceptable. Coadministration with only a strong CYP3A4 inhibitor (voriconazole) or CYP3A4/P-gp inhibitors (cobicistat and darunavir/cobicistat) resulted in increases in lenacapavir exposures that were lower, and not clinically meaningful. No dose adjustment or warning is suggested in the SmPC, this is acceptable.

For lenacapavir as a victim of induction, strong and moderate inducers of CYP3A4/P-gp, rifampicin and efavirenz, decreased lenacapavir exposures by 84% and 56%, respectively. The recommendation in the SmPC is that concomitant use of strong inducers of CYP3A4/P-gp with lenacapavir is contraindicated and moderate inducers of CYP3A4/P-gp with lenacapavir is not recommended. This is agreed.

Study GS-US-200-4333 is not considered adequate to describe all aspects of the complex interaction between lenacapavir and inducers, and it appears difficult to predict the anticipated effect of inducers on s c lenacapavir from this study. Lenacapavir is mainly eliminated via P-gp, as unchanged substance excreted into bile. Oral lenacapavir has a low bioavailability (4-7%) and is effluxed by P-gp in the intestine. Study GS-US-200-4333 does not cover the relative contribution in the interaction of systemic and intestinal P-gp and CYP3A4. To further complicate the interpretation of the interaction study performed, rifampicin is also an inhibitor of Pgp in the shorter time frame, and only a 12 h separation between the doses of lenacapavir and rifampicin was studied. In addition, oral lenacapavir shows dose dependent bioavailability, with less than dose-proportional increases in exposure with increased doses. The tested dose in the DDI study of 300 mg is lower than the clinical dose of 600 mg.

The Applicant has presented published clinical DDI data from a handful of other Pgp and/or CYP3A4 substrates where DDI data from both parenteral and oral administration of the substrate is available (tacrolimus, oxycodone, digoxin). For these drugs, a smaller DDI effect has indeed been observed in the case of parenteral administration of the substrate due to the lack of first pass effect. The presented compounds however have very different PK properties from lenacapavir when it comes to e g bioavailability, elimination routes and the magnitude of interaction with rifampicin. Thus, it is difficult to use these data quantitatively to deduce the anticipated magnitude of an interaction effect with inducers for parenteral lenacapavir.

For lenacapavir as a victim of an acid-reducing agent, administration of a single dose of lenacapavir 2 hours after famotidine did not result in clinically meaningful changes in lenacapavir PK. Accordingly, there are no restrictions for use of lenacapavir with acid-reducing agents.

Effect of lenacapavir on other medicines
Lenacapavir inhibited UGT1A1, MATE1 and BSEP in vitro, however the IC50 of 3.2, 2.39 and 1.21 µM, respectively are much higher than the cut-off concentration relevant for inhibition of systemically ($50*C_{max,u}$; i.e. 0.05 µM) expressed enzymes and transporters and the potential for clinically relevant drug-drug interaction are considered low.

For CYP2C9 and UGT1A1, no induction was seen in the concentration range 0.01-1 µM, but a greater than two-fold increase was seen in one donor at 3 and 10 µM. For CYP2B6, no induction was seen in the concentration range 0.01 to 0.1 µM, but at 0.3 µM a 2-fold increase was seen in two donors. At higher concentrations (1, 3 and 10 µM), no induction of CYP2B6 was seen. Considering the cut-offs used for evaluation of interaction potential in vivo, the concentrations relevant for induction of systemically ($50*C_{max,u}$; i.e. 0.05 µM) expressed enzymes are lower than 0.1 µM and the potential for clinically relevant drug-drug interaction due to induction of CYP2C9, UGT and CYP2B6 are considered low and no in vivo studies need to be performed.

For CYP3A4, a more than 2-fold increase in mRNA was observed in one of the three donors starting at 0.1 µM and the increase was concentration dependent (3.5-fold increase at 0.1 µM and 9.5-fold increase at 10 µM). The *in vitro* study is considered positive for CYP3A4 enzyme induction according to Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2** since a more than 100% increase in mRNA was seen in one donor and the increase was concentration dependent.

The applicant has used the mechanistic static model in report AD-200-2055 and concluded that lenacapavir is no potential inducer of CYP3A4 in vivo. This is not agreed since the mechanistic static model is not qualified in an adequate way and not acceptable in this case when aiming to estimate the exposure of a probe drug resulting from both induction and inhibition.

Lenacapavir was shown to be a moderate inhibitor of CYP3A4 as coadministration of lenacapavir with midazolam resulted in a 3.6-fold increase in midazolam AUCinf. Caution is advised if lenacapavir is coadministered with sensitive CYP3A substrates that have a narrow therapeutic index.

Time-dependent inhibition (TDI) in vitro data has been presented for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, with no signs of inhibition by lenacapavir.

Lenacapavir does not inhibit OATP transporters (as observed with coadministration of lenacapavir with pitavastatin). Lenacapavir inhibited P-gp transporters (as observed with coadministration of lenacapavir with tenofovir alafenamide resulting in a 32% increase in AUCinf) and BCRP transporters (as observed with coadministration of lenacapavir with rosuvastatin resulting in a 31% increase in AUCinf); however, these interactions are unlikely to be clinically meaningful. Therefore, substrates of P-gp, BCRP, and OATP can be coadministered with lenacapavir.

Exposure relevant for safety evaluation

There is no observed AUC or C_{max} at steady state in the target population. Simulated exposures at steady state are: AUC_{tau} = 257334 ng*h/mL (38.7%), C_{max} = 82.4 ng/mL (40.4%) and C_{trough} = 36.9 ng/mL (53.5%). The simulated C_{trough} corresponds well with the observed C_{trough} in PURPOSE 1 and PURPOSE 2.

Mechanism of action

LEN binds to cross-linked CA hexamer with KD = 1.4 ± 0.6 nM and affects both the rate and extent of capsid assembly resulting in short, misshaped and heterogeneous polymers and targets both an early and late stage capsid-mediated event essential for HIV-1 replication. Compared to other already approved antiretrovirals LEN has a different target and exhibits a new mechanism of action.

Primary and secondary pharmacology

The in vitro EC95 value in MT-4 cells was 0.23 nM. and a plasma protein binding-adjusted EC95 (paEC95) value of 4 nM was estimated which was then used for the estimation of clinical inhibitory quotient (IQ) for the projected trough concentration of LEN in humans.

The dosing regimen for PrEP was selected to target the same exposure as during HIV-1 treatment, where the lower bound of the 90% CI of the C_{trough} is above 15.5 ng/ml (at least 4-fold higher than the in vitro paEC95 (3.87 ng/mL = IQ1; MT-4 cells)) within a few days of dosing initiation and maintained through the end of the dosing interval (every 26 weeks). This is supported.

No cross resistance has been observed for LEN to the 4 main drug classes. Resistance mutations in HIV-1 protease, RT, and integrase did not affect the antiviral effect of LEN as demonstrated in site-directed

mutants as well as clinical isolates. Moreover, the antiviral activity of LEN was not affected by the presence of naturally occurring pre-existing Gag polymorphisms or Gag cleavage site mutations.

Lenacapavir shows high selectivity for HIV and is not anticipated to impact HBV.

Exposure-safety

The TQT study (GS-US-200-4332) support that it is unlikely that exposure to Lenacapavir has a clinically meaningful effect on QT/QTc prolongation.

Lenacapavir exposures were evaluated in relation to presence/absence of 5 common treatment emergent AEs (headache, nausea, dizziness, vomiting, diarrhoea) and injection site nodules. Furthermore, lenacapavir exposures were also evaluated in relation to presence/absence of treatment-emergent liver-related laboratory abnormalities. Regardless of the presence or absence of each of these aspects, lenacapavir exposures were similar. However, it should be noted that the information in the data is limited, given that most subjects in the analysis set did not have any PK samples taken.

6.2.6.2. Conclusions

The fundamental pharmacokinetic properties of lenacapavir have been described and assessed previously (Sunlenca EMEA/H/C/005638/0000). PK in the target population PWBP has been adequately described.

The mechanism of action and the preclinical characterization of antiviral activity is appropriate and has previously been established for lenacapavir (Sunlenca EMEA/H/C/005638/0000). Activity against HIV-1 is subtype independent. There is no indication of cross resistance with other drug classes. The intrinsic barrier to resistance is anticipated to be relatively low, as single and double mutants confer high level resistance. No activity against co-infecting viruses such as HBV is anticipated.

6.3. Clinical efficacy

6.3.1. Dose response study(ies)

Please see section 6.2.5 Dose selection and therapeutic window.

6.3.2. Main studies

6.3.2.1. GS-US-412-5624 (PURPOSE 1)

Study title

A Phase 3, Double-Blinded, Multicenter, Randomized Study to Evaluate Safety and Efficacy of Twice Yearly Long-Acting Subcutaneous Lenacapavir, and Daily Oral Emtricitabine/Tenofovir Alafenamide for Pre-Exposure Prophylaxis in Adolescent Girls and Young Women at Risk of HIV Infection

Study design

Study GS-US-412-5624 is an ongoing Phase 3, randomized, double-blind, multicentre study in cisgender AGYW to compare the HIV-1 incidence in each of the LEN and DVY PrEP groups with the counterfactual control of background HIV-1 (bHIV) incidence, defined as the estimated HIV-1 incidence in the screened population. Truvada serves as the internal active control.

As illustrated in **Figure 15**, the study includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a Pharmacokinetic (PK) Tail Phase.

The Incidence Phase estimated the bHIV incidence within the population screened for eligibility using recency assay results from samples that were positive for HIV-1 infection incorporated into a recent infection testing algorithm (RITA).

Participants determined to be HIV-1 negative and who met eligibility criteria proceeded to the Randomized Blinded Phase, where they were randomized in a 2:2:1 ratio to receive either LEN, DVY, or TVD, respectively. After the completion of the Randomized Blinded Phase, participants were offered the opportunity to receive open-label (OL) LEN in the LEN OLE Phase, which allows for further long-term efficacy and safety follow-up.

Participants who discontinued study drug during the Randomized Blinded Phase entered the PK Tail Phase, which provided a known efficacious OL regimen to provide HIV prevention for participants during the time when LEN concentrations decline.

If a participant prematurely discontinued blinded study drugs without an HIV-1 diagnosis, regardless of reason, transitioned to the PK Tail Phase (a random transition), and received at least 1 dose of study OL oral PrEP, the participant was included in the Open-Label Oral PrEP Analysis.

Enrolment of adolescents (participants ≥ 16 and < 18 years of age) commenced following the DMC review of unblinded safety data from the first 300 adult participants through 8 weeks of follow-up and recommendation to continue the study.

Study centres were located in South Africa (25 study sites) and Uganda (3 study sites).

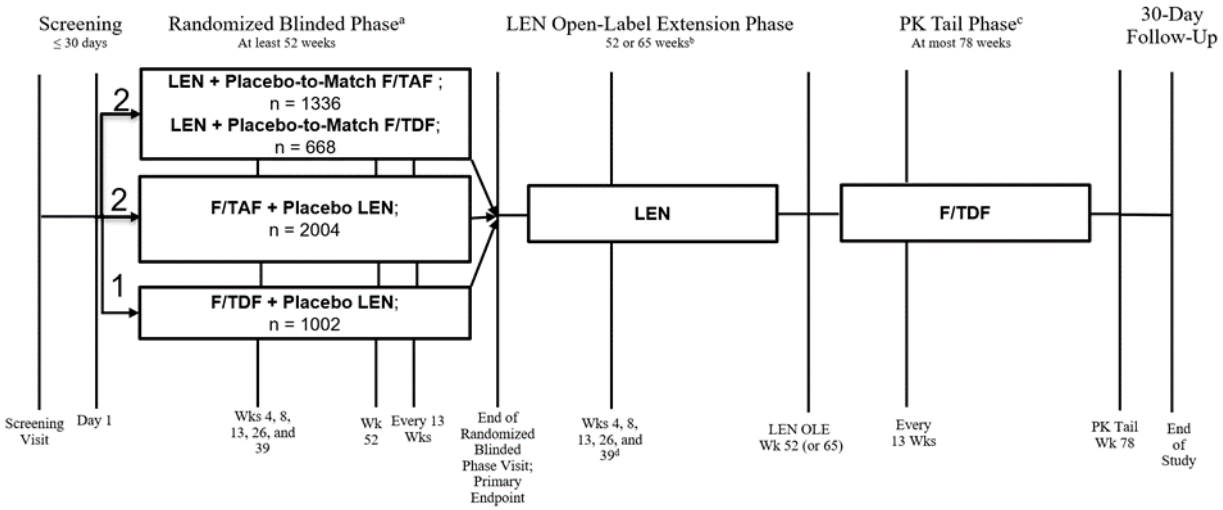


Figure 15. Study Schema – GS-US-412-5624

F/TAF = emtricitabine/tenofovir alafenamide (Descovy®; DVY); F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada®; TVD); LEN = lenacapavir; OL = open label; OLE = open-label extension; PK = pharmacokinetic(s)

a. Participants were to continue in the Randomized Blinded Phase until all randomized participants have completed at least 52 weeks of follow-up in the study and the Applicant completed the primary analysis. In the case that the Randomized Blinded Phase was stopped early for an efficacy outcome, some participants may have less than 52 weeks of follow up.
b. The duration will be dependent on timing of the OL LEN injection.
c. Participants who prematurely discontinued study drug during the Randomized Blinded Phase or LEN OLE Phase, or those randomized to LEN in the Randomized Blinded Phase who declined to participate in the LEN OLE Phase upon unblinding, will transition to the PK Tail Phase.
d. Week 4 and Week 8 visits are only required for participants who were randomized to oral DVY or TVD in the Randomized Blinded Phase.

Randomisation

Participants who met prebaseline criteria (Part B) were randomized in a 2:2:1 ratio to active LEN, once daily oral F/TAF, or once daily oral F/TDF starting on Day 1 using an interactive web response system (IWRS). There was no stratification for randomisation.

Blinding

During the Randomized Blinded Phase, participants and all personnel directly involved in the conduct of the study were blinded to study drug assignment. Specified personnel were unblinded based on their study role. Study drug was dispensed by the unblinded study pharmacist, or designee, in a blinded fashion to the participants.

Description of trial intervention

Approximately 5010 participants who met all eligibility criteria were randomized in a 2:2:1 ratio (LEN:DVY:TVD) into 1 of the study drug groups summarized in **Table 24**.

Participants were given study drugs (LEN, DVY, or TVD) for a planned minimum duration of 52 weeks in the Randomized Blinded Phase. In the LEN OLE Phase, participants will receive SC LEN injections every 26 weeks and complete study visits for a planned duration of up to 65 weeks. In the PK Tail Phase, participants will receive TVD for up to 78 weeks.

Table 24. Study drug regimens in the randomised blinded phase

LEN	SC LEN 927 mg + PTM oral DVY; oral loading LEN 600 mg (2 × 300 mg) on Days 1 and 2 SC LEN 927 mg + PTM oral TVD; oral loading LEN 600 mg (2 × 300 mg) on Days 1 and 2
DVY	Oral DVY + placebo SC LEN; oral loading PTM LEN (2 tablets) on Days 1 and 2
TVD	Oral TVD + placebo SC LEN; oral loading PTM LEN (2 tablets) on Days 1 and 2

DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); LEN = lenacapavir; OLE = open-label extension; PTM = placebo-to-match; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Descovy (DVY): 200 mg of emtricitabine and 25 mg of TAF.
Truvada (TVD): 200 mg of emtricitabine and 300 mg of TDF.

Concomitant and rescue therapies

If SC LEN/placebo could not be administered within the injection visit window due to extenuating circumstances, including the clinical hold on SC LEN implemented by the FDA (20 December 2021 through 16 May 2022), participants received open-label TVD starting when their next injection was due (before the approval of Protocol Amendment 2) or blinded once-weekly oral LEN 300 mg or PTM oral LEN, aligned with their original study drug assignment (after the approval of Protocol Amendment 2). Participants continued to receive daily oral study drug (TVD, PTM TVD, DVY, or PTM DVY) while also receiving once-weekly oral LEN or PTM oral LEN for bridging.

Study assessments

Efficacy assessments

Determination of HIV-1 infection during the Incidence Phase and the Randomized Blinded Phase are described below:

Incidence Phase

HIV testing in the Incidence Phase included rapid fourth generation HIV-1/2 Ab/Ag, central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative NAAT. Confirmatory testing with a central laboratory HIV-1/2 Ab differentiation assay was performed if the central fourth generation HIV-1/2 Ab/Ag test was positive; a central laboratory HIV-1 RNA qualitative NAAT was performed if the HIV-1/2 Ab differentiation assay was negative. HIV-1 infection in the Incidence Phase was defined by participants having at least 1 of the following laboratory results at the Incidence Phase screening visit:

- Positive HIV-1/2 Ab differentiation assay (performed only if central fourth generation HIV-1/2 Ab/Ag test was positive), OR

- Positive HIV-1 RNA qualitative NAAT (performed only if central fourth generation HIV-1/2 Ab/Ag test was positive and HIV-1/2 Ab differentiation assay was negative), OR
- HIV-1 RNA quantitative NAAT ≥ 200 copies/mL

All participants and personnel were blinded to the results of the Sedia Limiting Antigen Avidity Enzyme Immunoassay for recent infection or the estimated bHIV incidence.

Randomized Blinded Phase

HIV testing at each visit included rapid fourth generation HIV-1/2 Ab/Ag and central fourth generation HIV-1/2 Ab/Ag. Positive central fourth generation HIV-1/2 Ab/Ag tests were confirmed with an HIV-1/2 Ab differentiation assay and HIV-1/2 RNA qualitative NAAT if the HIV-1/2 Ab differentiation assay was negative. HIV-1 RNA quantitative NAAT was performed at the Day 1 visit and when resuming study drug after an interruption.

Retrospective HIV-1 RNA quantitative NAAT was performed using archived samples for incident HIV-1 cases to determine the earliest date with evidence of HIV-1 infection.

A blinded 3-physician adjudication committee reviewed all available HIV test results and determined the participant's HIV-1 status and earliest date with evidence of HIV-1 infection.

Study Drug Adherence

Participants self-reported adherence to daily oral study drug using computer-based surveys. Adherence to DVY and TVD were assessed objectively by measuring the concentrations of TFV-DP in DBS. Dried blood spot measurements were performed in a random 10% subset of study participants and in all participants who were diagnosed with HIV-1.

Adherence to LEN or PTM LEN was assessed by on-time injection.

Pharmacokinetic assessments

Single anytime blood samples were collected during the study to determine the plasma PK profiles of LEN and long-acting hormonal contraceptives. Optional breast milk and infant plasma samples from women who became pregnant and consented to remain on study drug were collected at the first 2 protocol-scheduled visits after delivery. Participants could subsequently opt out of breast milk and infant sample collection.

Safety assessments

- Monitoring of AEs and concomitant medications
- Clinical laboratory analyses
- Vital signs measurements
- Physical examinations
- Urine sample for urinalysis, urine proteins (UPs), urine chemistry (uric acid, phosphate, and creatinine), and urine pregnancy test

- Blood sample for estimated glomerular filtration rate calculated using the Cockcroft-Gault equation (eGFRCG)
- Pregnancy outcomes

Other assessments

- Sexual Risk and Behavior Questionnaire
- Adherence to Oral Study Product Questionnaire
- NPRS–Injection Pain
- Administration and Dosing Questionnaire for PrEP Medication (injection acceptability)
- PrEP Impacts and Administration Preference Questionnaire
- Experienced Preference for PrEP Medication Questionnaire (results not reported in this clinical study report [CSR])

Regular sexually transmitted infection (STI) testing is the standard of care for people taking PrEP. Furthermore, STI incidence was used as an indicator of sexual behaviour that might increase the participant's likelihood of HIV acquisition.

The participant-reported questionnaires were used to collect information on the participants' sexual behaviour, HIV risk perception, and perceptions about study drugs and participation in the study. The questionnaires may also have collected information on the mental health, and alcohol and drug use of the participants. Collection of these measures is appropriate and necessary to fully assess the HIV risk profile of study participants.

Patient population

Eligibility Criteria

Part A: Incidence phase - cross sectional study

Part B: Randomised blinded phase

Key inclusion criteria for enrolment into part A or part B

1) Cisgender female

2) Age $\geq$ 16 to $\leq$ 25 years at screening

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

4) Sexually active (has had > 1 vaginal intercourse within the last 3 months) with cisgender men

Additional inclusion criteria for enrolment into part A

1) Positive local rapid fourth generation HIV-1 antibody (Ab)/antigen (Ag) test (performed after criteria above are met) confirmed with central HIV-1 testing or
2) A positive result from central HIV-1 testing performed for participants who receive Part B pre-baseline assessments after a negative local rapid fourth generation HIV-1 Ab/Ag test

Additional inclusion criteria for part B

Participants who meet the inclusion criteria above and the following criteria will be randomized in Part B.

1) Negative local fourth generation HIV-1 Ab/Ag test confirmed with central HIV-1 testing

2) Estimated GFR ≥ 60 mL/min at screening according to the Cockcroft-Gault formula for CLcr {Cockcroft 1976}:

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

3) Body weight ≥ 35 kg

Key exclusion criteria for enrolment into part A or part B

Participants who meet any of the following exclusion criteria for each part are not eligible to be enrolled in this study.

1) Participation in any prior or current HIV vaccine or other PrEP study

2) Prior use of long-acting systemic PrEP

Selected additional exclusion criteria for part B

Participants who meet any of the following exclusion criteria for each part are not eligible to be randomized in this study.

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

3) Positive for HBV-DNA or HCV-RNA

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

4) Need for continued use of any contraindicated concomitant medications

5) Have a history of osteoporosis or bone fragility fractures

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

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

8) Women who are pregnant or breastfeeding prior to administration of the first study drug dose

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

Objectives and estimands

Primary objective

Incidence Phase

- To estimate the bHIV incidence

Randomised Blinded Phase

- To evaluate the efficacy of LEN for HIV-1 pre-exposure prophylaxis (PrEP) in adolescent girls and young women (AGYW) at risk of HIV-1 infection
- To evaluate the efficacy of DVY for HIV-1 PrEP in AGYW at risk of HIV-1 infection

Estimand for the primary objective

The estimand framework was not used in this trial.

Primary endpoints:

- Incidence Phase: Diagnosis of recent HIV-1 infection
- Randomised Blinded Phase: Diagnosis of HIV-1 infection

Statistical methods for estimation and sensitivity analysis on primary estimand

Analysis sets

The All Screened Set was the primary analysis set for estimating the bHIV incidence. It included all participants who were screened for HIV-1 in the Incidence Phase and had a nonmissing HIV-1 diagnosis based on HIV test results (defined as at least 1 nonmissing central laboratory HIV test including the HIV-1/2 Ab/Ag test, HIV-1/2 Ab differentiation assay, HIV-1/2 RNA qualitative NAAT, or HIV-1 RNA quantitative NAAT) at Incidence Phase screening.

Any additional participants who took at least 1 dose of any study drug (but were missing central laboratory HIV tests at Incidence Phase screening) were included in the All Screened Set and considered as HIV-1 negative.

The Full Analysis Set (FAS) was the primary analysis set for efficacy analyses for participants who entered the Randomised Blinded Phase of the study. The FAS included all randomised participants who received at least 1 dose of any study drug and had not been diagnosed with HIV-1 on or prior to the first dose date (as determined by the HIV Adjudication Committee confirming an HIV-1 infection diagnosis date on or prior to the first dose date of study drug).

Participants who had a negative rapid test at Day 1 were permitted to be dosed prior to receipt of the Day 1 central laboratory test results; however, participants who were diagnosed with HIV-1 based on central laboratory tests on or prior to first dose date were excluded from the FAS.

Planned analyses

The primary efficacy analysis was to be conducted when all participants had a minimum of 52 weeks (1 year) of follow-up in the randomised blinded phase (RBP) of the study or permanent discontinuation of study (whichever occurs first) after randomisation. However, the trial was stopped early for efficacy, so the interim analysis (which is described below) served as the primary analysis.

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

The background HIV (bHIV) incidence rate incidence was reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to Kassanjee et al (Epidemiol 2012;23:721) adjusting for participants with HIV-1 who may not have had recency assay results.

The background incidence rate was estimated by the formula:

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

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 take recency assay
N_{rec}: total number of positive recency assay results
T: cutoff time (around 2 years) for the definition of true recent infections
Ω: Mean duration of recent infections (MDRI)
β: False recency rate (FRR)

The assay parameters given by Kassanjee et al (AIDS 2016;30:2361) were used for bHIV estimation. Since subtype data were not available in this trial, country was used to estimate the percentage of each subtype instead. It was assumed all HIV-1 infections from South Africa to be subtype C, and infections from Uganda to be 56% subtype A, 41% subtype D, and 3% subtype C.

The variance of the background HIV incidence rate was estimated on the log scale using the delta method (Gao et al., Stat Commun Infect Dis 2021;13:20200009). A 95% confidence interval was calculated based on a normal distribution.

The primary efficacy evaluations were comparisons of the observed HIV-1 incidences in the LEN and DVY groups versus the bHIV incidence. The incidence rate ratios of the LEN group versus the bHIV incidence and the DVY group versus the bHIV incidence were calculated. The associated 95% CIs and *P* values were estimated using the delta method (Gao et al., Stat Commun Infect Dis 2021;13:20200009) or a likelihood-based method if there were 0 infections {Shao and Gao, Stat Commun Infect Dis 2024;16:20230004). The likelihood-based method was specified in the statistical analysis plan but not in the protocol.

In general, missing data were not imputed unless methods for handling missing data were specified.

Sample size

A total sample size of 5010 was considered for this study. More than 95% power is achieved with 2000 participants in each of the LEN and the F/TAF study drug groups to show a significant difference with the background incidence rate. In this sample size analysis, the following assumptions were made:

Background incidence rate of 3.00/100PY.

LEN rate of 0.6/100PY, with 80% risk reduction

Mean duration of recent infection (MDRI) of 173 days, with relative standard error (rSE) of 6.5%

False recency rate (FRR) of 1.5%, with relative standard error (rSE) of 70%

Average follow up of 1 year

2:2:1 allocation for LEN: F/TAF: F/TDF

Alpha level of 0.0125 (1-sided) for each of the comparisons

The background incidence rate was estimated based on the results of a study by the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium (Lancet 2019;394:303).

The MDRI and FRR were based on the Sedia LAg assay (Kassanjee et al., AIDS 2016;30:2361).

The power calculation is based on the formula in Gao et al. (Stat Commun Infect Dis 2021;13:20200009) using the test statistics for rate ratio.

The study was not powered to detect a difference between the randomised study groups.

Interim analyses

A planned interim analysis of the safety data was conducted for the Data Monitoring Committee (DMC) when the first 300 adult participants completed their Week 8 visit. Enrolment of adolescent participants (≥16 and <18 years of age) commenced following this DMC review meeting of the safety data.

A planned interim analysis of efficacy and futility data was conducted for the DMC after 50% of the planned number of participants had completed at least 52 weeks of follow-up or prematurely discontinued from the study. The DMC recommended stopping the Randomised Blinded Phase early if the prespecified efficacy or futility evaluation criteria were met, and the interim analysis would then serve as the primary analysis.

The original interim stopping criteria specified in the study protocol required only the superiority of LEN versus bHIV, with the point estimate of $LEN/bHIV \leq 0.5$. After discussions with the FDA on 28 Nov 2023 (Type C meeting), the stopping criteria were updated to require not only superiority of LEN versus bHIV but also superiority of LEN versus F/TDF. This update was included in the statistical analysis plan but not in the protocol.

Multiplicity

There were 8 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed below.

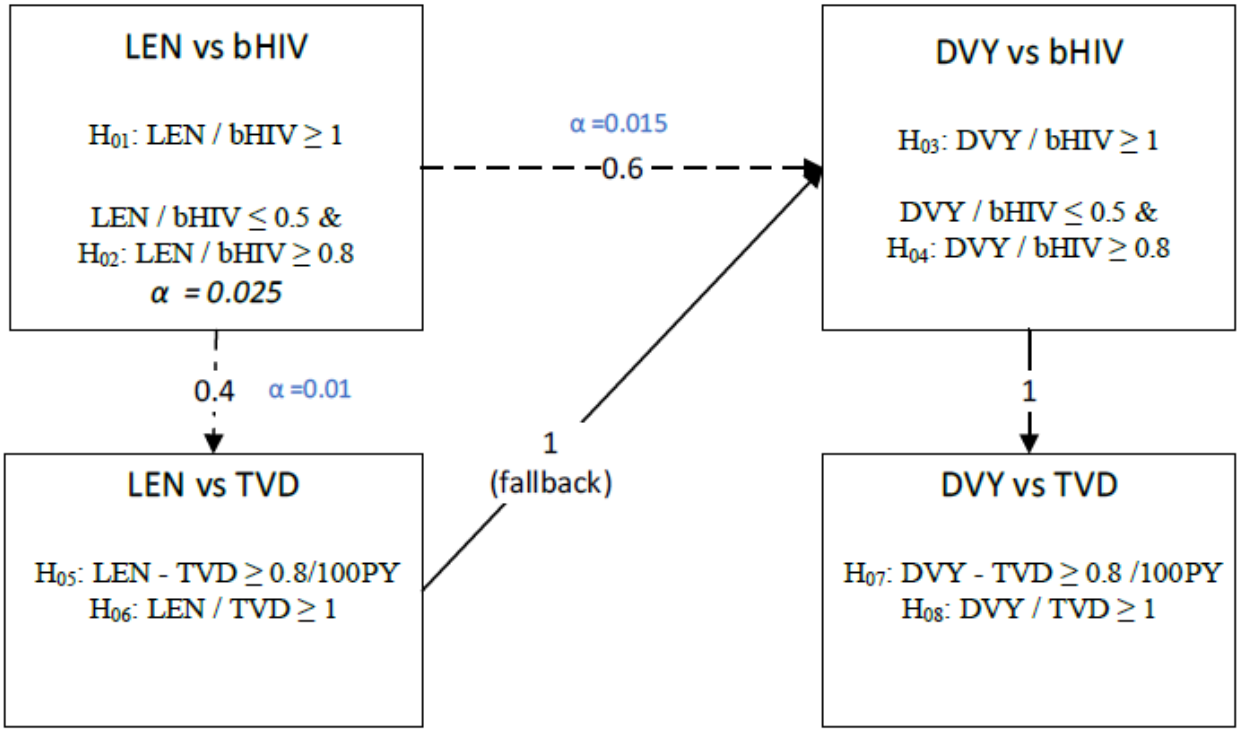
Table 25. Testing sequence of null hypotheses

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

The overall alpha in the study was 0.025 (one-sided).

A Bonferroni type spending function was used, so that an alpha = 0.0026 was used for the interim analysis and the remainder, alpha = 0.0224, was used at the primary analysis.

Figure 16 illustrates the multiple testing procedure that was specified in the protocol. This multiple testing procedure was to be used at both the interim analysis (with an overall alpha of 0.0026 instead of 0.025) and at the primary analysis (with an overall alpha of 0.0224 instead of 0.025). However, the statistical analysis plan revised this multiple testing procedure for the interim analysis, so that the alpha split of 0.4 and 0.6 was replaced by a hierarchical testing procedure in which the arrow '0.6' was removed and the arrow '0.4' was increased to 1.0. The Applicant justified this protocol deviation by the change in the early stopping criteria, where not only superiority of LEN versus bHIV was required but also superiority of LEN versus F/TDF.



bHIV = background HIV-1 incidence; DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); LEN = lenacapavir; PY = person-years; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Displayed alpha levels were the planned overall 1-sided alpha (total alpha for both the interim and primary analyses). Testing within each block was to be sequential. Transitional weights from 1 node to another indicate the fraction of the local significance level at the first node that was to be added to the local significance level at the second node if the first node was rejected.

Figure 16. GS-US-412-5624 overall testing procedure

Changes to the planned analysis

As explained above, the following changes were made:

The statistical method that was used in case of 0 infections was prespecified in the statistical analysis plan but not in the protocol.

The interim stopping criteria that were specified in the protocol were changed in the statistical analysis plan.

The multiple testing procedure used at the interim analysis was prespecified only in the statistical analysis plan, and it deviated from the procedure specified in the protocol.

Secondary objective

Randomised Blinded Phase

- To compare the efficacy of LEN with emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®; TVD) for HIV-1 PrEP in AGYW at risk of HIV-1 infection
- To evaluate the efficacy of LEN for HIV-1 PrEP in AGYW at risk of HIV-1 infection in

participants adherent to LEN
- To evaluate the efficacy of DVY for HIV-1 PrEP in AGYW at risk of HIV-1 infection in participants adherent to DVY
- To compare the efficacy of DVY with TVD for HIV-1 PrEP in AGYW at risk of HIV-1 infection
- To evaluate the safety and tolerability of LEN, DVY, and TVD for HIV-1 PrEP in AGYW at risk of HIV-1 infection
- To evaluate the safety and tolerability of LEN and DVY for HIV-1 PrEP in AGYW $\geqslant$ 16 to < 18 years of age who have sex with male partners and are at risk for HIV-1 infection

Estimand for the secondary objective

The estimand framework was not used in this trial.

The randomized Blinded Phase of the trial had two secondary endpoints:

- Diagnosis of HIV-1 infection, including among participants while adherent to study drug
- Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN, DVY, and TVD for HIV-1 PrEP

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The ratio of HIV-1 incidences was used to evaluate the superiority of LEN or DVY versus TVD. The incidence rate ratios of the LEN group versus the TVD group and the DVY group versus the TVD group were calculated. The associated 95% CIs and *P* values were estimated using a generalized Poisson regression model or an exact conditional Poisson regression model if there were 0 infections. The exact conditional Poisson regression model was specified in the statistical analysis plan but not in the protocol.

The difference in HIV-1 incidences was used to evaluate the comparability of LEN relative to TVD. In order to test this hypothesis, a 95% CI was constructed using a hybrid approach, with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI (Li et a., Communications in Statistics - Simulation and Computation 2011;40:1478). The associated *P* value was obtained using the duality of hypothesis testing and CI (Rohatgi VK. Statistical Inference. In: Professor Emeritus Bowling Green State University, ed. Mathematical statistics. I. Dover Publications, Inc. Mineola, New York: 1984). It was concluded that LEN was comparable to TVD if the upper bound of the 95% CI of the incidence rate difference (LEN – TVD) was less than 0.8 per 100 PY. The comparability of DVY and TVD was evaluated similarly.

Exploratory objectives

Randomized Blinded Phase

- To assess the adherence rate to LEN as assessed by on-time LEN injection
- To assess LEN plasma levels

- To assess the adherence rate to DVY and TVD using intracellular tenofovir-diphosphate (TFV-DP) levels in dried blood spot (DBS)
- To evaluate the acceptability of a once every 6 months LEN injection for HIV-1 PrEP in AGYW at risk of HIV-1 infection
- To assess study drug levels of interest in pregnant and postpartum women, in breast milk, and in infants
- To explore concentrations of hormonal contraceptives in LEN participants

Results

Participant flow and numbers analysed

Table 26. Key study dates

Event	Date
First participant screened	30 August 2021
First participant randomized	28 September 2021
Last participant randomized	15 September 2023
Last participant last visit for this report[a]	08 May 2024
Database finalization	29 May 2024
DMC meeting and recommendation to stop Randomized Blinded Phase	18 June 2024
Study drug group unblinding for the interim analysis[b]	18 June 2024

DMC = data monitoring committee
a Date of the last visit recorded in the electronic data capture database for this report.
b Date when Gilead personnel, independent from the blinded study team, were unblinded to review the interim analysis results after the DMC recommendation to stop the Randomized Blinded Phase early.

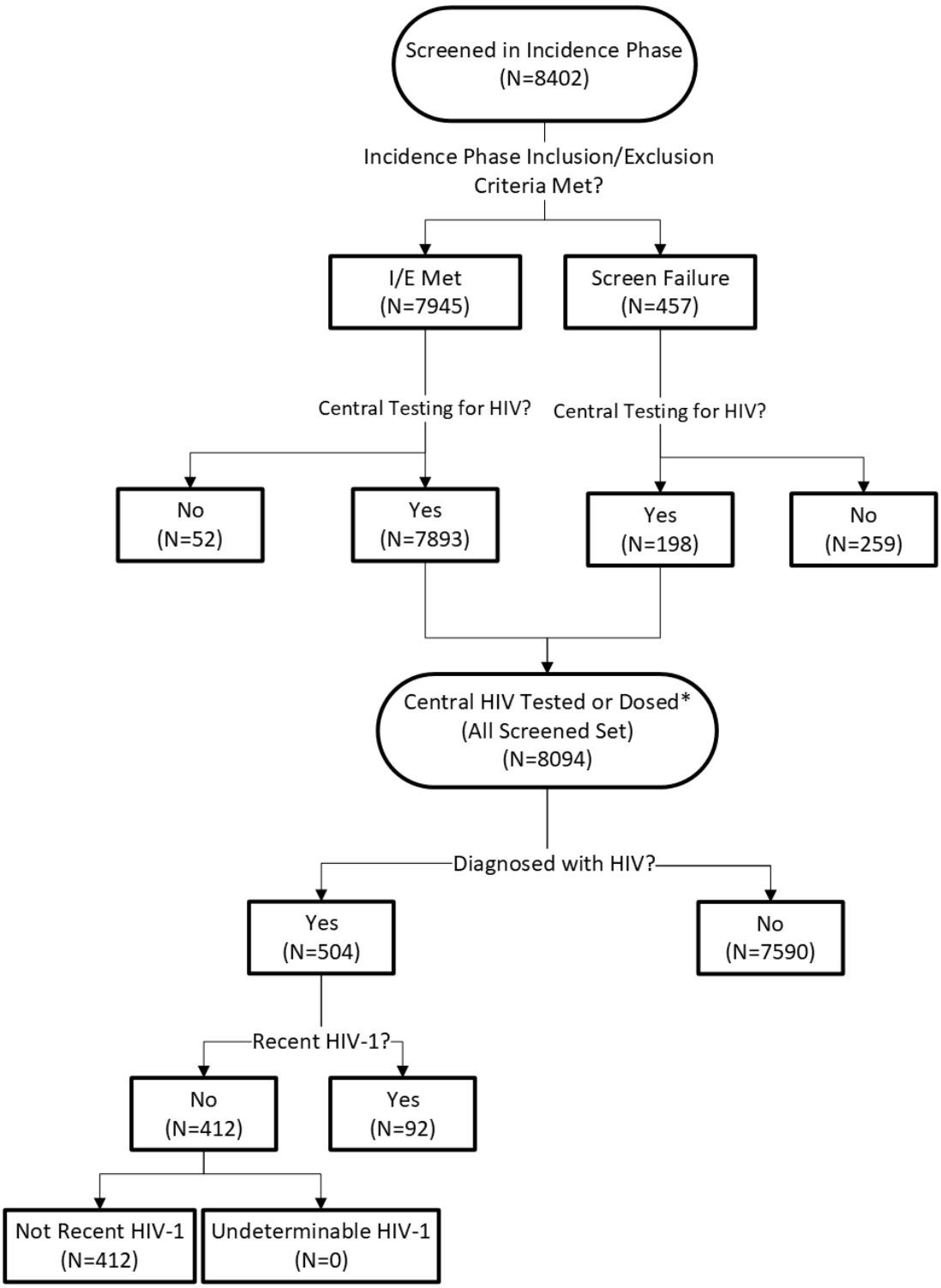


Figure 17. GS-US-412-5624: Disposition of participants in the incidence phase (screened participants)

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

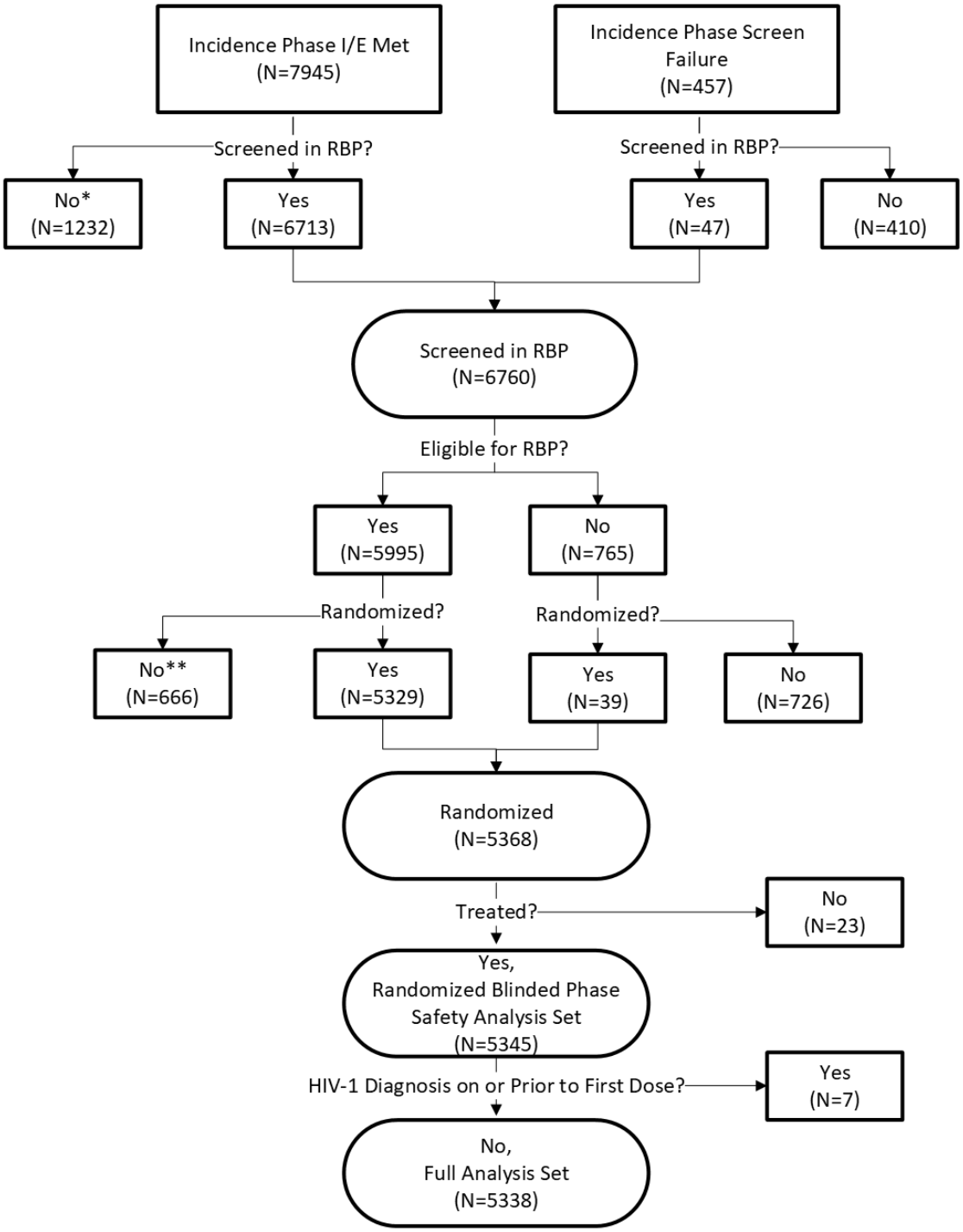


Figure 18. GS-US-412-5624: Disposition of participants in the randomised blinded phase (efficacy)

HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion criteria; RBP = Randomized Blinded Phase

* Reasons not screened in RBP despite meeting Incidence Phase I/E criteria include adverse event (1), investigator's discretion (96), lost to follow-up (83), outside of visit window (146), study enrolment closed (6), withdrew consent (18), other (880), and missing (2). ** Reasons not randomized despite meeting RBP I/E criteria include investigator's discretion (37), lost to follow-up (94), outside of visit window (264), study enrolment closed (5), withdrew consent (127), screen failed Incidence Phase (4), and other (135).

Table 27. GS-US-412-5624: Disposition of participants in the randomised blinded phase (safety, screened participants)

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

DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PrEP = pre-exposure prophylaxis; RBP = Randomized Blinded Phase; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Denominators for percentages are the RBP Safety Analysis Set for study drug (or study) status.
Treated participants discontinued the study only once (either in RBP or Open-Label Oral PrEP Analysis); those that discontinued the study in the RBP could not be included in the Open-Label Oral PrEP Analysis.
Data through data cutoff date (08 May 2024).
Participants' study drugs grouped by 1) randomized study drug for the Full Analysis Set, and 2) actual study drug received otherwise.

Oral Bridging

Overall, of the 41 participants with their screening (Incidence Phase or Randomized Blinded Phase), randomization, or first dose interrupted due to the clinical hold, 23 were repeat screened and confirmed not to have HIV-1.

Of the 44 participants (0.8%) who received oral study drug bridging during the clinical hold, 13 (0.2%) received open label TVD and 31 (0.6%) received blinded once-weekly oral LEN or PTM oral LEN (10 received oral LEN and 21 received placebo-to-match oral LEN). Among the 10 participants who received once weekly oral LEN, the median duration of dosing during the clinical hold was 1.6 weeks (range: 1.0 10.4).

All 13 participants who received open label TVD resumed Randomized Blinded Phase study drug after the clinical hold was lifted. Of the 31 participants who received once-weekly oral LEN or placebo-to-match oral LEN, 29 resumed Randomized Blinded Phase study drug injections while 2 participants who received placebo-to-match oral LEN did not.

Deviations from study plan

The original protocol (13 January 2021) was amended 3 times.

22 November 2021:

The purpose of Protocol Amendment 1, dated 22 November 2021, is to add details on the collection of breast milk from lactating participants and collection of blood from infants for pharmacokinetic analysis.

02 February 2022:

Add information to allow weekly oral lenacapvir (LEN)/placebo dosing if a participant is not able to receive subcutaneous (SC) LEN or SC placebo (LEN/placebo oral bridging) within the protocol-specified window and its rationale. Provide recommendations on monitoring requirement for injection site reactions.

17 October 2023:

Revisions for clarity in multiple sections.

Changes from protocol-specified analyses

The statistical methods that were used in case of 0 infections were specified in the statistical analysis plan but not in the protocol.

The interim stopping criteria that were specified in the protocol were changed in the statistical analysis plan.

The multiple testing procedure used at the interim analysis was specified only in the statistical analysis plan, and it deviated from the procedure specified in the protocol.

Table 28. GS-US-412-5624: Important protocol deviations (screened participants)

Protocol Deviation Category	All Screened Set (N = 8094)	Total (N = 8402)
Participants with at least 1 important protocol deviation	939 (11.6%)	943 (11.2%)
Participants with 1 important protocol deviation	764 (9.4%)	768 (9.1%)
Participants with 2 important protocol deviations	123 (1.5%)	123 (1.5%)
Participants with 3 or more important protocol deviations	52 (0.6%)	52 (0.6%)
Total number of important protocol deviations	1183	1187
Missing data	362	365
Other study drug compliance issue	298	298
Informed consent	280	281
Wrong study drug or incorrect dose	93	93
Other	78	78
Eligibility criteria	56	56
Excluded concomitant medication	15	15
Unintended unblinding	1	1

Protocol deviations are not mutually exclusive. Participants may be represented multiple times across protocol deviation categories.

Baseline data

Table 29. GS-US-412-5624: Demographics and baseline characteristics (randomised blinded phase, safety analysis set)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Age (years)				
N	2140	2135	1070	5345
Mean (SD)	21 (2.2)	21 (2.1)	21 (2.1)	21 (2.1)
Median	21	21	21	21
Q1, Q3	19, 23	19, 23	19, 23	19, 23
Min, max	16, 25	16, 26	16, 25	16, 26
Age categories (years)				
16 to < 18	56 (2.6%)	45 (2.1%)	23 (2.1%)	124 (2.3%)
≥ 18	2084 (97.4%)	2090 (97.9%)	1047 (97.9%)	5221 (97.7%)
Sex assigned at birth				

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Male	0	0	0	0
Female	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Race				
Black	2137 (99.9%)	2134 (100.0%)	1068 (99.8%)	5339 (99.9%)
Multiracial–other	3 (0.1%)	1 (< 0.1%)	1 (< 0.1%)	5 (< 0.1%)
Not multiracial–other	0	0	1 (< 0.1%)	1 (< 0.1%)
Ethnicity				
Not Hispanic or Latino	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Baseline weight (kg)				
N	2140	2135	1070	5345
Mean (SD)	66.8 (17.44)	68.5 (18.27)	67.6 (17.26)	67.6 (17.75)
Median	63.0	64.2	63.5	63.5
Q1, Q3	54.4, 76.0	55.0, 77.7	54.7, 76.2	54.8, 76.7
Min, max	37.1, 192.1	37.8, 174.5	38.0, 150.5	37.1, 192.1
Baseline body mass index (kg/m^2)				
N	2140	2135	1070	5345
Mean (SD)	26.5 (6.53)	27.1 (6.84)	26.8 (6.48)	26.8 (6.65)
Median	24.9	25.6	25.2	25.2
Q1, Q3	21.7, 30.1	22.1, 30.7	21.9, 30.4	21.9, 30.4
Min, max	15.0, 62.7	15.0, 55.7	14.8, 51.4	14.8, 62.7
Highest education level				
Did not attend primary school	17 (0.8%)	19 (0.9%)	3 (0.3%)	39 (0.7%)
Some primary school education	169 (7.9%)	155 (7.3%)	73 (6.8%)	397 (7.4%)
Primary school complete	66 (3.1%)	68 (3.2%)	33 (3.1%)	167 (3.1%)
Some secondary school education	905 (42.3%)	926 (43.4%)	459 (42.9%)	2290 (42.9%)
Secondary school degree complete	797 (37.3%)	767 (36.0%)	392 (36.7%)	1956 (36.6%)
Some college or university degree	184 (8.6%)	197 (9.2%)	109 (10.2%)	490 (9.2%)
- Missing -	2	3	1	6
Modified VOICE Risk Score				
N	2076	2080	1037	5193
Mean (SD)	6.3 (1.31)	6.3 (1.28)	6.3 (1.29)	6.3 (1.29)
Median	7.0	7.0	7.0	7.0
Q1, Q3	5.0, 7.0	5.0, 7.0	5.0, 7.0	5.0, 7.0
Min, max	0.0, 8.0	1.0, 8.0	0.0, 8.0	0.0, 8.0
Modified VOICE Risk Score				
0	1 (< 0.1%)	0	2 (0.2%)	3 (< 0.1%)
1	3 (0.1%)	4 (0.2%)	1 (< 0.1%)	8 (0.2%)
2	12 (0.6%)	11 (0.5%)	10 (1.0%)	33 (0.6%)
3	49 (2.4%)	48 (2.3%)	16 (1.5%)	113 (2.2%)
4	121 (5.8%)	110 (5.3%)	46 (4.4%)	277 (5.3%)
5	402 (19.4%)	381 (18.3%)	201 (19.4%)	984 (18.9%)
6	411 (19.8%)	393 (18.9%)	210 (20.3%)	1014 (19.5%)
7	737 (35.5%)	819 (39.4%)	395 (38.1%)	1951 (37.6%)
8	340 (16.4%)	314 (15.1%)	156 (15.0%)	810 (15.6%)
- Missing -	64	55	33	152

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Modified VOICE Risk Score				
< 5	186 (9.0%)	173 (8.3%)	75 (7.2%)	434 (8.4%)
≥ 5	1890 (91.0%)	1907 (91.7%)	962 (92.8%)	4759 (91.6%)
- Missing -	64	55	33	152

DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Age (in years) was collected on the first dose date of study drug (Day 1). Participants who were 25 at screening might have been 26 by the first dose date.
"Prefer not to answer" and "missing" were excluded from the calculation of percentages.
Body mass index (kg/m^2) = (Weight [kg]/Height [cm]^2) × 10,000.
Components of the modified VOICE score {Balkus 2016} were collected at screening.
Frequency of alcohol use in the past 3 months was collected at screening by the sites (not electronic participant-reported outcomes).

Baseline HIV Risk Characteristics

Table 30. GS-US-412-5624: Other baseline HIV risk characteristics (randomised blinded phase, safety analysis set)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Any chlamydia, gonorrhea, trichomonas vaginalis, or syphilis				
Yes	727 (34.0%)	775 (36.3%)	373 (34.9%)	1875 (35.1%)
No	1413 (66.0%)	1360 (63.7%)	697 (65.1%)	3470 (64.9%)
Chlamydia (urethral/urine)				
Detected	520 (24.3%)	562 (26.3%)	263 (24.6%)	1345 (25.2%)
Indeterminate	2 (< 0.1%)	1 (< 0.1%)	0	3 (< 0.1%)
Not detected	1618 (75.6%)	1572 (73.6%)	807 (75.4%)	3997 (74.8%)
Gonorrhea (urethral/urine)				
Detected	197 (9.2%)	178 (8.3%)	90 (8.4%)	465 (8.7%)
Indeterminate	2 (< 0.1%)	1 (< 0.1%)	0	3 (< 0.1%)
Not detected	1941 (90.7%)	1956 (91.6%)	980 (91.6%)	4877 (91.2%)
Trichomonas vaginalis (urethral/urine)				
Detected	154 (7.2%)	165 (7.7%)	82 (7.7%)	401 (7.5%)
Indeterminate	0	0	0	0
Not detected	1986 (92.8%)	1970 (92.3%)	988 (92.3%)	4944 (92.5%)
Syphilis diagnosis (investigator report)				
Yes	57 (2.7%)	63 (3.0%)	29 (2.7%)	149 (2.8%)
No	2083 (97.3%)	2072 (97.0%)	1041 (97.3%)	5196 (97.2%)
Syphilis stage				
Primary	0	0	0	0
Early latent	26 (45.6%)	31 (49.2%)	15 (51.7%)	72 (48.3%)
Secondary	3 (5.3%)	2 (3.2%)	1 (3.4%)	6 (4.0%)
Tertiary	0	0	0	0

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Late latent	27 (47.4%)	30 (47.6%)	13 (44.8%)	70 (47.0%)
Other	1 (1.8%)	0	0	1 (0.7%)
Male sex partners in past 3 months				
N	1992	2015	998	5005
Mean (SD)	21 (84.4)	24 (97.7)	24 (100.0)	23 (93.1)
Median	2	2	2	2
Q1, Q3	1, 3	1, 3	1, 3	1, 3
Min, max	0, 999	0, 999	0, 999	0, 999
Male sex partners in past 3 months				
0	122 (6.1%)	138 (6.8%)	72 (7.2%)	332 (6.6%)
1-2	1171 (58.8%)	1231 (61.1%)	583 (58.4%)	2985 (59.6%)
3-5	340 (17.1%)	283 (14.0%)	162 (16.2%)	785 (15.7%)
6-9	58 (2.9%)	38 (1.9%)	23 (2.3%)	119 (2.4%)
≥ 10	301 (15.1%)	325 (16.1%)	158 (15.8%)	784 (15.7%)
Prefer not to answer	139	113	69	321
- Missing -	9	7	3	19
Male sex partners with HIV in past 3 months				
N	1853	1887	924	4664
Mean (SD)	8 (66.0)	6 (60.9)	7 (59.0)	7 (62.6)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 990	0, 999
Male sex partners with HIV in past 3 months				
0	1544 (83.3%)	1599 (84.7%)	773 (83.7%)	3916 (84.0%)
1-2	212 (11.4%)	196 (10.4%)	93 (10.1%)	501 (10.7%)
3-5	29 (1.6%)	31 (1.6%)	10 (1.1%)	70 (1.5%)
6-9	6 (0.3%)	8 (0.4%)	6 (0.6%)	20 (0.4%)
≥ 10	62 (3.3%)	53 (2.8%)	42 (4.5%)	157 (3.4%)
Prefer not to answer	276	240	142	658
- Missing -	11	8	4	23
Vaginal sex acts in past 3 months				
N	1976	1964	975	4915
Mean (SD)	53 (141.3)	45 (131.9)	45 (124.7)	48 (134.4)
Median	9	8	9	9
Q1, Q3	3, 27	3, 24	3, 27	3, 25
Min, max	0, 999	0, 999	0, 999	0, 999
Vaginal sex acts in past 3 months				
0	112 (5.7%)	127 (6.5%)	46 (4.7%)	285 (5.8%)
1-2	236 (11.9%)	266 (13.5%)	128 (13.1%)	630 (12.8%)
3-5	404 (20.4%)	389 (19.8%)	201 (20.6%)	994 (20.2%)
6-9	244 (12.3%)	275 (14.0%)	119 (12.2%)	638 (13.0%)
≥ 10	980 (49.6%)	907 (46.2%)	481 (49.3%)	2368 (48.2%)
Prefer not to answer	155	164	92	411
- Missing -	9	7	3	19
Condomless vaginal sex acts in past 3 months				
N	1921	1911	941	4773
Mean (SD)	27 (92.1)	21 (72.2)	26 (91.7)	24 (84.6)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Median	3	3	3	3
Q1, Q3	1, 11	1, 10	1, 11	1, 10
Min, max	0, 999	0, 999	0, 999	0, 999
Condomless vaginal sex acts in past 3 months				
0	429 (22.3%)	415 (21.7%)	181 (19.2%)	1025 (21.5%)
1-2	397 (20.7%)	412 (21.6%)	216 (23.0%)	1025 (21.5%)
3-5	366 (19.1%)	377 (19.7%)	175 (18.6%)	918 (19.2%)
6-9	149 (7.8%)	160 (8.4%)	75 (8.0%)	384 (8.0%)
≥ 10	580 (30.2%)	547 (28.6%)	294 (31.2%)	1421 (29.8%)
Prefer not to answer	208	217	125	550
- Missing -	11	7	4	22
Anal sex acts in past 3 months				
N	2001	2002	989	4992
Mean (SD)	11 (86.0)	10 (84.1)	10 (81.0)	10 (84.3)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 999	0, 999
Anal sex acts in past 3 months				
0	1782 (89.1%)	1782 (89.0%)	873 (88.3%)	4437 (88.9%)
1-2	85 (4.2%)	94 (4.7%)	45 (4.6%)	224 (4.5%)
3-5	36 (1.8%)	45 (2.2%)	16 (1.6%)	97 (1.9%)
6-9	15 (0.7%)	10 (0.5%)	8 (0.8%)	33 (0.7%)
≥ 10	83 (4.1%)	71 (3.5%)	47 (4.8%)	201 (4.0%)
Prefer not to answer	130	126	78	334
- Missing -	9	7	3	19
Condomless anal sex acts in past 3 months				
N	1986	1988	980	4954
Mean (SD)	6 (66.7)	3 (38.2)	7 (65.9)	5 (56.8)
Median	0	0	0	0
Q1, Q3	0, 0	0, 0	0, 0	0, 0
Min, max	0, 999	0, 999	0, 999	0, 999
Condomless anal sex acts in past 3 months				
0	1818 (91.5%)	1830 (92.1%)	891 (90.9%)	4539 (91.6%)
1-2	85 (4.3%)	83 (4.2%)	37 (3.8%)	205 (4.1%)
3-5	25 (1.3%)	28 (1.4%)	16 (1.6%)	69 (1.4%)
6-9	10 (0.5%)	10 (0.5%)	6 (0.6%)	26 (0.5%)
≥ 10	48 (2.4%)	37 (1.9%)	30 (3.1%)	115 (2.3%)
Prefer not to answer	145	138	87	370
- Missing -	9	9	3	21
Primary partner (HIV status) in past 3 months				
Yes	1609 (76.8%)	1609 (76.9%)	820 (77.9%)	4038 (77.1%)
HIV negative	1015 (48.5%)	1025 (49.0%)	523 (49.7%)	2563 (48.9%)
HIV positive	15 (0.7%)	13 (0.6%)	4 (0.4%)	32 (0.6%)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Do not know	568 (27.1%)	565 (27.0%)	289 (27.4%)	1422 (27.1%)
Prefer not to answer	11 (0.5%)	6 (0.3%)	4 (0.4%)	21 (0.4%)
No	485 (23.2%)	484 (23.1%)	233 (22.1%)	1202 (22.9%)
Prefer not to answer	37	35	14	86
- Missing -	9	7	3	19
Sex for financial and/or material support (consider sex worker) in past 3 months				
Yes	493 (23.4%)	503 (23.9%)	251 (23.8%)	1247 (23.7%)
Sex worker	161 (7.6%)	167 (7.9%)	92 (8.7%)	420 (8.0%)
Not sex worker	327 (15.5%)	329 (15.6%)	155 (14.7%)	811 (15.4%)
Prefer not to answer	5 (0.2%)	7 (0.3%)	4 (0.4%)	16 (0.3%)
No	1617 (76.6%)	1604 (76.1%)	804 (76.2%)	4025 (76.3%)
Prefer not to answer	21	21	12	54
- Missing -	9	7	3	19
Frequency of alcohol use in past 3 months				
Never	479 (22.7%)	461 (21.9%)	226 (21.4%)	1166 (22.1%)
Monthly or less	718 (34.1%)	771 (36.7%)	354 (33.5%)	1843 (35.0%)
2 to 4 times a month	599 (28.4%)	588 (28.0%)	309 (29.2%)	1496 (28.4%)
2 to 3 times a week	205 (9.7%)	188 (8.9%)	115 (10.9%)	508 (9.6%)
4 or more times a week	105 (5.0%)	93 (4.4%)	54 (5.1%)	252 (4.8%)
Prefer not to answer	25	27	9	61
- Missing -	9	7	3	19
Six or more drinks on one occasion in past 12 weeks				
Never	708 (33.9%)	701 (33.9%)	337 (32.2%)	1746 (33.5%)
Less than monthly	638 (30.5%)	631 (30.5%)	316 (30.2%)	1585 (30.5%)
Monthly	460 (22.0%)	451 (21.8%)	226 (21.6%)	1137 (21.8%)
Weekly	244 (11.7%)	233 (11.3%)	136 (13.0%)	613 (11.8%)
Daily or almost daily	39 (1.9%)	54 (2.6%)	31 (3.0%)	124 (2.4%)
Prefer not to answer	42	58	21	121
- Missing -	9	7	3	19
Alcohol before or during sex in past 12 weeks				
Yes	812 (38.4%)	793 (37.6%)	431 (40.8%)	2036 (38.6%)
No	1305 (61.6%)	1315 (62.4%)	625 (59.2%)	3245 (61.4%)
Prefer not to answer	14	20	11	45
- Missing -	9	7	3	19
Take drugs before or during sex (chemsex) in past 12 weeks				
Yes	88 (4.1%)	74 (3.5%)	44 (4.1%)	206 (3.9%)
No	2036 (95.9%)	2047 (96.5%)	1020 (95.9%)	5103 (96.1%)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
Prefer not to answer	7	7	3	17
- Missing -	9	7	3	19
Number of cigarettes smoked per day in the past 3 months				
Yes	329 (15.5%)	303 (14.3%)	177 (16.6%)	809 (15.2%)
Less than 10 cigarettes per day	279 (13.1%)	254 (12.0%)	150 (14.1%)	683 (12.9%)
Between 10 and 20 cigarettes per day	17 (0.8%)	21 (1.0%)	9 (0.8%)	47 (0.9%)
More than 20 cigarettes per day	7 (0.3%)	4 (0.2%)	2 (0.2%)	13 (0.2%)
Prefer not to answer	26 (1.2%)	24 (1.1%)	16 (1.5%)	66 (1.2%)
No	1793 (84.5%)	1820 (85.7%)	888 (83.4%)	4501 (84.8%)
Prefer not to answer	9	5	2	16
- Missing -	9	7	3	19
Any substance use in past 12 weeks				
Yes	626 (30.4%)	614 (29.8%)	329 (31.8%)	1569 (30.5%)
No	1432 (69.6%)	1445 (70.2%)	704 (68.2%)	3581 (69.5%)
Prefer not to answer	73	69	34	176
- Missing -	9	7	3	19
Cannabis use in past 12 weeks				
Yes	291 (14.1%)	309 (14.8%)	189 (18.2%)	789 (15.2%)
No	1778 (85.9%)	1775 (85.2%)	849 (81.8%)	4402 (84.8%)
Prefer not to answer	62	44	29	135
- Missing -	9	7	3	19
Cocaine use in past 12 weeks				
Yes	125 (6.0%)	120 (5.7%)	58 (5.5%)	303 (5.8%)
No	1974 (94.0%)	1983 (94.3%)	989 (94.5%)	4946 (94.2%)
Prefer not to answer	32	25	20	77
- Missing -	9	7	3	19
Amphetamine-type stimulants use in past 12 weeks				
Yes	75 (3.6%)	57 (2.7%)	35 (3.3%)	167 (3.2%)
No	2016 (96.4%)	2026 (97.3%)	1012 (96.7%)	5054 (96.8%)
Prefer not to answer	40	45	20	105
- Missing -	9	7	3	19
Inhalants use in past 12 weeks				
Yes	73 (3.5%)	56 (2.7%)	38 (3.6%)	167 (3.2%)
No	2028 (96.5%)	2027 (97.3%)	1014 (96.4%)	5069 (96.8%)
Prefer not to answer	30	45	15	90
- Missing -	9	7	3	19
Sedatives or sleeping pills use in past 12 weeks				
Yes	173 (8.2%)	165 (7.9%)	72 (6.8%)	410 (7.8%)
No	1928 (91.8%)	1927 (92.1%)	983 (93.2%)	4838 (92.2%)
Prefer not to answer	30	36	12	78
- Missing -	9	7	3	19
Hallucinogens use in past 12 weeks				
Yes	72 (3.4%)	86 (4.1%)	26 (2.5%)	184 (3.5%)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
No	2020 (96.6%)	2000 (95.9%)	1023 (97.5%)	5043 (96.5%)
Prefer not to answer	39	42	18	99
- Missing -	9	7	3	19
Opioids use in past 12 weeks				
Yes	66 (3.1%)	60 (2.9%)	25 (2.4%)	151 (2.9%)
No	2039 (96.9%)	2042 (97.1%)	1027 (97.6%)	5108 (97.1%)
Prefer not to answer	26	26	15	67
- Missing -	9	7	3	19
Prescription drugs for nonprescription purpose use in past 12 weeks				
Yes	204 (9.7%)	194 (9.3%)	107 (10.2%)	505 (9.7%)
No	1900 (90.3%)	1888 (90.7%)	938 (89.8%)	4726 (90.3%)
Prefer not to answer	27	46	22	95
- Missing -	9	7	3	19

DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); HIV = human immunodeficiency virus; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)

"Missing" and "prefer not to answer" (except within a dynamic subquestion) were excluded from the percentage calculations.

Laboratory results based on central laboratory or local laboratories for gonorrhea, chlamydia, and trichomonas vaginalis, and local laboratories only for syphilis.

Responses for condomless sex acts or sex partners with HIV were imputed as 0 (or "prefer not to answer") when responses for sex acts or sex partners were 0 (or "prefer not to answer").

Baseline Medical Characteristics

Table 31. GS-US-412-5624: Baseline medical characteristics (randomised blinded phase, safety analysis set)

	SC LEN (N = 2140)	DVY (N = 2135)	TVD (N = 1070)	Total (N = 5345)
HBV infection status				
Yes	0	0	0	0
No	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
HCV infection status				
Yes	0	0	0	0
No	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Estimated glomerular filtration rate by Cockcroft-Gault (mL/min)				
N	2140	2135	1070	5345
Mean (SD)	140.2 (41.84)	143.2 (42.62)	142.0 (40.53)	141.7 (41.91)
Median	132.0	133.8	133.8	133.2
Q1, Q3	111.6, 160.2	112.2, 165.6	113.4, 162.0	112.2, 162.6
Min, max	60.0, 505.8	62.4, 387.0	62.4, 356.4	60.0, 505.8
Serum creatinine (mg/dL)				
N	2140	2135	1070	5345
Mean (SD)	0.68 (0.098)	0.68 (0.098)	0.68 (0.099)	0.68 (0.098)
Median	0.68	0.68	0.68	0.68
Q1, Q3	0.61, 0.75	0.62, 0.75	0.61, 0.75	0.61, 0.75
Min, max	0.41, 1.07	0.32, 1.12	0.43, 1.07	0.32, 1.12
Proteinuria toxicity grade by urinalysis (dipstick)				
Grade 0	2003 (93.6%)	1991 (93.3%)	998 (93.3%)	4992 (93.4%)
Grade 1	122 (5.7%)	133 (6.2%)	65 (6.1%)	320 (6.0%)
Grade 2	11 (0.5%)	11 (0.5%)	7 (0.7%)	29 (0.5%)
Grade 3	4 (0.2%)	0	0	4 (< 0.1%)

DNA = deoxyribonucleic acid; DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); HBV = hepatitis B virus; HCV = hepatitis C virus; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; RNA = ribonucleic acid; SC = subcutaneous; SD = standard deviation; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
HCV infection = positive HCV antibody and quantifiable HCV RNA (≥ 15 IU/mL).
HBV infection = (1) positive hepatitis B surface antigen or (2) negative hepatitis B surface antibody, positive hepatitis B core antibody, and quantifiable HBV DNA (≥ 20 IU/mL).

Number of Participants (Planned and Analyzed)

Planned: Approximately 5010 participants in the Randomized Blinded Phase.

Table 32. GS-US-412-5624: Analysis set

Analysis Set Reason for Exclusion	SC LEN	DVY	TVD	Total
Screened for Incidence Phase	—	—	—	8402
Without central HIV test at Incidence Screening and not dosed	—	—	—	308
All Screened Set	—	—	—	8094
All Randomized Analysis Set	2148	2147	1073	5368
Participants never dosed study drug	10 (0.5%)	10 (0.5%)	3 (0.3%)	23 (0.4%)
RBP Safety Analysis Set	2140 (100.0%)	2135 (100.0%)	1070 (100.0%)	5345 (100.0%)
Full Analysis Set	2134 (99.3%)	2136 (99.5%)	1068 (99.5%)	5338 (99.4%)
Diagnosed with HIV-1 on or prior to first dose	4 (0.2%)	1 (< 0.1%)	2 (0.2%)	7 (0.1%)
Modified Full Analysis Set	2104 (98.0%)	2108 (98.2%)	1053 (98.1%)	5265 (98.1%)
First dose before the clinical hold	30 (1.4%)	28 (1.3%)	15 (1.4%)	73 (1.4%)
Open-Label Oral PrEP Safety Analysis Set	87 (4.1%)	73 (3.4%)	35 (3.3%)	195 (3.6%)
LEN PK Analysis Set	429 (20.0%)	0	0	429 (8.0%)
LEN PK Breast Milk Analysis Set	10 (0.5%)	0	0	10 (0.2%)
LEN PK Infant Analysis Set	15 (0.7%)	0	0	15 (0.3%)
Hormone PK Analysis Set	228 (10.7%)	0	0	228 (4.3%)
DBS Cohort Analysis Set	0	210 (9.8%)	110 (10.3%)	320 (6.0%)
DBS Case-Control Analysis Set	0	196 (9.2%)	89 (8.3%)	285 (5.3%)

DBS = dried blood spot; DVY = emtricitabine/tenofovir alafenamide (F/TAF; Descovy®); HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s); PrEP = pre-exposure prophylaxis; RBP = Randomized Blinded Phase; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Denominators = 1) randomized for All Randomized Analysis Set, Full Analysis Set, modified Full Analysis Set, and associated exclusion reasons and 2) Randomized Blinded Phase Safety Analysis Set otherwise. Participants' study drugs grouped by 1) randomized drug for All Randomized Analysis Set, Full Analysis Set, and modified Full Analysis Set and
2) actual drug received otherwise.

Outcomes and estimation

Primary Efficacy Endpoint

Diagnosis of HIV-1 Infection

At the interim analysis data cut date, a total of 1939.35 and 949.38 PY of follow-up were accrued in the LEN and TVD groups, respectively (Table below). The numbers of participants with incident HIV-1 infection and the HIV-1 incidences during the study in the LEN and TVD groups (FAS) were as follows:

- LEN: 0 of 2134 participants; 0.000 infections per 100 PY (95% CI: 0.000 to 0.190)
- TVD: 16 of 1068 participants; 1.685 infections per 100 PY (95% CI: 0.963 to 2.737)

Table 33. GS-US-412-5624: HIV-1 infections in study and estimated HIV-1 incidence in LEN and TVD Groups (full analysis set)

	Full Analysis Set		Full Analysis Set Excluding Participants Who Did Not Meet All Incidence Phase Eligibility Criteria	
	SC LEN (N = 2134)	TVD (N = 1068)	SC LEN (N = 2124)	TVD (N = 1062)
Number of diagnoses of HIV-1				
In study	0	16	0	15
On randomized study drug	0	14	0	13
On open-label oral PrEP	0	0	0	0
Off study drug PrEP	0	2	0	2
HIV-1 incidence in study				
Person-years of follow-up	1939.35	949.38	1930.56	943.76
HIV-1 incidence per 100 person-years	0.000	1.685	0.000	1.589
95% CI	(0.000, 0.190)	(0.963, 2.737)	(0.000, 0.191)	(0.890, 2.621)
HIV-1 incidence on randomized study drug				
Person-years of follow-up	1883.58	926.20	1877.01	920.57
HIV-1 incidence per 100 person-years	0.000	1.512	0.000	1.412
95% CI	(0.000, 0.196)	(0.826, 2.536)	(0.000, 0.197)	(0.752, 2.415)

CI = confidence interval; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s); PrEP = pre-exposure prophylaxis; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Confidence intervals for the HIV incidence in the randomized groups are exact based on the single Poisson rate parameter method {Ulm 1990}.
In Study includes the Randomized Blinded Phase and follow-up time of participants who discontinued the randomized blinded study drug early (regardless of reason) and may have received open-label oral PrEP administered via the PK Tail Phase or stopped taking any PrEP during the study.
On Randomized Study Drug is defined as the first dose date up to the earliest of a) last dose date + 10 days (TVD), b) later of last oral LEN dose date + 60 days or last SC LEN dose date + 28 weeks, or c) start of any nonrandomized PrEP drug. Person-year is sum of all participants' total number of years (1 year = 365.25 days) of follow-up between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date for participants without HIV-1.

Comparison of the HIV-1 Incidence in the LEN Group Versus the bHIV Incidence

Table 34. GS-US-412-5624: Statistical comparisons of the HIV-1 incidence in the LEN group versus the bHIV incidence (full analysis set and all screened set)

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

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

Secondary Efficacy Analyses

Comparison of LEN Versus TVD

Table 35. GS-US-412-5624: Statistical comparisons of the HIV-1 incidences in the LEN versus TVD groups (full analysis set)

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

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

Retrospective HIV-1 RNA Testing in Incident HIV-1 Cases

In the TVD group, 3 of 16 participants with incident HIV-1 infection were found to be HIV-1 RNA positive prior to serologic positivity, based on retrospective HIV-1 RNA quantitative NAAT results using archived samples. All 3 participants were found to be HIV-1 RNA positive 1 visit prior to serologic positivity, which corresponded to a time from HIV-1 RNA positivity to serologic positivity ranging from 87 to 97 days. None of the participants were HIV-1 RNA positive for more than 1 visit prior to serologic positivity.

Adherence

SC LEN Injection

In the LEN group, SC LEN injections were administered on time (≤ 28 weeks from the previous injection) in 91.1% of participants at Week 26 and 93.5% of participants at Week 52. Overall, 161 participants had at least 1 late (> 28 weeks from the previous injection) or missing SC LEN injection and were considered nonadherent to on-time SC LEN injections in the Randomized Blinded Phase.

Prescribed Adherence by Pill Count

Median (Q1, Q3) pill count-derived overall prescribed adherence rates (calculated for the duration of participation in the Randomized Blinded Phase while HIV negative) were as follows: DVY 99.4% (94.7%, 100.0%); TVD 99.6% (94.7%, 100.0%). The majority of participants (DVY 74.3%; TVD 74.4%) were ≥ 95% adherent to study drug by pill counts while in the Randomized Blinded Phase.

Oral PrEP

Adherence by TFV-DP in red blood cells from dried blood spot samples among the preselected 10% random sampling of participants, the majority in both the DVY and TVD groups had low adherence (consistent with dosing < 2 days per week); adherence declined over time in both study drug groups.

Pre-defined and post-hoc subgroup analyses

No participants in the LEN group had incident HIV-1 infection, therefore data in pre-defined subgroups are not considered relevant.

6.3.2.2. GS-US-528-9023 (PURPOSE 2)

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 design

Study GS-US-528-9023 is an ongoing Phase 3, randomized, double-blind, multicentre study to compare HIV-1 incidence in the LEN group with the counterfactual control of bHIV incidence, defined as the estimated HIV-1 incidence in the screened population. Truvada is the internal active control.

As illustrated in **Figure 19**, the study includes a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a Pharmacokinetics (PK) Tail Phase.

The Incidence Phase estimated the bHIV incidence within the population screened for eligibility using recency assay results from samples that were positive for HIV-1 infection incorporated into a recent infection testing algorithm (RITA). Participants determined to be HIV-1 negative and who met eligibility criteria proceeded to the Randomized Blinded Phase, in which they were randomized in a 2:1 ratio to receive LEN or TVD, respectively. After completion of the Randomized Blinded Phase, participants were offered the opportunity to receive open-label LEN in the LEN OLE Phase, which allows for further long-term efficacy and safety follow-up. Participants who discontinued study drug during the Randomized Blinded Phase entered the PK Tail Phase, which provides a known efficacious open-label regimen to provide HIV prevention for participants during the time when LEN concentrations decline.

If a participant prematurely discontinued blinded study drugs without an HIV-1 diagnosis, regardless of reason, transitioned to the PK Tail Phase (a random transition), and received at least 1 dose of study OL oral PrEP, the participant was included in the Open-Label Oral PrEP Analysis.

Enrolment of adolescents (participants ≥16 and < 18 years of age) commenced following the data monitoring committee (DMC) review of unblinded safety data from the first 300 adult participants through 8 weeks of follow-up and recommendation to continue the study.

Participants were screened or randomized across 96 study sites in the US (65), Brazil (9), Thailand (7), South Africa (6), Peru (5), Argentina (3), and Mexico (1).

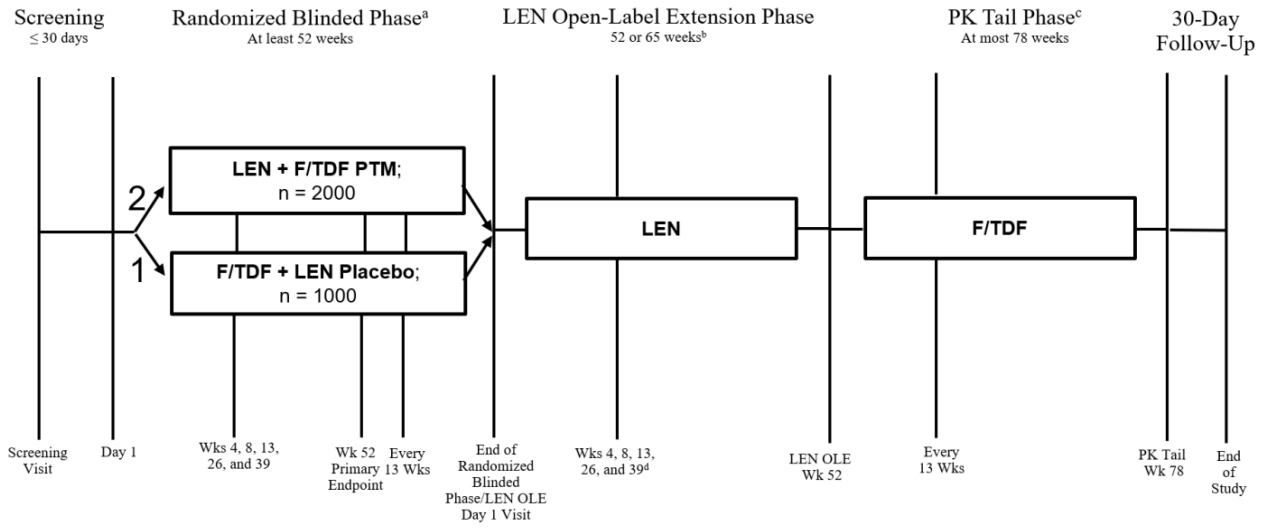


Figure 19. Study schema GS-US-528-9023
DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); F/TDF = emtricitabine/tenofovir disoproxil fumarate (Truvada®; TVD); LEN = lenacapavir; OL = open label; OLE = open-label extension; PK = pharmacokinetic; PTM = placebo-to-match;SC = subcutaneous

a. Participants were to continue in the Randomized Blinded Phase until all enrolled participants completed at least 52 weeks of follow-up in the study and the Applicant completed the primary analysis. In the case that the Randomized Blinded Phase was stopped early for an efficacy outcome, some participants may have less than 52 weeks of follow-up.
b. The duration will be dependent on timing of the OL LEN injection.
c. Participants who prematurely discontinued study drug during the Randomized Blinded Phase or LEN OLE Phase, or those randomized to LEN in the Randomized Blinded Phase who declined to participate in the LEN OLE Phase upon unblinding, will transition to the PK Tail Phase. Participants in the United States could receive either OL oral TVD or DVY in the PK Tail Phase.
d. Week 4 and 8 visits were only required for participants who were randomized to oral TVD in the Randomized Blinded Phase.

Randomisation

Participants were randomized in a 2:1 ratio to either active LEN or once daily oral F/TDF starting on Day 1/Injection 1 using an interactive web response system (IWRS). There was no stratification for randomisation.

Blinding

During the Randomized Blinded Phase, participants and all personnel directly involved in the conduct of the study were blinded to study drug assignment. Specified personnel were unblinded based on their study role. Study drug was dispensed by the unblinded study pharmacist, or designee, in a blinded fashion to the participants.

Description of trial intervention

Approximately 3000 participants who met all eligibility criteria were randomized in a 2:1 ratio (LEN:TVD) into 1 of the study drug groups summarized in the table below. Participants who prematurely discontinued study drug during the Randomized Blinded Phase transitioned to the PK Tail Phase and received open-label

oral TVD once daily. Participants in the US could receive either open-label oral TVD or DVY once daily during the PK Tail Phase.

Table 36. Study Drug Regimens in the Randomized Blinded Phase

	Study Drug Regimen
LEN	SC LEN 927 mg + PTM oral TVD; oral loading LEN 600 mg (2 × 300 mg) on Days 1 and 2
TVD	Oral TVD + placebo SC LEN; oral loading PTM LEN (2 tablets) on Days 1 and 2

LEN = lenacapavir; PTM = placebo-to-match; SC = subcutaneous; TVD = 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (coformulated; Truvada®).

Concomitant and rescue therapies

If SC LEN/placebo could not be administered within the injection visit window due to extenuating circumstances, including the clinical hold implemented by the Food and Drug Administration (FDA) on SC LEN (20 December 2021 through 16 May 2022), participants received open-label TVD (or open-label DVY for US sites only) starting when their next injection was due (before the approval of Protocol Amendment 2) or blinded once-weekly oral LEN 300 mg or PTM oral LEN, aligned with their original study drug assignment (after the approval of Protocol Amendment 2). Participants continued to receive daily oral study drug (TVD or PTM TVD) while also receiving once-weekly oral LEN or PTM oral LEN for bridging.

Study assessments

Efficacy assessment

Determination of HIV-1 infection during the Incidence Phase and the Randomized Blinded Phase are described below:

Incidence Phase

HIV testing in the Incidence Phase included rapid fourth generation HIV-1/2 Ab/Ag test, central fourth generation HIV-1/2 Ab/Ag test, and HIV-1 RNA quantitative NAAT. Confirmatory testing with a central laboratory HIV-1/2 Ab differentiation assay was performed if the central fourth generation HIV-1/2 Ab/Ag test was positive; a central laboratory HIV-1 RNA qualitative NAAT was performed if the HIV-1/2 Ab differentiation assay was negative. The HIV-1 infection in the Incidence Phase was defined by participants having at least 1 of the following laboratory results at the Incidence Phase screening visit:

- Positive HIV-1/2 Ab differentiation assay (performed only if central fourth generation HIV-1/2 Ab/Ag test was positive), OR
- Positive HIV-1 RNA qualitative NAAT (performed only if central fourth generation HIV-1/2 Ab/Ag test was positive and HIV-1/2 Ab differentiation assay was negative), OR
- HIV-1 RNA quantitative NAAT ≥ 200 copies/mL.

All participants and personnel were blinded to the results of the Sedia Limiting Antigen Avidity Enzyme Immunoassay for recent infection or the estimated bHIV incidence.

Randomized Blinded Phase

HIV testing at each visit included rapid fourth generation HIV-1/2 Ab/Ag and central fourth generation HIV-1/2 Ab/Ag tests. Positive central fourth generation HIV-1/2 Ab/Ag tests were confirmed with an HIV-1/2 Ab differentiation assay and HIV-1/2 RNA qualitative NAAT if the HIV-1/2 Ab differentiation assay was negative. The HIV-1 RNA quantitative NAAT was performed at the Day 1 visit and when resuming study drug after an interruption.

Retrospective HIV-1 RNA quantitative NAAT was performed using archived samples for incident HIV-1 cases to determine the earliest date with evidence of HIV-1 infection.

A blinded 3-physician adjudication committee reviewed all available HIV test results and determined the participant's HIV-1 status and earliest date with evidence of HIV-1 infection.

Study drug adherence

Participants self-reported adherence to daily oral study drug using computer-based surveys. In addition, adherence to TVD was assessed objectively by measuring the concentrations of TFV-DP in DBS. Dried blood spot measurements were performed in a random 10% subset of study participants and in all participants who were diagnosed with HIV-1.

Adherence to SC LEN and placebo SC LEN injection was assessed by on-time injection.

Pharmacokinetic Assessments

Single anytime blood samples were collected during the study to determine the PK profiles of LEN and exogenous hormones given as part of GAHT.

Safety Assessments

- Monitoring of AEs and concomitant medications
- Clinical laboratory analyses
- Vital signs measurements
- Physical examinations
- Urine sample for urinalysis, urine proteins (UP), urine chemistry (uric acid, phosphate, and creatinine), and urine pregnancy test for participants assigned female at birth who were of childbearing potential
- Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$)

Other Assessments

- Sexual Behavior and Substance Use Questionnaire
- Adherence to Oral Study Product Questionnaire
- PrEP Impacts and Administration Preference Questionnaire
- NPRS–Injection Pain Questionnaire
- Administration and Dosing Questionnaire for PrEP Medication (injection acceptability)
- Experienced Preference for PrEP Medication Questionnaire (administered during the OLE Phase and therefore not reported in this clinical study report [CSR])

Regular sexually transmitted infection (STI) testing is standard-of-care for people taking PrEP. Furthermore, STI incidence was used as an indicator of sexual behaviour that might increase the participant's likelihood of HIV acquisition.

Patient population

Key eligibility Criteria for the Incidence Phase

1) CGM, TGW, TGM, and GNB who have receptive anal sex with partners assigned male at birth and are at risk for HIV infection.
2) Age ≥ 16 years at screening. Enrollment of participants aged 16 and 17 years will commence following the first independent DMC meeting.
3) HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months
4) Sexually active with ≥ 1 partner assigned male at birth (condomless anal sex) in the last 12 months and 1of the following:
    a. Condomless anal sex with ≥ 2 partners in the last 12 weeks
    b. Documented 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

Key exclusion Criteria for the Incidence Phase

1) Prior use of long-acting systemic PrEP (including cabotegravir or islatravir trials)

2) Prior vaccine trial participation

Key eligibility Criteria for the Randomised Phase

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

1) Negative local rapid fourth generation HIV-1 Ab/Ag test confirmed with central HIV-1 testing
2) Estimated GFR ≥ 60 mL/min at screening according to the Cockcroft-Gault formula for CLcr {Cockcroft 1976}:

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

3) Body weight ≥ 35 kg

Exclusion Criteria for the Randomised Phase

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

1) Known hypersensitivity to the study drug, the metabolites, or formulation excipient
2) Acute viral hepatitis A, B or C or evidence of chronic hepatitis B or C infection
3) Positive for HBV-DNA or HCV-RNA
4) Have a suspected or known active, serious infection(s) (eg, active tuberculosis, etc) Need for continued use of any contraindicated concomitant medications
5) Have a history of osteoporosis or bone fragility fractures
6) Current alcohol or substance abuse judged by the investigator to be problematic such that it potentially interferes with participant study adherence
7) Grade 3 or Grade 4 proteinuria or glycosuria at screening that is unexplained or not clinically manageable
8) Participants of childbearing potential must have a negative pregnancy test at screening and Day 1, and must use an acceptable form of contraception during trial participation (see "Definition of Childbearing Potential" and "Contraception Requirements for Participant Assigned Female at Birth" Appendix 6) and not be lactating
9) Any other clinical or psychosocial condition or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with dosing requirements

Objectives and estimands

Primary objective

Estimand for the primary objective

The estimand framework was not used in this trial.

Primary endpoints:

- *Incidence Phase:* Diagnosis of recent HIV-1 infection
- *Randomized Blinded Phase*: Diagnosis of HIV-1 infection

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

Analysis sets

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

The Full Analysis Set (FAS) was the primary analysis set for efficacy analyses for participants who entered the Randomized Blinded Phase of the study. The FAS included all randomised participants who took at least 1 dose of any study drug and had not been diagnosed with HIV-1 on or prior to first dose date (as determined by the HIV Adjudication Committee confirming an HIV-1 infection diagnosis date on or prior to the first dose date of study drug). This is the primary analysis set for efficacy analyses for participants who entered the RBP of the study. Participants who have a negative rapid test at Day 1 were permitted to be dosed prior to receipt of the Day 1 central lab test results; however, participants who were diagnosed with HIV-1 based on central lab tests on or prior to first dose date were excluded from the FAS.

Planned analyses

The primary analysis was to be conducted when all participants had a minimum of 52 weeks (1 year) of follow-up in the RBP of the study or permanent discontinuation of study (whichever occurs first) after randomisation. However, the trial was stopped early for efficacy, so the interim analysis (described below) served as the primary analysis.

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

The background HIV (bHIV) incidence rate incidence was reported per 100 PY for the All Screened Set based on a RITA using an HIV-1 incidence formula similar to Kassanjee et al (Epidemiol 2012;23:721) adjusting for participants with HIV-1 who may not have had recency assay results.

The background incidence rate was estimated by the formula:

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

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 take recency assay
N_{rec}: total number of positive recency assay results
T: cutoff time (around 2 years) for the definition of true recent infections
Ω: Mean duration of recent infections (MDRI)
β: False recency rate (FRR)

The assay parameters given by Kassanjee et al (AIDS 2016;30:2361) were used for bHIV estimation. Since subtype data were not available in this trial, country was used to estimate the percentage of each subtype instead. It was assumed that all HIV-1 infections from South Africa belonged to subtype C, all infections from Mexico, United States, Peru, and Argentina belonged to subtype B, infections from Thailand to be 12% subtype B and 88% subtype AE, and infections from Brazil to be 92% subtype B and 8% subtype C.

The primary efficacy evaluations were comparisons of the observed HIV-1 incidences in the LEN and DVY groups versus the bHIV incidence. The incidence rate ratios of the LEN group versus the bHIV incidence and the DVY group versus the bHIV incidence were calculated. The associated 95% CIs and *P* values were estimated using the delta method (Gao et al., Stat Commun Infect Dis 2021;13:20200009) or a likelihood-based method if there were 0 infections {Shao and Gao, Stat Commun Infect Dis 2024;16:20230004). The likelihood-based method was specified in the statistical analysis plan but not in the protocol.

In general, missing data were not imputed unless methods for handling missing data were specified.

Sample size

A total sample size of 3000 was considered for this study. More than 95% power is achieved with 2000 participants in each of the LEN and the F/TAF study drug groups to show a significant difference with the background incidence rate. In this sample size analysis, the following assumptions were made:

- Background incidence rate of 3.00/100PY.
- LEN rate of 0.6/100PY, with 80% risk reduction
- Mean duration of recent infection (MDRI) of 173 days, with relative standard error (rSE) of 6.5%
- False recency rate (FRR) of 1.5%, with relative standard error (rSE) of 70%
- Average follow up of 1 year
- 2:1 allocation for LEN: F/TDF
- Alpha level of 0.0125 (1-sided) for each of the comparisons

The background incidence rate was estimated based on the results of a study by the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium (Lancet 2019;394:303).

The MDRI and FRR were based on the Sedia LAg assay (Kassanjee et al., AIDS 2016;30:2361).

The power calculation is based on the formula in Gao et al. (Stat Commun Infect Dis 2021;13:20200009) using the test statistics for rate ratio.

The study was not powered to detect a difference between the randomized study groups.

Interim analyses

A planned interim analysis of the safety data was conducted for the Data Monitoring Committee (DMC) when the first 300 adult participants completed their Week 8 visit. Enrolment of adolescent participants (≥16 and <18 years of age) commenced following this DMC review meeting of the safety data.

A planned interim analysis of efficacy and futility data was conducted for the DMC after 50% of the planned number of participants had completed at least 52 weeks of follow-up or prematurely discontinued from the study. The DMC recommended stopping the Randomized Blinded Phase early if the prespecified efficacy or futility evaluation criteria were met, and the interim analysis would then serve as the primary analysis.

The original interim stopping criteria specified in the study protocol required only the superiority of LEN versus bHIV, with the point estimate of $LEN/bHIV \leq 0.5$. After discussions with the FDA on 28 Nov 2023 (Type C meeting), the stopping criteria were updated to require not only superiority of LEN versus bHIV but also superiority of LEN versus F/TDF. This update was included in the statistical analysis plan but not in the protocol.

Multiplicity

There were 4 alpha-controlled efficacy evaluations planned for this study and the null hypothesis for each one is listed in the table below. For simplicity, LEN and TVD are used to denote the HIV-1 incidences for the LEN arm and F/TDF arm, respectively.

Table 37. Testing sequence of null hypotheses

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

At both the interim and primary analyses, the 1-sided Type I error rate was controlled using a fixed-sequence gatekeeping testing strategy (ie, tested sequentially in the order given above).

The overall alpha was 0.025 (one-sided).

A Bonferroni type spending function was used, so that an overall alpha = 0.0026 was used for the interim analysis and the remainder, alpha = 0.0224, was used at the primary analysis.

Changes from protocol-specified analyses

As explained above, the following changes were made:

- The statistical method that was used in case of 0 infections was prespecified in the statistical analysis plan but not in the protocol.
- The interim stopping criteria that were specified in the protocol were changed in the statistical analysis plan.

Secondary objectives

Randomized Blinded Phase

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

As secondary efficacy evaluations, the difference in HIV-1 incidence was used to evaluate comparability of LEN relative to TVD, and the incidence rate ratio was used to evaluate superiority of LEN versus TVD.

Estimands for the secondary objectives

The estimand framework was not used in this trial.

The Randomized Blinded Phase had two secondary endpoints:

- Diagnosis of HIV-1 infection, including among participants while adherent to study drug
- Occurrence of treatment-emergent adverse events (TEAEs) and treatment-emergent clinical laboratory abnormalities to evaluate safety and tolerability of LEN and TVD for HIV-1 PrEP

The ratio of HIV-1 incidences was used to evaluate the superiority of LEN or DVY versus TVD. The incidence rate ratios of the LEN group versus the TVD group and the DVY group versus the TVD group were calculated. The associated 95% CIs and *P* values were estimated using a generalized Poisson regression

model or an exact conditional Poisson regression model if there were 0 infections. The exact conditional Poisson regression model was specified in the statistical analysis plan but not in the protocol.

The difference in HIV-1 incidences was used to evaluate the comparability of LEN relative to TVD. In order to test this hypothesis, a 95% CI was constructed using a hybrid approach, with an additional modification to use the exact CI for the single Poisson rate parameter instead of the approximate CI (Li et a., Communications in Statistics - Simulation and Computation 2011;40:1478). The associated *P* value was obtained using the duality of hypothesis testing and CI (Rohatgi VK. Statistical Inference. In: Professor Emeritus Bowling Green State University, ed. Mathematical statistics. I. Dover Publications, Inc. Mineola, New York: 1984). It was concluded that LEN was comparable to TVD if the upper bound of the 95% CI of the incidence rate difference (LEN – TVD) was less than 0.8 per 100 PY. The comparability of DVY and TVD was evaluated similarly.

Exploratory objectives

Randomized Blinded Phase

- To assess the adherence rate to LEN as assessed by on-time LEN injection
- To assess LEN plasma levels
- To assess the adherence rate to TVD using intracellular tenofovir-diphosphate (TFV-DP) levels in dried blood spot (DBS)
- To evaluate the acceptability of a once every 6 months LEN injection for HIV-1 PrEP in participants at risk of HIV-1
- To explore concentrations of LEN in participants on exogenous hormones
- To explore concentrations of estradiol and testosterone in LEN participants on exogenous hormones

Results

Participant flow and numbers analysed

Table 38. GS-US-528-9023: Key study date

Event	Date
First participant screened	28 June 2021
First participant randomized	12 July 2021
Last participant randomized	12 December 2023
Last participant last visit for this report[a]	05 August 2024
Database finalization	22 August 2024
DMC meeting and recommendation to stop Randomized Blinded Phase	11 September 2024
Study drug group unblinding for the interim analysis[b]	11 September 2024

DMC = data monitoring committee

a Date of the last visit recorded in the electronic data capture database for this report.

b Date when Gilead personnel independent from the blinded study team were unblinded to review the interim analysis results after the DMC recommendation to stop the Randomized Blinded Phase early.

Incidence phase

Overall, 4807 participants were screened in the Incidence Phase and 3868 participants proceeded to Randomized Blinded Phase screening. Besides a positive HIV test (348 participants), the most common reasons for not proceeding to Randomized Blinded Phase screening were participant decision (216 participants) and outside of visit window (36 participants).

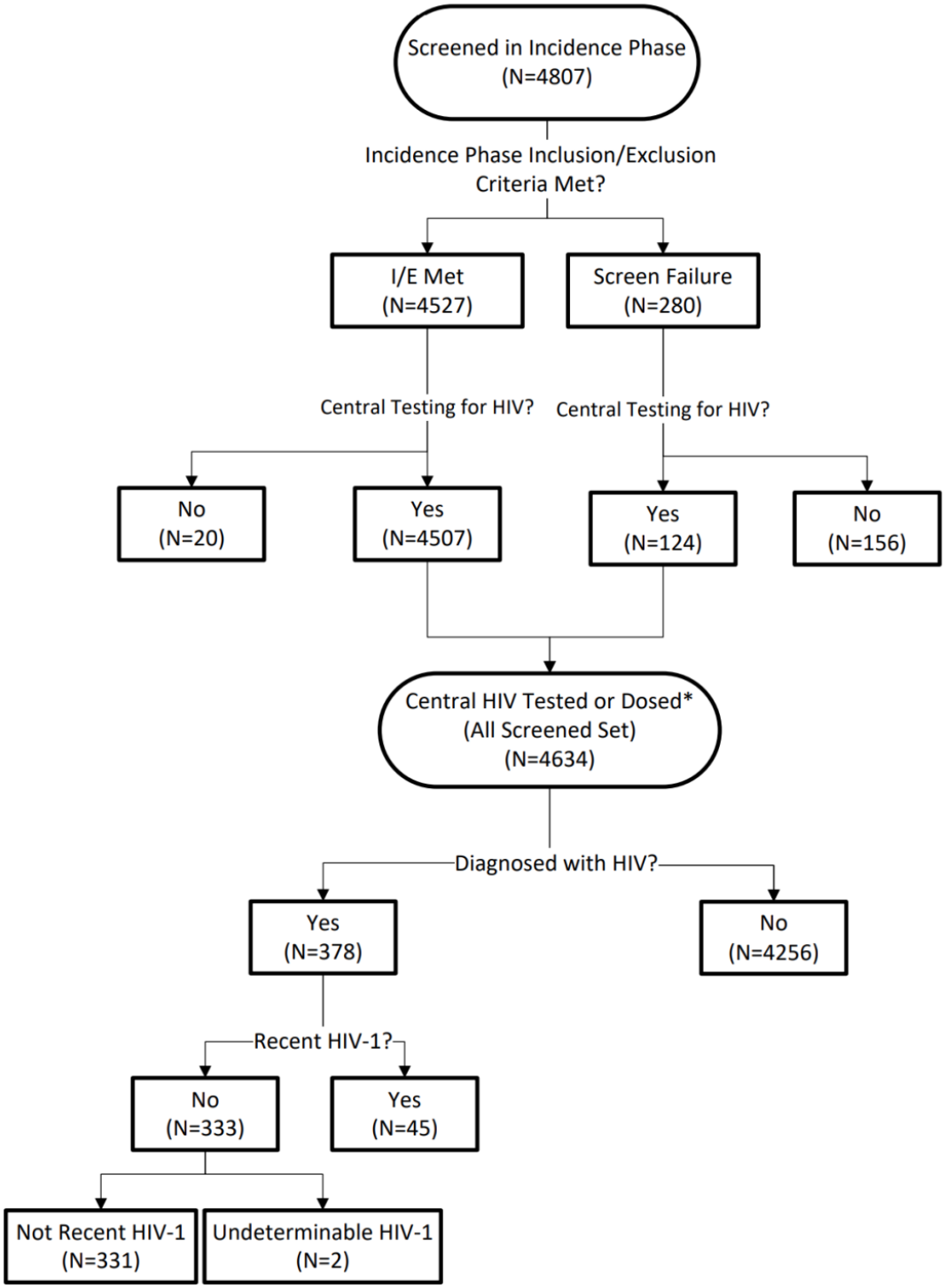


Figure 20. GS-US-528-9023: Disposition of participants in the incidence phase (screened participants)

HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion criteria
* Includes 3 participants with central HIV tests performed after initial screening, prior to randomization, and were randomized and dosed in Randomized Blinded Phase

Randomised blinded phase

Of those who were eligible for randomization but were not randomized, the most common reasons were outside of visit window (121 participants), study enrolment closed (105 participants) and lost to follow-up (61 participants).

Of the 3271 participants who were randomized and received study drugs, 6 participants were subsequently confirmed to have had baseline HIV-1 infections based on central testing. A total of 532 participants (16.3%) discontinued study drugs in the Randomized Blinded Phase. The most common reasons for discontinuation of study drugs were participant decision (301 participants [9.2%]), lost to follow-up (119 participants [3.6%]), and AEs (includes ISRs to study SC injection) (42 participants [1.3%]).

Among the 301 study drug discontinuations which were investigator-reported as due to participant decision, 98 (LEN 85; TVD 13) were related to participant concerns about injection.

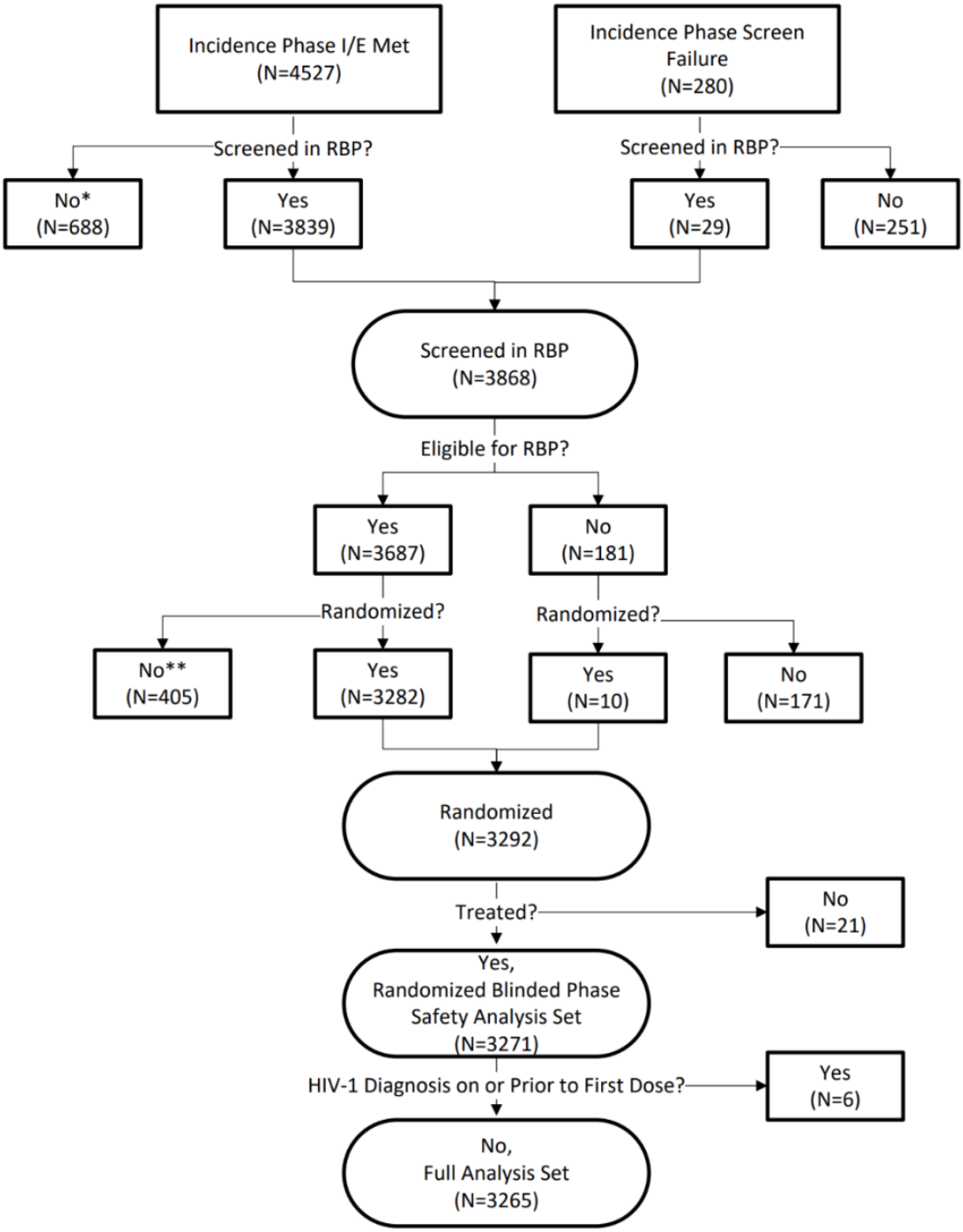


Figure 21. GS-US-528-9023: Disposition of participants in the randomised blinded phase (efficacy)
HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; I/E = inclusion/exclusion criteria; RBP = Randomized Blinded Phase

* Reasons not screened in RBP despite meeting Incidence Phase I/E criteria include investigator's discretion (12), lost to follow-up (31), outside of visit window (36), study enrollment closed (12), withdrew consent (18), and other (579, including positive HIV test = 348).** Reasons not randomized despite meeting RBP I/E criteria include investigator's discretion (5), lost to follow-up (61), outside of visit window (121), study enrollment closed (105), withdrew consent (32), screen failed Incidence Phase (15), and other (66).

Table 39. GS-US-528-9023: Disposition of participants in the randomized blinded phase (safety, screened participants)

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

HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PrEP = pre-exposure prophylaxis; RBP = Randomized Blinded Phase; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Denominators for percentages are the RBP Safety Analysis Set for study drug (or study) status.

Treated participants discontinued the study only once (either in RBP or Open-Label Oral PrEP Analysis); those who discontinued the study in the RBP could not be included in the Open-Label Oral PrEP Analysis.
Data through data cutoff date (05 August 2024).

Oral Bridging

Overall, of the 18 participants with their screening (Incidence Phase or Randomized Blinded Phase), randomization, or first dose interrupted due to the clinical hold, 9 were repeat screened and confirmed not to have HIV-1. Of the 92 participants (2.8%) who received oral study drug bridging during the clinical hold, 4 (0.1%) received open-label TVD, 32 (1.0%) received open-label DVY, 1 (< 0.1%) received both open-label TVD and DVY, and 55 (1.7%) received blinded once-weekly oral LEN or PTM oral LEN (39 received oral LEN and 16 received PTM oral LEN).

A total of 29 participants who received open-label TVD and/or open-label DVY resumed Randomized Blinded Phase study drug after the clinical hold was lifted. Of the 55 participants who received once-weekly oral LEN or PTM oral LEN, 36 resumed Randomized Blinded Phase study drug injections while 19 participants did not.

In addition, 2 participants received once-weekly PTM oral LEN outside of the clinical hold.

Deviations from study plan

The original global protocol (13 January 2021) was amended three times, below are the main amendments.

08 June 2021

The purpose of this amendment 1 was to align with health authority feedback on the original version 2 protocol. Amendments included clarifications, updates and addition of background and descriptions.

31 January 2022

The primary reasons for this amendment are to: Add information to allow weekly oral lenacapvir (LEN)/placebo dosing if a participant is not able to receive subcutaneous (SC) LEN or SC placebo (LEN/placebo oral bridging) within the protocol-specified window and its rationale; Provide recommendations on monitoring requirement for injection site reactions.

25 October 2023

Country specific requirements and mainly clarifications. 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.

Changes from protocol-specified analyses

- The statistical methods that were used in case of 0 infections were specified in the statistical analysis plan but not in the protocol.
- The interim stopping criteria that were specified in the protocol were changed in the statistical analysis plan.

Table 40. GS-US-528-9023: Important protocol deviations (screened participants)

Protocol Deviation Category	All Screened Set (N = 4634)	Total (N = 4807)
Participants with at least 1 important protocol deviation	1018 (22.0%)	1018 (21.2%)
Participants with 1 important protocol deviation	737 (15.9%)	737 (15.3%)
Participants with 2 important protocol deviations	209 (4.5%)	209 (4.3%)
Participants with 3 or more important protocol deviations	72 (1.6%)	72 (1.5%)
Total number of important protocol deviations	1407	1407
Informed consent	546	546
Missing data	480	480
Other study drug compliance issue	247	247
Wrong study drug or incorrect dose	51	51
Excluded concomitant medication	32	32
Other	27	27
Eligibility criteria	24	24

Protocol deviations are not mutually exclusive. Participants may be represented multiple times across protocol deviation categories.

Baseline data

Table 41. GS-US-528-9023: Demographic and baseline characteristics (randomised blinded phase safety analysis set)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
Age (years)			
N	2183	1088	3271
Mean (SD)	30 (8.7)	31 (9.5)	30 (9.0)
Median	28	29	29
Q1, Q3	24, 34	24, 36	24, 35
Min, max	17, 74	17, 73	17, 74
Age categories (years)			
16 to < 18	3 (0.1%)	1 (< 0.1%)	4 (0.1%)
18 to ≤ 25	749 (34.3%)	343 (31.5%)	1092 (33.4%)
> 25 to < 35	912 (41.8%)	423 (38.9%)	1335 (40.8%)
35 to < 50	454 (20.8%)	267 (24.5%)	721 (22.0%)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
≥ 50	65 (3.0%)	54 (5.0%)	119 (3.6%)
Sex assigned at birth			
Male	2140 (98.0%)	1064 (97.8%)	3204 (98.0%)
Female	43 (2.0%)	24 (2.2%)	67 (2.0%)
Gender identity			
Cisgender man (CGM)	1697 (77.7%)	846 (77.8%)	2543 (77.7%)
Transgender man (TGM)	29 (1.3%)	14 (1.3%)	43 (1.3%)
Transgender woman (TGW)	315 (14.4%)	161 (14.8%)	476 (14.6%)
Nonbinary	136 (6.2%)	63 (5.8%)	199 (6.1%)
Assigned male at birth	122 (5.6%)	53 (4.9%)	175 (5.4%)
Assigned female at birth	14 (0.6%)	10 (0.9%)	24 (0.7%)
Other	6 (0.3%)	4 (0.4%)	10 (0.3%)
Travesti	3 (0.1%)	3 (0.3%)	6 (0.2%)
Assigned male at birth	3 (0.1%)	3 (0.3%)	6 (0.2%)
Any other	3 (0.1%)	1 (< 0.1%)	4 (0.1%)
Assigned male at birth	3 (0.1%)	1 (< 0.1%)	4 (0.1%)
Sexual orientation			
Straight/heterosexual	148 (6.8%)	66 (6.1%)	214 (6.6%)
Gay	1634 (75.4%)	806 (74.7%)	2440 (75.1%)
Lesbian	2 (< 0.1%)	0	2 (< 0.1%)
Bisexual	322 (14.9%)	166 (15.4%)	488 (15.0%)
Other	62 (2.9%)	41 (3.8%)	103 (3.2%)
Pansexual	46 (2.1%)	26 (2.4%)	72 (2.2%)
Homosexual	3 (0.1%)	3 (0.3%)	6 (0.2%)
Queer	10 (0.5%)	12 (1.1%)	22 (0.7%)
Any other	3 (0.1%)	0	3 (< 0.1%)
Prefer not to disclose	15	9	24
Race			
American Indian or Alaska Native	20 (0.9%)	13 (1.2%)	33 (1.0%)
Asian	269 (12.4%)	144 (13.3%)	413 (12.7%)
Black	584 (26.9%)	301 (27.7%)	885 (27.1%)
Native Hawaiian or Pacific Islander	3 (0.1%)	0	3 (< 0.1%)
White	722 (33.2%)	344 (31.7%)	1066 (32.7%)
Hispanic or Latino	592 (27.2%)	278 (25.6%)	870 (26.7%)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
Not Hispanic or Latino	130 (6.0%)	66 (6.1%)	196 (6.0%)
Black/White	185 (8.5%)	98 (9.0%)	283 (8.7%)
Black/Asian	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Black/American Indian or Alaska Native	5 (0.2%)	1 (< 0.1%)	6 (0.2%)
Black/Native Hawaiian or Pacific Islander	2 (< 0.1%)	0	2 (< 0.1%)
Asian/White	3 (0.1%)	4 (0.4%)	7 (0.2%)
Asian/Native Hawaiian or Pacific Islander	1 (< 0.1%)	0	1 (< 0.1%)
White/American Indian or Alaska Native	316 (14.5%)	141 (13.0%)	457 (14.0%)
White/Native Hawaiian or Pacific Islander	1 (< 0.1%)	2 (0.2%)	3 (< 0.1%)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
Multiracial—other	53 (2.4%)	34 (3.1%)	87 (2.7%)
Coloured	5 (0.2%)	1 (< 0.1%)	6 (0.2%)
Pardo	1 (< 0.1%)	3 (0.3%)	4 (0.1%)
Black/Brown	12 (0.6%)	8 (0.7%)	20 (0.6%)
Black/Coloured	7 (0.3%)	4 (0.4%)	11 (0.3%)
Black/Pardo	15 (0.7%)	7 (0.6%)	22 (0.7%)
White/Brown	6 (0.3%)	2 (0.2%)	8 (0.2%)
Any other	7 (0.3%)	9 (0.8%)	16 (0.5%)
Not multiracial—other	10 (0.5%)	3 (0.3%)	13 (0.4%)
Unknown	10 (0.5%)	3 (0.3%)	13 (0.4%)
Not permitted	8	2	10
Ethnicity			
Hispanic or Latino	1378 (63.2%)	675 (62.0%)	2053 (62.8%)
Not Hispanic or Latino	804 (36.8%)	413 (38.0%)	1217 (37.2%)
Not permitted	1	0	1
Baseline weight (kg)			
N	2183	1088	3271
Mean (SD)	78.4 (19.82)	79.2 (19.58)	78.6 (19.74)
Median	75.3	75.2	75.2
Q1, Q3	64.5, 88.0	65.3, 90.2	64.8, 88.5
Min, max	37.8, 195.4	42.0, 178.7	37.8, 195.4
Baseline body mass index (kg/m^2)			
N	2183	1088	3271
Mean (SD)	26.1 (6.13)	26.4 (5.86)	26.2 (6.04)
Median	25.1	25.2	25.1
Q1, Q3	21.9, 28.9	22.3, 29.3	22.0, 29.0
Min, max	13.7, 89.6	15.6, 67.4	13.7, 89.6
Highest education level			
Did not attend primary school	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Some primary school education	11 (0.5%)	11 (1.0%)	22 (0.7%)
Primary school complete	68 (3.1%)	48 (4.4%)	116 (3.5%)
Some secondary school education	260 (11.9%)	114 (10.5%)	374 (11.4%)
Secondary school degree complete	737 (33.8%)	338 (31.1%)	1075 (32.9%)
Some college or university degree	1105 (50.6%)	574 (52.9%)	1679 (51.4%)
Missing	1	2	3

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®) Age (in years) was collected on the first dose date of study drug (Day 1).

"Not permitted" = local regulators or participants did not allow collection of race or ethnicity information. "Not permitted," "prefer not to disclose," or "missing" were excluded for calculation of percentage. Body mass index (kg/m^2) = (Weight [kg]/Height [cm]^2) × 10,000.

Table 42. GS-US-528-9023: Baseline HIV risk characteristics (randomised blinded phase safety analysis set)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
Urethral/urine chlamydia			
Detected	55 (2.6%)	21 (1.9%)	76 (2.4%)
Indeterminate	1 (< 0.1%)	0	1 (< 0.1%)
Not detected	2099 (97.4%)	1057 (98.1%)	3156 (97.6%)
Missing	28	10	38
Rectal chlamydia			
Detected	177 (8.2%)	92 (8.5%)	269 (8.3%)
Indeterminate	12 (0.6%)	7 (0.6%)	19 (0.6%)
Not detected	1982 (91.3%)	986 (90.9%)	2968 (91.2%)
Missing	12	3	15
Pharyngeal chlamydia			
Detected	51 (2.3%)	22 (2.0%)	73 (2.2%)
Indeterminate	2 (< 0.1%)	1 (< 0.1%)	3 (< 0.1%)
Not detected	2125 (97.6%)	1063 (97.9%)	3188 (97.7%)
Missing	5	2	7
Urethral/urine gonorrhea			
Detected	18 (0.8%)	3 (0.3%)	21 (0.6%)
Indeterminate	1 (< 0.1%)	0	1 (< 0.1%)
Not detected	2136 (99.1%)	1075 (99.7%)	3211 (99.3%)
Missing	28	10	38
Rectal gonorrhea			
Detected	104 (4.8%)	54 (5.0%)	158 (4.9%)
Indeterminate	12 (0.6%)	7 (0.6%)	19 (0.6%)
Not detected	2055 (94.7%)	1024 (94.4%)	3079 (94.6%)
Missing	12	3	15
Pharyngeal gonorrhea			
Detected	129 (5.9%)	81 (7.5%)	210 (6.4%)
Indeterminate	2 (< 0.1%)	1 (< 0.1%)	3 (< 0.1%)
Not detected	2047 (94.0%)	1004 (92.4%)	3051 (93.5%)
Missing	5	2	7
Trichomonas vaginalis (urethral/urine)			
Detected	1 (1.6%)	0	1 (0.9%)
Indeterminate	0	0	0
Not detected	63 (98.4%)	44 (100.0%)	107 (99.1%)
Not Tested	2119	1044	3163
Syphilis diagnosis (investigator report)			
Yes	84 (3.8%)	43 (4.0%)	127 (3.9%)
No	2099 (96.2%)	1045 (96.0%)	3144 (96.1%)
Syphilis stage			

Primary	2 (2.4%)	0	2 (1.6%)
Early latent	37 (44.0%)	17 (39.5%)	54 (42.5%)
Secondary	8 (9.5%)	4 (9.3%)	12 (9.4%)
Tertiary	0	0	0
Late latent	35 (41.7%)	20 (46.5%)	55 (43.3%)
Other	2 (2.4%)	2 (4.7%)	4 (3.1%)
Sex partners in past 3 months			
N	2043	1016	3059
Mean (SD)	14 (49.8)	16 (63.9)	15 (54.9)
Median	5	5	5
Q1, Q3	3, 10	3, 10	3, 10
Min, max	0, 900	0, 999	0, 999
Sex partners in past 3 months			
0	40 (2.0%)	24 (2.4%)	64 (2.1%)
1	120 (5.9%)	58 (5.7%)	178 (5.8%)
2	258 (12.6%)	142 (14.0%)	400 (13.1%)
3	312 (15.3%)	147 (14.5%)	459 (15.0%)
4-5	392 (19.2%)	190 (18.7%)	582 (19.0%)
6-10	436 (21.3%)	221 (21.8%)	657 (21.5%)
≥ 11	485 (23.7%)	234 (23.0%)	719 (23.5%)
Prefer not to answer	53	31	84
Missing	87	41	128
Sex partners with HIV in past 3 months			
N	1019	522	1541
Mean (SD)	1 (7.5)	2 (24.4)	1 (15.4)
Median	0	0	0
Q1, Q3	0, 1	0, 1	0, 1
Min, max	0, 213	0, 545	0, 545
Sex partners with HIV in past 3 months			
0	710 (69.7%)	367 (70.3%)	1077 (69.9%)
1	194 (19.0%)	92 (17.6%)	286 (18.6%)
2	55 (5.4%)	25 (4.8%)	80 (5.2%)
3	33 (3.2%)	13 (2.5%)	46 (3.0%)
4-5	12 (1.2%)	12 (2.3%)	24 (1.6%)
6-10	10 (1.0%)	9 (1.7%)	19 (1.2%)
≥ 11	5 (0.5%)	4 (0.8%)	9 (0.6%)
Prefer not to answer	71	37	108
I don’t know	1006	487	1493
Missing	87	42	129
Condomless receptive anal sex acts in past 3 months			
N	2002	983	2985
Mean (SD)	7 (32.0)	6 (22.4)	7 (29.2)
Median	2	2	2
Q1, Q3	1, 5	1, 5	1, 5
Min, max	0, 800	0, 444	0, 800
Condomless receptive anal sex acts in past 3 months			
0	442 (22.1%)	214 (21.8%)	656 (22.0%)

1	303 (15.1%)	168 (17.1%)	471 (15.8%)
2	330 (16.5%)	151 (15.4%)	481 (16.1%)
3	231 (11.5%)	110 (11.2%)	341 (11.4%)
4-5	218 (10.9%)	123 (12.5%)	341 (11.4%)
6-10	262 (13.1%)	123 (12.5%)	385 (12.9%)
≥ 11	216 (10.8%)	94 (9.6%)	310 (10.4%)
Prefer not to answer	91	62	153
Missing	90	43	133
Taken drugs before or during sex (chemsex acts) in past 3 months			
Yes	549 (26.4%)	286 (27.6%)	835 (26.8%)
No	1530 (73.6%)	750 (72.4%)	2280 (73.2%)
Prefer not to answer	17	11	28
Missing	87	41	128

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

Baseline Medical Characteristics

Table 43. GS-US-528-9023: Baseline medical characteristics (randomised blinded phase safety analysis set)

	SC LEN (N = 2183)	TVD (N = 1088)	Total (N = 3271)
HBV infection status			
Yes	1 (< 0.1%)	0	1 (< 0.1%)
No	2182 (100.0%)	1088 (100.0%)	3270 (100.0%)
HCV infection status			
Yes	0	0	0
No	2183 (100.0%)	1088 (100.0%)	3271 (100.0%)
Estimated glomerular filtration rate by Cockcroft-Gault (mL/min)			
N	2183	1088	3271
Mean (SD)	133.3 (40.51)	132.9 (39.71)	133.1 (40.24)
Median	124.8	124.1	124.6
Q1, Q3	106.2, 151.4	106.0, 152.0	106.2, 151.4
Min, max	56.4, 476.1	48.0, 385.3	48.0, 476.1
Serum creatinine (mg/dL)			
N	2183	1088	3271
Mean (SD)	0.91 (0.152)	0.92 (0.149)	0.91 (0.151)

Median	0.90	0.90	0.90
Q1, Q3	0.81, 1.01	0.81, 1.00	0.81, 1.01
Min, max	0.51, 1.66	0.42, 1.65	0.42, 1.66
Proteinuria toxicity grade by urinalysis (dipstick)			
Grade 0	2012 (92.2%)	1003 (92.2%)	3015 (92.2%)
Grade 1	153 (7.0%)	79 (7.3%)	232 (7.1%)
Grade 2	16 (0.7%)	5 (0.5%)	21 (0.6%)
Grade 3	1 (< 0.1%)	1 (< 0.1%)	2 (< 0.1%)
Missing	1	0	1

DNA = deoxyribonucleic acid; HBV = hepatitis B virus; HCV = hepatitis C virus; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; RNA = ribonucleic acid; SC = subcutaneous; SD = standard deviation; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
HCV infection = positive HCV antibody and quantifiable HCV RNA (≥ 15 IU/mL).
HBV infection = (1) positive hepatitis B surface antigen or (2) negative hepatitis B surface antibody, positive hepatitis B core antibody, and quantifiable HBV DNA (≥ 20 IU/mL).
"Missing" was excluded from percentage calculation.

Number of Participants (Planned and Analyzed)

Planned: approximately 3000 participants in the Randomized Blinded Phase.
Analysed:

Table 44. GS-US-528-9023: Analysis set

Analysis Set Reason for Exclusion	SC LEN	TVD	Total
Screened for Incidence Phase			4807
Without central HIV test at Incidence Screening and not dosed			173
All Screened Set			4634
All Randomized Analysis Set	2195	1097	3292
Participants never dosed study drug	12 (0.5%)	9 (0.8%)	21 (0.6%)
RBP Safety Analysis Set	2183 (100.0%)	1088 (100.0%)	3271 (100.0%)
Full Analysis Set	2179 (99.3%)	1086 (99.0%)	3265 (99.2%)
Diagnosed with HIV-1 on or prior to first dose	4 (0.2%)	2 (0.2%)	6 (0.2%)
Modified Full Analysis Set	2070 (94.3%)	1032 (94.1%)	3102 (94.2%)
First dose before the clinical hold	109 (5.0%)	54 (4.9%)	163 (5.0%)
Open-Label Oral PrEP Safety Analysis Set	119 (5.5%)	31 (2.8%)	150 (4.6%)
LEN PK Analysis Set	536 (24.6%)	0	536 (16.4%)
Hormone PK Analysis Set	138 (6.3%)	0	138 (4.2%)
DBS Cohort Analysis Set	0	111 (10.2%)	111 (3.4%)

DBS = dried blood spot; FAS = Full Analysis Set; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; mFAS = modified Full Analysis Set; PK = pharmacokinetic(s); PrEP = pre-exposure prophylaxis; RBP = Randomized Blinded Phase; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Denominators: 1) randomized for All Randomized Analysis Set, FAS, mFAS, and associated exclusion reasons and 2) RBP Safety Analysis otherwise. Participants' study drugs grouped by 1) randomized drug for All Randomized Analysis Set, FAS, and mFAS and 2) actual drug received otherwise.

Outcomes and estimation

Primary Efficacy Endpoint

Diagnosis of HIV-1 Infection

At the interim analysis data cut date, a total of 1938.07 and 966.54 PY of follow-up were accrued in the LEN and TVD groups, respectively. The numbers of participants with incident HIV-1 infection and the HIV-1 incidences during the study in the LEN and TVD groups (FAS) were as follows:

- LEN: 2 of 2179 participants; 0.103 infections per 100 PY (95% CI: 0.012 to 0.373)
- TVD: 9 of 1086 participants; 0.931 infections per 100 PY (95% CI: 0.426 to 1.768)

Table 45. GS-US-528-9023: HIV-1 infections in study and estimated HIV-1 incidence in LEN and TVD groups (full analysis set)

	Full Analysis Set		Full Analysis Set Excluding Participant Who Did Not Meet All Incidence Phase Eligibility Criteria	
	SC LEN (N = 2179)	TVD (N = 1086)	SC LEN (N = 2175)	TVD (N = 1086)
Number of diagnosis of HIV-1				
In study	2	9	2	9
On randomized study drug	2	6	2	6
On open-label oral PrEP	0	0	0	0
Off study drug PrEP	0	3	0	3
HIV-1 incidence in study				
Person-years of follow-up	1938.07	966.54	1935.03	966.54
HIV-1 incidence per 100 person-years	0.103	0.931	0.103	0.931
95% CI	(0.012, 0.373)	(0.426, 1.768)	(0.013, 0.373)	(0.426, 1.768)
HIV-1 incidence on randomized study drug				
Person-years of follow-up	1841.55	937.02	1838.52	937.02
HIV-1 incidence per 100 person-years	0.109	0.640	0.109	0.640
95% CI	(0.013, 0.392)	(0.235, 1.394)	(0.013, 0.393)	(0.235, 1.394)

CI = confidence interval; HIV = human immunodeficiency virus; HIV-1 = human immunodeficiency virus type 1; LEN = lenacapavir; PK = pharmacokinetic(s); PrEP = pre-exposure prophylaxis; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Confidence intervals for the HIV incidence in the randomized groups are exact based on the single Poisson rate parameter method {Ulm 1990}.
In Study includes the Randomized Blinded Phase and follow-up time of participants who discontinued the randomized blinded study drug early (regardless of reason) and may have received open-label oral PrEP administered via the PK Tail Phase or stopped taking any PrEP during the study.
On Randomized Study Drug is defined as the first dose date up to the earliest of a) last dose date + 10 days (TVD), b) later of last oral LEN dose date + 60 days or last SC LEN dose date + 28 weeks, or c) start of any nonrandomized PrEP drug.
Person-year is sum of all participants' total number of years (1 year = 365.25 days) of follow-up between the first dose date and either 1) the HIV-1 diagnosis date for participants with HIV-1, or 2) the latest postbaseline HIV laboratory test date for participants without HIV-1.

Comparison of the HIV-1 Incidence in the LEN Group Versus the bHIV Incidence

Table 46. GS-US-528-9023: Statistical comparisons of the HIV-1 incidence in the LEN group versus the bHIV incidence (full analysis set and all screened set)

	SC LEN (N = 2179)	bHIV Incidence (N = 4634)
Number of diagnosis of HIV-1		
In study	2	—
On randomized study drug	2	—
On open-label oral PrEP	0	—

Off study drug PrEP	0	—
HIV-1 incidence in study		
Person-years of follow-up	1938.07	—
HIV-1 incidence per 100 person-years	0.103	2.374
95% CI	(0.012, 0.373)	(1.649, 3.417)
Rate ratio (SC LEN over bHIV incidence)	0.043	—
95% CI	(0.010, 0.182)	—
One-sided *P* value for rate ratio ≥ 1 (H_{01})	< 0.0001	—
One-sided *P* value for rate ratio ≥ 0.8 (H_{02})	< 0.0001	—

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

Secondary Efficacy Analyses

Comparison of LEN Versus TVD

Table 47. GS-US-528-9023: Statistical comparisons of the HIV-1 incidences in the LEN versus TVD groups (full analysis set)

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

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

Retrospective HIV-1 RNA Testing in Incident HIV-1 Cases

Neither of the participants in the LEN group with incident HIV-1 infection were found to be HIV-1 RNA positive prior to serologic positivity, based on retrospective HIV-1 RNA quantitative NAAT results using archived samples. Single-copy HIV-1 RNA testing, done retrospectively for prior visits including baseline, was positive for 1 participant at Week 8 (37 days before serologic positivity) with a value of 4.8 copies/mL. In the TVD group, 2 of 9 participants with incident HIV-1 infection were found to be HIV-1 RNA positive prior to serologic positivity. Both participants in the TVD group were found to be HIV-1 RNA positive 1 visit prior to serologic positivity, which corresponded to a time from HIV-1 RNA positivity to serologic positivity of 38 and 100 days, respectively.

Adherence

SC LEN Injection

Of the participants in the LEN group, 87.2% received the Week 26 SC LEN injection within 28 weeks of the first injection, and 92.7% received the Week 52 SC LEN injection within 28 weeks of the previous injection.

SC LEN Injection and HIV-1 Incidence

Both of the participants in the LEN group with incident HIV-1 infection had all on-time SC LEN injections (≤ 28 weeks from the previous injection) and were considered adherent to on-time SC LEN injections. A total of 231 participants had at least 1 late (> 28 weeks from the previous injection) or missing SC LEN injection and were considered nonadherent to on-time SC LEN injections in the Randomized Blinded Phase.

Prescribed Adherence by Pill Count

The median (Q1, Q3) pill count-derived overall prescribed adherence rate (calculated for the duration of participation in the RBP while HIV negative) in the TVD group was 97.9% (90.9%, 100.0%). The majority of participants in the TVD group (63.4%) were ≥ 95% adherent to study drug by pill counts while in the RBP.

Adherence by TFV-DP in Red Blood Cells From Dried Blood Spot Samples

Among the preselected 10% random sampling of participants, the majority of participants in the TVD group had high adherence (consistent with dosing ≥ 4 days per week). Through 52 weeks of follow-up, the proportion of participants with high adherence declined from 82.4% at Week 8 to 62.2% at Week 52.

Pre-defined and post-hoc subgroup analyses

With the limited number of HIV-1 infections in the LEN group, data in pre-defined subgroups are not considered relevant.

6.3.3. Clinical virology

Resistance Analysis Population

The Resistance Analysis Population (RAP) included all randomized participants who received at least one dose of study drug, acquired HIV-1 while on study, and had a plasma sample with HIV-1 RNA ≥ 200 copies/mL available for testing.

Upon diagnosis of HIV-1 acquisition, plasma samples were collected for HIV-1 RNA quantification and resistance analyses. Samples with HIV-1 RNA ≥ 200 copies/mL were analysed for genotypic resistance in the HIV-1 CA, PR, RT, and IN coding regions. As necessary, additional plasma samples from later time points could be also used for resistance analyses.

Table 48. GS-US-412-5624: Resistance substitutions by antiretroviral class

Drug Class	Drugs and Codon Mutations[a]
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (N[t]RTIs)	Abacavir, Emtricitabine, Lamivudine, Tenofovir, Zidovudine, Didanosine, Stavudine

Primary NRTI resistance (-R) substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analog Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219E/Q/N/R
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Delavirdine, Doravirine, Efavirenz, Etravirine, Nevirapine, Rilpivirine
Primary NNRTI-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C/L, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I/T, V179D/F/T, G190E, F227I/R/V, L234I
Capsid Inhibitors (CIs)	Lenacapavir
Primary CI-R substitutions	L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/S, A105S/T, T107N
Protease Inhibitors (PIs)	Atazanavir, Darunavir, Lopinavir, Tipranavir, Fosemprenavir, Indinavir, Nelfinavir, Saquinavir, Ritonavir
Primary PI-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Entry Inhibitors (EIs)	Enfuvirtide, Maraviroc, Fostemsavir
Resistance associated substitutions in envelope gene	G36D/S, I37V, V38A/E/M, Q39R, Q40H, N42T, N43D
Integrase Strand Transfer Inhibitors (INSTIs)	Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir, Raltegravir
Primary INSTI-R substitutions	T66I/A/K, E92Q/G/V, G118R, F121C/Y, G140R, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, L68V/I, L74M, T97A, S119P/R/T, E138K/A/T, G140A/C/S, P145S, Q146R/I/K/L/P, V151A/I/L, S153F/Y, E157K/Q, S230R

a. Adapted from the current International Antiviral Society-USA (IAS-USA) lists with some modifications {Wensing 2022}.
b. Reversion mutations at RT codon T215, including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either emtricitabine or tenofovir.

GS-US-412-5624 (PURPOSE 1)

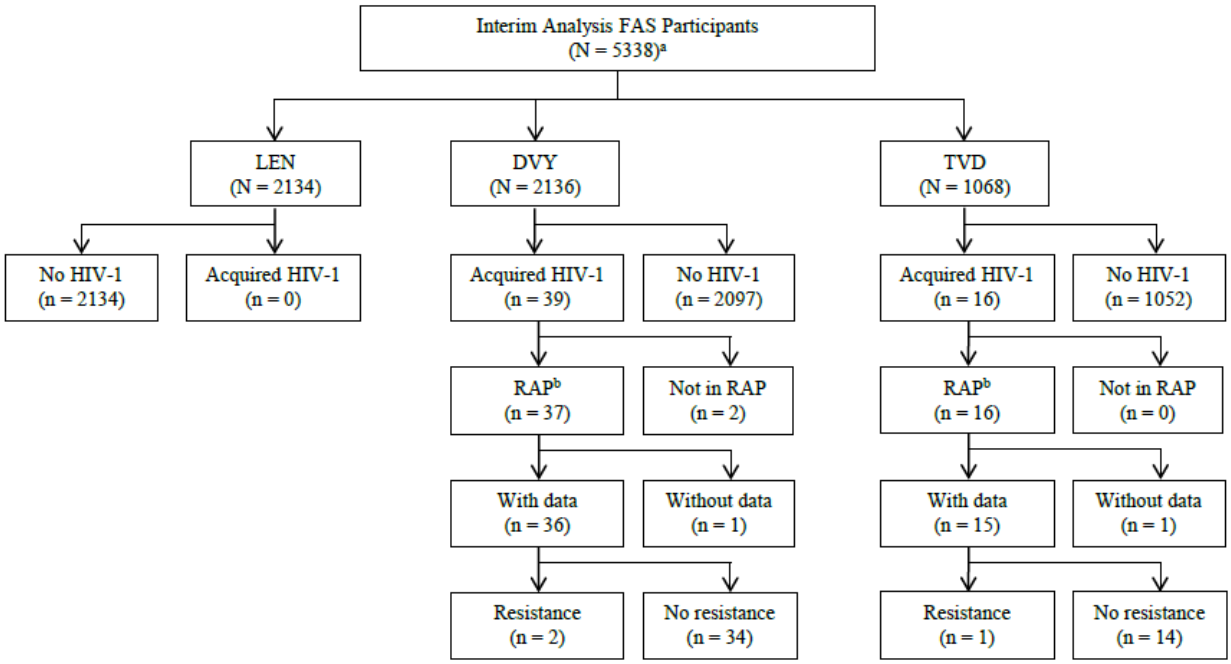


Figure 22. GS-US-412-5624: Resistance analysis population inclusion criteria and genotypic results

DVY = Descovy: emtricitabine/tenofovir alafenamide; FAS = Full Analysis Set; LEN = lenacapavir; RAP = resistance analysis population; TVD = Truvada: emtricitabine/ tenofovir disoproxil fumarate

a. Participants who received study drug but were found to have acquired HIV-1 infection at baseline after Day 1 central lab testing were excluded from the FAS, per the SAP.
b. Criteria for inclusion in the RAP are no HIV-1 infection at baseline, acquisition of HIV-1 while on study drugs and HIV-1 RNA ≥ 200 copies/mL.

Resistance in Participants Who Acquired HIV-1

The resistance analysis population (RAP) comprised 53 participants who acquired HIV-1 infection during the study, had an HIV RNA viral load of >200 copies/mL and consented to resistance testing, including 37 of 53 (69.8%) participants from the emtricitabine/tenofovir alafenamide (F/TAF; DVY) group, and 16 of 53 (30.2%) participants from the emtricitabine/tenofovir disoproxil fumarate (F/TDF; TVD) group.

There were 2 participants in the LEN group (not included in the RAP above) who acquired HIV-1 after the time of the primary analysis. One of the infections occurred in a participant after LEN exposures fell below the target concentration following discontinuation and virus from this participant had no LEN resistance-associated capsid substitutions detected. The second participant had viral loads that were too low for genotyping.

The M184V/I substitution, conferring resistance to FTC, was observed in 2 participants from the DVY group and in 1 participant in the TVD group. For one of these participants in the DVY group, the K65R substitution in RT, conferring resistance to tenofovir, was also observed (Table below).

Table 49. GS-US-412-5624: Summary of HIV-1 genotypic resistance

Resistance Category[a]	Number of Participants Who Acquired HIV-1, n (%)			
	LEN (N = 2134)	DVY (N = 2136)	TVD (N = 1068)	P Value[b]
RAP (% of FAS)	0	37 (1.7)	16 (1.5)	<0.0001; 0.67
Participants with data (any gene)	0	37 (1.7)	16 (1.5)	
Genotypic resistance to study drugs detected	0	2 (0.001)	1 (0.001)	NA
Genotypic resistance to non-study drugs detected	0	11 (0.005)	7 (0.007)	NA
Any Primary NRTI-R detected (% of RAP)	0	2 (5.4)	1 (6.3)	
M184V/I	0	2 (5.4)	1 (6.3)	
K65R	0	1 (2.7)	0	
Any Primary NNRTI-R detected (% of RAP)	0	10 (27)	7 (44)	
Any Primary PI-R detected (% of RAP)	0	0	0	
Any Primary INSTI-R detected (% of RAP)	0	1 (2.7)	0	
Any CAI-R detected (% of RAP)	0	1 (0.05)	0	

CAI = capsid inhibitor; DVY = Descovy (emtricitabine/tenofovir alafenamide); FAS = full analysis set; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; NA = not applicable; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAP = resistance analysis population; TVD = Truvada (emtricitabine/ tenofovir disoproxil fumarate)

a. Drug resistance substitutions are defined in the table above.
b. Fisher's exact test comparing the proportions of LEN and DVY versus TVD using the whole population as the denominator.

Non-study Drug Resistance Detected

Non-study drug resistance was detected in 18 out of 53 (34.0%) of participants in the RAP with data in at least 1 gene.

In the DVY group, 11 out of 37 (29.7%) participants with data in at least 1 gene had non-study drug resistance, including the NNRTI resistance mutations K103N, V106M, E138A/Q, Y188L, and G190A and the INSTI resistance mutation T66I, demonstrating transmitted drug resistance in this population. The CAI resistance mutation K70R was also detected in 1 South African participant with a subtype C virus and no exposure to LEN, as a very rare polymorphism. The K70R mutation has been reported in subtype C at very low frequencies (0.1%, 1 out of 834 subtype C sequences in the Los Alamos HIV Database evaluated) {Nka 2022}. The K70R as a single mutation is associated with a minor reduction in susceptibility to LEN (1.2-fold reduction).

In the TVD group, 7 out of 16 (43.8%) participants with data in at least 1 gene had non-study drug resistance, including the NNRTI resistance mutations K103N, E138A, Y181C, and P225H.

Resistance in Participants With HIV-1 Infection Present at Baseline Who Received Study Drugs on Day 1

Baseline HIV-1 infections were discovered in 7 participants who acquired HIV-1 prior to Day 1 but had a negative rapid HIV test at screening, were randomized, and received study drugs on Day 1. These

participants were excluded from the FAS and are not part of the RAP. Four of these participants received SC LEN, 1 participant received oral DVY, and 2 participants received oral TVD.

Time between the date of HIV-1 diagnosis and initiating an ART regimen varied from 5-140 days. Resistance testing was done at Day 1 and the last study visit with HIV-1 > 200 copies/mL (range of 8 to 271 days). Baseline and postbaseline resistance data was available for 6 of the 7 participants.

Two out of 4 baseline infection cases who received LEN developed resistance-associated mutation N74D. Virologic suppression were delayed due to participant lost to follow-up or initially declining ART, however, both participants reportedly eventually received ART. None of the participant had LEN resistance on Day 1. The N74D mutation was detected at follow-up visits, at Day 8 in one of the participants and for the other participant, who continued to be viraemic, it was found approximately 9 months after Day 1.

The participant with the emerging DVY resistance showed no resistance mutations at Day 1, but the FTC resistance associated mutation M184M/V was found to have emerged 41 days later.

Study GS-US-528-9023 (PURPOSE 2)

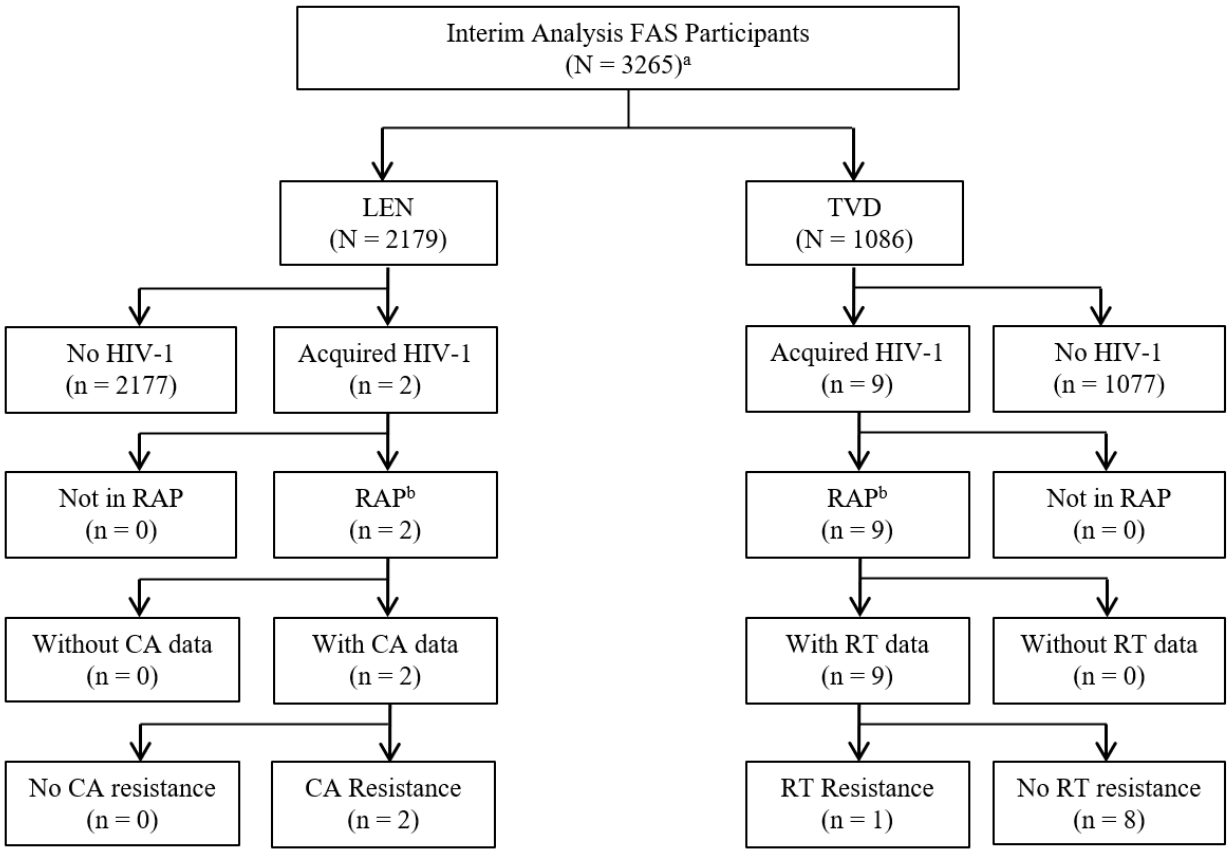


Figure 23. GS-US-528-9023: Resistance analysis population inclusion criteria and genotypic results

FAS = Full Analysis Set; LEN = lenacapavir; RAP = resistance analysis population; TVD = Truvada: emtricitabine/ tenofovir disoproxil fumarate

a. Participants who received study drug but were found to have acquired HIV-1 infection at baseline after Day 1 central lab testing were excluded from the FAS, per the statistical analysis plan.
b. Criteria for inclusion in the RAP are no HIV-1 infection at baseline, acquisition of HIV-1 while on study drugs and HIV-1 RNA ≥ 200 copies/mL.

Resistance in Participants Who Acquired HIV-1

In the LEN group, 2 participants acquired HIV while on study drug and were included in the study RAP and analysed for resistance development. The N74D substitution in CA, associated with reduced susceptibility to LEN, was detected in 2 of 2 (100.0%) participants. One additional infection occurred in a participant in the LEN group after the time of the primary analysis (not included in the RAP above). The LEN resistance-associated substitutions Q67H/K70R were detected in this participant.

In the TVD group, 9 participants were included in the study RAP and analysed for resistance development. RT genotypic data were available for 9 of 9 (100.0%) participants. The M184V substitutions in RT, associated with resistance to TVD, was detected in 1 of 9 (11.1%) participants.

Table 50. GS-US-528-9023: Summary of HIV-1 genotypic resistance

Resistance Category[a]	Number of Participants Who Acquired HIV-1, n (%)		
	LEN (N = 2179)	TVD (N = 1086)	P Value[b]
RAP (% of FAS)	2 (0.1)	9 (0.8)	0.0013
Participants with data (any gene)	2 (0.1)	9 (0.8)	
Genotypic resistance to study drugs detected	2 (0.1)	1 (0.1)	1.0
Genotypic resistance to non-study drugs detected	1 (0.05)	2 (0.2)	0.26
Any Primary NRTI-R detected (% of RAP)	0	1 (11.1)	
M184V	0	1 (11.1)	
Any Primary NNRTI-R detected (% of RAP)	1 (50.0)	1 (11.1)	
Any Primary PI-R detected (% of RAP)	0	1 (11.1)	
Any Primary INSTI-R detected (% of RAP)	0	0	
Any CAI-R detected (% of RAP)	2 (100.0)	0	
N74D	2 (100.0)	0	

CAI = capsid inhibitor; FAS = full analysis set; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; NA = not applicable; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAP = resistance analysis population; TVD = Truvada (emtricitabine/ tenofovir disoproxil fumarate)

a. Drug resistance substitutions are defined in Table above
b. Fisher's exact test comparing the proportions of LEN versus TVD using the whole population as the denominator.

Non-study Drug Resistance Detected

Non-study drug resistance was detected in 2 of 11 (18.2%) participants in the RAP. In the LEN group, 1 of 2 (50.0%) participants in the RAP had non-study drug resistance detected, consisting of the NNRTI resistance-associated substitution K103N in RT found in combination with N74D in CA.

In the TVD group, 2 of 9 (22.2%) participants in the RAP had non-study drug resistance detected, consisting of the NNRTI resistance-associated substitution K103N in RT in one participant and the PI resistance-associated substitution V82L in PR with and without M184V in RT in another participant.

Resistance in Participants With HIV-1 Infection Present at Baseline Who Received Study Drugs on Day 1

Baseline HIV-1 infections were discovered in 6 participants who acquired HIV-1 prior to Day 1 but had a negative rapid HIV test at screening, were randomized, and received study drugs on Day 1. These participants were excluded from the FAS and are not part of the RAP. Of these 6 participants, 4 participants received SC LEN and 2 participants received oral TVD. All participants who acquired HIV-1 were advised of

their status by the sites and initiated antiretroviral therapy (ART) as soon as possible. Resistance testing was done at Day 1 and the final visit when the viral load was >200 cp/mL (range of 22 to 116 days).

Emergent resistance to study drugs was detected in 2 participants who were HIV-1 positive at baseline and who received LEN. The LEN resistance-associated substitution, N74D, was found to have emerged on Day 111 and on Day 77 in the two participants respectively.

The one participant who were HIV-1 positive at baseline and received TVD was found to have FTC resistance-associated substitution M184M/V emerging at Day 70.

6.3.4. Clinical studies in special populations

Table 51. Clinical studies in special populations

	Controlled Trials	***Non-controlled trials***
Renal impairment* patients (Subjects number /total number)	0/8616	10/40
Hepatic impairment** patients (Subjects number /total number)	0/8616	10/40
Paediatric patients <18 years (Subjects number /total number)	128/8616	0/40
Older patients; Age 65-74 (Subjects number /total number)	18/8616	13/40
Age 75-84 (Subjects number /total number)	0/8616	1/40
Age 85+ (Subjects number /total number)	0/8616	0/40
Other (Subjects number /total number)	8475/8616	26/40

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

The controlled studies includes participants from Studies GS-US-412-5624 (PURPOSE 1: LEN, F/TAF or F/TDF) and GS-US-528-9023 (PURPOSE 2: LEN, F/TDF), whereas the non-controlled studies includes participants from Phase 1 Studies GS-US-200-4330 (severe renal impairment, defined as 15 $\leqslant$ CLcr $\leqslant$ 29 mL/min using the Cockcroft Gault equation) and GS-US-200-4331 (moderate hepatic impairment, defined as Child-Pugh-Turcotte Class B impairment).

The denominator corresponds to the number of participants who received at least 1 dose of study drug.

6.3.5. In vitro biomarker test for patient selection for efficacy

Not applicable

6.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

6.3.7. Overall discussion and conclusions on clinical efficacy

6.3.7.1. Discussion

Design and conduct of the clinical studies

The applicant has performed two double-blind, multicentre and randomised phase 3 studies, GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2).

GS-US-412-5624

Eligible participants were cisgender adolescent girls and young women (AGYW) ≥ 16 to ≤ 25 years of age, who have sex with cisgender males. Participants were to have unknown HIV-1 status at screening and no prior HIV-1 testing within the last 3 months. Study sites were located in South Africa (25 sites) and Uganda (3 sites).

The applicant used an HIV risk scoring tool designed to predict HIV-1 acquisition in African women (VOICE). The components (participant age, married or living with husband/primary partner, any alcohol use in the past 3 months, partner provides financial or material support, partner has other sexual partners) of the modified VOICE score were collected at screening. The majority of the participants (91.6%) had a score ≥ 5 which has been associated with a sharp increase in HIV-incidence, thus, indicating that the majority of participants in the study were at high risk of acquiring HIV-1 within a year.

Pregnant and breastfeeding women were excluded from entering the study, which can be considered appropriate from a safety perspective, however, these populations could also benefit from PrEP. It should be noted that women who became pregnant during the study had the option to remain on study drug after discussion of potential risks and benefits and provision of additional informed consent.

The study included a cross-sectional study (Incidence Phase), a Randomised Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a Pharmacokinetic (PK) Tail Phase. The Incidence Phase estimated the bHIV incidence within the population screened for eligibility (n=8094).

Those determined to be HIV-1 negative proceeded to the Randomised Blinded Phase, where they were randomised in a 2:2:1 ratio to receive either LEN (n=2134), DVY (F/TAF, n=2136), or TVD (F/TDF), n=1068), respectively.

The participants were to continue in the Randomised Blinded Phase until all randomised participants have completed at least 52 weeks of follow-up in the study. The design of the study (randomised phase, OLE phase, PK phase and follow up) is considered appropriate. The incidence phase is discussed below.

The primary efficacy evaluations were comparisons of the HIV-1 incidence in the LEN or DVY group during the study versus the bHIV incidence in AGYW.

The main secondary efficacy evaluation was the comparison of LEN versus TVD as HIV-1 PrEP in AGYW. Daily TVD is recommended standard care for women at risk for HIV and when taken with high adherence has shown to be highly effective as PrEP. TVD is considered an acceptable comparator in this study. This comparison was type 1 error protected in a hierarchical scheme.

GS-US-528-9023

Similar to GS-US-412-5624 the primary objective was to evaluate the efficacy of LEN in preventing the risk of HIV-1 infection relative to the background HIV-1 (bHIV) incidence in the screened population, TVD was the active control. The study was designed with a cross-sectional study (Incidence Phase), a Randomised Blinded Phase, an OLE Phase, and PK Tail Phase.

Eligible participants were cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender nonbinary (GNB) ≥ 16 years old who have receptive anal sex with partners assigned male at birth. Participants were to have unknown HIV-1 status at screening and no prior HIV-1 testing within the last 3 months. Study sites were located in the US (65), Brazil (9), Thailand (7), South Africa (6), Peru (5), Argentina (3), and Mexico (1). The studied population is considered at high risk of acquiring HIV-1.

The Incidence Phase estimated the bHIV incidence within the population screened for eligibility (n=4634) and those determined to be HIV-1 negative proceeded to the Randomised Blinded Phase, where they were randomized in a 2:1 ratio to receive either LEN (n=2179) or TVD (n=1086). The participants were to continue in the Randomised Blinded Phase until all randomised participants have completed at least 52 weeks of follow-up in the study.

The primary efficacy evaluation was the comparison of the HIV-1 incidence in the LEN group during the study versus the bHIV incidence.

The main secondary efficacy evaluation was the comparison of LEN with TVD as HIV-1 PrEP. TVD is recommended per World Health Organization (WHO) guidelines as part of HIV prevention standard of care for individuals at risk for HIV and is considered an acceptable comparator in this study. These analyses were type 1 protected in a hierarchical scheme.

HIV testing strategy

The main assessment concerned HIV testing. The algorithm used in the randomised phase included local rapid fourth generation HIV-1/2 Ab/Ag and central fourth generation HIV-1/2 Ab/Ag testing. Positive central fourth generation HIV-1/2 Ab/Ag tests were confirmed with an HIV-1/2 Ab differentiation assay and HIV-1/2 RNA qualitative NAAT if the HIV-1/2 Ab differentiation assay was negative. This strategy is adequate. In both studies a blinded 3-physician adjudication committee reviewed all available HIV test results and determined the participant's HIV-1 status and earliest date with evidence of HIV-1 infection. This is appropriate.

Participant flow

In both studies there were participants who were found to be not eligible for inclusion in the randomised blinded phase of the study after screening, but who were still randomised. In Study GS-US-412-5624 there were 39 participants and in GS-US-528-9023 there were 10 participants. Reasons for not being eligible included for example, participating in other trials, HIV-1 positive or pregnant/breastfeeding. This issue was not pursued, as no impact on the outcome of the assessment was anticipated.

Interim efficacy analyses

Both GS-US-412-5624 and GS-US-528-9023 were stopped early for efficacy based on the results of pre-specified interim analyses, which were conducted when 50% of participants had completed at least 52 weeks of follow-up or had prematurely discontinued the trial. These interim analyses included not only the

data of the first 50% of participants, but also the data of subsequent patients that had been collected at the time of the interim analyses.

In GS-US-412-5624, the interim efficacy analysis was introduced in protocol amendment 1.0, which was issued on 22 November 2021, approximately 2 months after the first patient had been randomised (on 28 September 2021) and almost 2 years before the last patient had been randomised (on 15 September 2023). Since the amendment was issued early in the trial, and since the trial was double blind, the interim efficacy analysis can be considered pre-specified.

In GS-US-528-9023, the interim efficacy analysis was pre-specified, as it was introduced in protocol amendment 1, which was issued before the first patient had been randomised (protocol amendment 1.0 was issued on 08 June 2021 and the first patient was randomised on 12 July 2021).

The protocols of GS-US-412-5624 and GS-US-528-9023 stated that the trials would be stopped for efficacy if the HIV incidence in the lenacapavir arm was at least 50% lower than the background HIV incidence and if this difference was statistically significant. However, the statistical analysis plans included an additional criterion: a significant reduction in HIV incidence in the lenacapavir arm compared to the F/TDF arm. Since the stopping criteria were made stricter, these deviations from the protocols do not harm the integrity of the trials.

Multiple testing procedures

In both GS-US-528-9023 and GS-US-412-5624, multiplicity was controlled across the two analysis timepoints (interim and primary) using an alpha split. An alpha of 0.0026 was used in the interim analysis and 0.0224 in the primary analysis, totalling an overall alpha of 0.0026 + 0.0224 = 0.025 (one-sided).

Study GS-US-528-9023 had 4 statistical hypotheses that were tested according to a protocol-specified, multiple testing procedure.

Study GS-US-412-5624 initially had 2 hypotheses, but this number was increased to 8 hypotheses in protocol amendment 1 (dated 22 November 2021). As this amendment was issued early in the trial, and since the trial was also double blind, this protocol amendment can be considered adequately pre-specified.

In study GS-US-412-5624, the multiple testing procedure that was used in the interim analysis deviated from that which was pre-specified in the protocol. However, this deviation does not affect the type-1 error for two reasons. Firstly, the statistical analysis plan was finalised before unblinding (finalised date: 24 May 2024; unblinding date: 18 June 2024). Secondly, the revision has not affected the conclusions of the trial; the comparisons of lenacapavir versus bHIV and lenacapavir versus F/TDF would have been statistically significant with the original multiple testing procedure too.

Analysis sets

In both trials, patients were excluded from the analysis if they did not receive study medication or if they had an HIV-1 diagnosis on or prior to the first dose of study medication. In GS-US-412-5624, 30 of the 5368 randomised patients were excluded for this reason. In GS-US-528-9023, 27 out of 3292 randomised patients were excluded. Ideally, the FAS should comprise of all randomised patients irrespective of receiving any drug dose, so that possible lack of adherence to assigned PrEP would be incorporated in the resulting estimate. Since these numbers are small, and since the exclusions were based on baseline data rather than post-randomisation data, the exclusions should not have had any substantial effect on the results.

Study discontinuation

In GS-US-528-9023, the percentage of patients that did not complete the randomised and blinded phase of the trial was 11% in the lenacapavir arm and 12% in the TVD arm. In GS-US-412-5624, these percentages were 6% in the lenacapavir arm and 9% in the TVD arm. There was no concern that these study discontinuations had biased the efficacy results in favour of lenacapavir.

Calculation of background HIV (bHIV) incidence

In both trials, the primary analysis was a comparison of the HIV incidence in the lenacapavir arm to the bHIV incidence rate.

The bHIV incidence was estimated in the screened population using recency assay results from samples that were positive for HIV-1 infection incorporated into a recent infection testing algorithm (RITA). This method has not previously been accepted to support efficacy claims for an investigational PrEP product.

The applicant has justified the RITA-based bHIV incidence counterfactual design by discussing the limitations of alternative randomised controlled study designs. Placebo-controlled studies are now considered unethical for PrEP studies due to the availability of safe and effective HIV prevention options globally. While superiority to an active comparator has been successfully implemented in other PrEP studies, it fundamentally relies on nonadherence to the active comparator to succeed, as the efficacy of TVD for PrEP approaches 99% when taken with high adherence. Noninferiority studies would become increasingly infeasible to conduct since they require large sample sizes and long durations if adherence to the comparator drug is high. Additionally, noninferiority studies are challenging to conduct in populations where efficacy results for the active comparator have been inconsistent in prior clinical studies which preclude the determination of an accurate noninferiority margin.

The Applicant’s arguments are acknowledged. However, it is not agreed that comparing the HIV incidence in the lenacapavir arm to the RITA-based bHIV incidence is a robust way to estimate the efficacy of lenacapavir. The validity of the RITA-based method relies on the assumption that HIV-1 status was completely random at screening, meaning that those who were HIV-1 negative (and who were therefore randomised) would subsequently contract HIV-1 at the same rate as was seen in the historical cohort including patients that were already infected (these participants were not randomised). This assumption is untenable because the rate may well have been higher in those who were HIV-1 positive (that is, in those who had previously contracted HIV-1). If so, the bHIV incidence would be overestimated, which would lead to an overestimation of the efficacy of lenacapavir. Such a bias is not acceptable to support efficacy or labelling claims. Therefore, the primary analysis was not included in the SmPC.

Efficacy data and additional analyses

Both GS-US-412-5624 and GS-US-528-9023 were stopped early for efficacy based on the results of pre-specified interim analyses. As a result, the interim analysis also served as the primary analysis for each study, as specified in the clinical study protocols.

GS-US-412-5624

In the Randomized Blinded Phase, demographics and baseline characteristics were generally similar between study drug groups. Overall, participants were healthy with few reported medical conditions and normal renal and liver function.

A total of 610 participants (11.4%) discontinued study drugs in the Randomized Blinded Phase. The most common reasons for discontinuation of study drugs were participant decision (308 participants [5.8%]), lost to follow-up (92 participants [1.7%]), and pregnancy (89 participants [1.7%]).

The primary analysis was the comparison of HIV-1 incidence in the LEN groups versus bHIV-incidence. There were no HIV-1 infections in the LEN group and the bHIV incidence was 2.407 infections per 100 PY. Thus, the primary analysis showed that HIV-1 incidence in LEN is significantly lower than bHIV (H01, P-value <0.0001), and sequential testing of following endpoints were performed.

The fifth key alpha-controlled statistical hypothesis (H05) was the rate difference for the HIV-1 incidence (LEN vs TVD). The rate difference was −1.685 (95% CI: −2.737 to −0.939; P < 0.0001).

The sixth key alpha-controlled statistical hypothesis (H06) was then tested. Using the rate ratio method LEN was demonstrated to be superior to TVD (rate ratio: 0.000; 95% CI: 0.000 to 0.101; P < 0.0001). The analysis of LEN versus TVD is considered clinically relevant and should be the only analysis presented in the SmPC.

The Applicant has also provided time-to-infection analyses and the results further support the conclusions based on the primary analyses.

Given the concerns of a potential difference in the risk of acquiring HIV-1 between the screened HIV-1 positive and the HIV-1 negative participants that are later randomised into the study (see comment above), the primary analysis is considered to be unreliable. However, the efficacy of LEN is still considered established because the trial had a statistically significant and multiplicity-controlled secondary analysis showing that LEN is superior to TVD in the prevention of HIV-1.

Adherence to LEN injections was high with on-time injection for 91.1% of participants at Week 26 and 93.5% of participants at Week 52. Based on pill counts adherence to TVD seemed high, the majority of participants (74.4%) were ≥ 95% adherent to study drug while in the Randomized Blinded Phase. However, based on TFV-DP in red blood cells from dried blood spots low adherence consistent with dosing < 2 days per week was observed. Adherence to TVD, in general, has been reported as low in this population of AGYW.

GS-US-528-9023

In the Randomized Blinded Phase, demographics and baseline characteristics were generally similar between study drug groups. The majority were cisgender men (77.7%) and gay (75.1%). STIs were

detected at baseline and the most common were rectal chlamydia (8.3%), pharyngeal gonorrhoea (6.4%), and rectal gonorrhoea (4.9%).

The majority had multiple partners (64% had 4 or more partners) and one or more condomless receptive anal sex acts (78% of the participants) in the past 3 months. In general, they were healthy with few reported medical conditions and normal renal and liver function.

A total of 532 participants (16.3%) discontinued study drugs in the Randomized Blinded Phase. The most common reasons for discontinuation of study drugs were participant decision (301 participants [9.2%]), lost to follow-up (119 participants [3.6%]), and AEs (includes ISRs to study SC injection) (42 participants [1.3%]).

The primary analysis was the comparison of HIV-1 incidence. In the LEN group there were 0.103 infections per 100 PY which was significantly lower than the bHIV incidence of 2.374 infections per 100 PY (H01; rate ratio: 0.043; 95% CI: 0.010 to 0.182; P < 0.0001). The primary endpoint was met, and sequential testing of following endpoints was performed.

The third key alpha-controlled statistical hypothesis (H03) was the rate difference for the HIV-1 incidence in the LEN group versus the TVD group (−0.828; 95% CI: −1.669 to −0.255; P < 0.0001).

The fourth key alpha-controlled statistical hypothesis (H04) was then tested. Using the rate ratio method LEN was demonstrated to be superior to TVD (rate ratio: 0.111; 95% CI: 0.024 to 0.513; P = 0.00245).

Concerning the non-acceptability of the primary endpoint, see above.

The efficacy of LEN has been demonstrated by the comparison of LEN versus TVD which is a statistically significant and multiplicity-controlled secondary analysis. This is the only analysis that will be presented in the SmPC.

The two individuals in the LEN group who were infected with HIV-1 before the primary data cut-off both received their injections on time (≤ 28 weeks from the previous injection) and had plasma concentrations above IQ4 before and at the time of HIV-1 diagnosis. The reasons for these participants becoming infected with HIV-1 are unclear. Both had the N74D capsid mutation, and one also had the K103N NNRTI mutation revealed by genotyping at the time of HIV-1 diagnosis. The number of breakthrough infections was too small to reliably investigate baseline factors that could be related to failure. Unfortunately, as both participants refused further follow-up, also no information is available regarding the subsequent course of their HIV-1 infection.

As lenacapavir levels only slowly decline after treatment discontinuation, it is important to understand the impact this may have on development of potential resistance mutations in circulating viruses and related to this future treatment options. No data are available at present. However, the Applicant is planning to conduct a non-interventional study of LEN for PrEP in a real-world setting. Details of this study will be provided when available.

Of the participants in the LEN group, 87.2% received the Week 26 SC LEN injection within 28 weeks of the first injection, and 92.7% received the Week 52 SC LEN injection within 28 weeks of the previous injection. Adherence to the TVD was rather high in this population. The TFV-DP in red blood cells from dried blood spot samples indicated dosing ≥ 4 days per week.

Clinical virology

In study GS-US-528-9023 two participants acquired HIV while on study drug and both had N74D substitution in CA at HIV diagnosis.

Moreover, baseline HIV-1 infections were discovered in 4 participants on LEN in each of the studies GS-US-412-5624 and GS-US-528-9023. These participants acquired HIV-1 prior to Day 1 but had a negative rapid HIV test at screening, were randomized, and received LEN on Day 1. These participants essentially received LEN monotherapy as initial ART. Out of these 8 HIV-1 positive participants 4 developed resistance-associated mutation N74D.

The barrier to resistance of lenacapavir monotherapy is low.

6.3.7.2. Conclusions on the clinical efficacy

The data provided from two pivotal phase 3 studies support the efficacy of lenacapavir in preventing HIV-1 infection. The primary analyses of HIV-1 incidence in the lenacapavir PrEP groups versus the bHIV-incidence are not considered reliable. However, lenacapavir was demonstrated to be superior to TVD in both studies and these analyses were statistically significant and considered clinically relevant.

6.4. Clinical safety

Please refer to the table of studies in section 6.3.2

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

6.4.1. Safety data collection

The safety data supporting this submission are from interim analyses of Study GS-US-412-5624 (PURPOSE 1) and Study GS-US-528-9023 (PURPOSE 2) that occurred when 50% of the planned sample size in each study had completed at least 52 weeks of follow-up or prematurely discontinued from the study (cut off date 5 May 2024 and 5 Aug 2024, respectively). These later became the primary analyses for the respective studies, as prespecified efficacy criteria were met and both randomised blinded phases stopped.

Study GS-US-412-5624 (PURPOSE 1) is an ongoing, double-blinded, randomized Phase 3 study conducted in sexually active cisgender women in 28 study sites in South Africa and Uganda. Participants were randomised to receive LEN (n = 2134), once daily FTC/TAF (n = 2136), or once daily FTC/TDF (n = 1068) in a 2:2:1 ratio.

Study GS-US-528-9023 (PURPOSE 2) is an ongoing, double-blind randomized Phase 3 study conducted in in sexually active cisgender men, transgender women, transgender men, and gender nonbinary individuals. The study was conducted in 96 study sites globally. Participants were randomised to receive LEN (n = 2179) or once daily FTC/TDF (n = 1086) in a 2:1 ratio.

(See 6.3.2. Main studies above for detailed information on the study design).

Safety was evaluated through the incidence of treatment-emergent (TE) adverse events (AEs) (TEAEs) and TE laboratory abnormalities. Data was collected at baseline, week 26, 52, and up to 78 weeks for the PK-tail phase. Graded laboratory abnormalities were defined using the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events. Additional analysis of AEs was performed for injection site reactions (ISRs), renal safety, hypersensitivity events, and liver-related laboratory evaluations. Kidney and liver have not been to date identified as target organs for toxicity for LEN, and these additional analyses seem to serve the purpose of providing focused safety comparison with the active comparators used in the pivotal studies FTC/TDF (and less so FTC/TAF), for which renal and liver toxicity are known issues.

The Safety Analysis Set included participants who received at least one dose of study drug in GS-US-412-5624 and GS-US-528-9023. While the Applicant presented data per study and pooled, the assessment focuses on the studies separately because of the differences in study populations.

Supportive safety data

Supportive safety data for LEN given in alternative injection sites are provided from Study GS US 200 4540 regarding healthy volunteers.

The safety of LEN during oral bridging is further supported with data from Studies GS US 200 4334 and GS US-200-4625, performed in treatment-experienced individuals living with HIV.

6.4.2. Patient exposure

Table 52. Studies providing clinical safety data

Study ID	Number of Patients exposed to LEN	Age Range	Stage/Severity of Disease	Healthy Subjects	Safety database Size: 12 Months' follow-up	Median exposure time
GS-US-412-5624 (PURPOSE 1)	2148	16-26	High-risk adults and adolescents	N/A	2148	42.6 weeks (median, Q1, Q3: 38.1, 53.4)

GS-US-528-9023 (PURPOSE 2)	2195	16-74	High-risk adults and adolescents	N/A	2195	LEN group: 39.3 weeks (median, Q1, Q3: 28.4, 54.1)
GS-US-200-4540	40	21-54	Healthy subjects	40	N/A	42.6 (38.1, 53.4)
GS-US-200-4334	121	18-65	People living with HIV	0	N/A	oral LEN 42.6 (38.1, 53.4) weeks; SC LEN 42.6 (38.1, 53.4) weeks
GS-US-200-4625	57	18-65	People living with HIV	0	N/A	oral LEN 42.6 (38.1, 53.4) weeks; SC LEN 42.6 (38.1, 53.4) weeks

The Randomized Blinded Phase Safety Analysis Sets included all participants who received at least 1 dose of any study drug for both studies GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2).

Safety data for up to 12-months of exposure are available for 4323 patients across the two pivotal studies, but substantial long-term data regarding exposure beyond this time frame are not available. The study is still ongoing for the PK-tail follow-up. Long term safety (beyond 12 months) is listed as *Missing information.* in the Safety Specification of the Risk Management Plan (RMP).

Patient demographics see 6.3.2. Main studies above.

6.4.3. Adverse events

The majority of participants receiving LEN in GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2) reported at least one TEAE (88.5% and 92.9% respectively). The rates of Grade 3+ TEAEs (0.4%, 0.5%), serious TEAEs (2.8%, 3.3%), TEAEs leading to study drug (0.4%, 1.5%) or study (<0.1%, 0.2%) discontinuation, and deaths (0%, 0.2%) were, however, very low across both LEN arms.

Tabulated summaries of the most common treatment-emergent adverse events by Preferred Term in studies GS-US-412-5624 (PURPOSE 1), GS-US-528-9023 (PURPOSE 2) are presented below, for side-by-side comparison.

Table 53. GS-US-412-5624 (PURPOSE 1): Adverse events reported in ≥ 5% of participants in either the LEN or TVD group by preferred term (randomised blinded phase, safety analysis set)

Preferred Term	SC LEN (N = 2140)	TVD (N = 1070)
Number (%) of participants with any treatment-emergent adverse events	1893 (88.5%)	881 (82.3%)
Injection site nodule	1365 (63.8%)	183 (17.1%)
Injection site pain	669 (31.3%)	237 (22.1%)
Urinary tract infection	307 (14.3%)	163 (15.2%)
Headache	285 (13.3%)	155 (14.5%)
Genitourinary chlamydia infection	300 (14.0%)	129 (12.1%)
Upper respiratory tract infection	271 (12.7%)	121 (11.3%)
Nausea	144 (6.7%)	142 (13.3%)
Vomiting	125 (5.8%)	107 (10.0%)
Vaginal discharge	166 (7.8%)	87 (8.1%)
Vulvovaginal candidiasis	146 (6.8%)	67 (6.3%)
Genitourinary tract gonococcal infection	141 (6.6%)	66 (6.2%)
Diarrhoea	133 (6.2%)	67 (6.3%)
Dizziness	120 (5.6%)	79 (7.4%)

AE = adverse event; HLT = high-level term; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Adverse events coded according to MedDRA Version 27.0.
All injection site reactions (both to study SC injections or other injections) included.
Treatment-emergent events began on or after study drug first dose date up through last exposure date for the study phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Multiple AEs counted only once per participant for the highest severity grade for each preferred term.

Table 54. GS-US-528-9023 (PURPOSE 2): Adverse events reported in ≥ 5% of participants in either the LEN or TVD group by preferred term (randomised blinded phase, safety analysis set)

Preferred Term	SC LEN (N = 2183)	TVD (N = 1088)
Number (%) of participants with any treatment-emergent adverse events	2029 (92.9%)	976 (89.7%)
Injection site pain	1231 (56.4%)	581 (53.4%)
Injection site nodule	1383 (63.4%)	427 (39.2%)
Injection site erythema	377 (17.3%)	211 (19.4%)
Injection site induration	342 (15.7%)	110 (10.1%)

Preferred Term	SC LEN (N = 2183)	TVD (N = 1088)
Anal chlamydia infection	289 (13.2%)	128 (11.8%)
Oropharyngeal gonococcal infection	283 (13.0%)	119 (10.9%)
Anal gonococcal infection	233 (10.7%)	99 (9.1%)
Injection site swelling	149 (6.8%)	104 (9.6%)
Upper respiratory tract infection	148 (6.8%)	77 (7.1%)
Diarrhoea	146 (6.7%)	75 (6.9%)
Headache	119 (5.5%)	76 (7.0%)
Influenza	120 (5.5%)	66 (6.1%)
Latent syphilis	114 (5.2%)	44 (4.0%)
Nausea	89 (4.1%)	67 (6.2%)

AE = adverse event; HLT = high-level term; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; SC = subcutaneous; TVD = emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®)
Adverse events coded according to MedDRA Version 27.0.
All injection site reactions (both to study SC injections or other injections) included.
Treatment-emergent events began on or after study drug first dose date up through last exposure date for the study phase after permanent discontinuation of study drug or led to premature study drug discontinuation.
Treatment-emergent injection site reactions to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Multiple AEs counted only once per participant for the highest severity grade for each preferred term.

Hypersensitivity events

In study GS-US-412-5624 (PURPOSE 1) adverse events potentially associated with hypersensitivity were reported in 129 participants (6.0%) in the LEN group and 58 participants (5.4%) in the TVD group during the Randomized Blinded Phase.

Grade 3 hypersensitivity AEs were reported in 2 participants in the LEN group (dermatitis psoriasiform and dermatitis in 1 participant each) and 1 participant in the TVD group (urticaria). There were no grade 4 events.

In Study GS-US-528-9023 (PURPOSE 2), adverse events potentially associated with hypersensitivity were reported in 120 participants (5.5%) in the LEN group and 50 participants (4.6%) in the TVD group during the Randomized Blinded Phase

Grade 3 hypersensitivity AEs, which were reported in 3 participants in the LEN group and no participant in the TVD group, included drug hypersensitivity, urticaria, and injection site dermatitis (1 participant each). There were no grade 4 hypersensitivity reactions reported.

Assessment of causality of hypersensitivity AEs showed that the majority reported hypersensitivity events were likely miscategorised injection site reactions. The remaining events did not show any relation to lenacapavir injection. One isolated event of rash led to discontinuation of LEN.

Safety of alternative injection sites

GS-US-200-4540 (a Phase 1, open-label, parallel design, single-dose, multicohort study in 40 healthy participants) found that subcutaneous LEN injection into alternative injection sites (thigh, upper arm, and gluteal region) was safe and well tolerated. The majority of adverse events (AEs) reported were Grade 1 or 2 in severity, and no Grade 4 AEs were reported. The only Grade 3 AE was injection site erythema in a participant who received SC LEN in the upper arm. Excluding injection site reactions (ISRs), the only AEs reported in more than 1 participant were COVID-19 infections, back pain, and pain in extremity. All were assessed as not related to LEN and were Grade 1 except for 1 Grade 2 event of pain in extremity.

The most common study drug-related ISR AEs were injection site pain (90.0%, 36 of 40 participants), injection site induration (72.5%, 29 participants), and injection site erythema (70.0%, 28 participants). The incidence of ISRs was generally comparable across injection sites. The frequency of study drug-related injection site nodules was (15.0%).

In addition, safety data of alternative injection sites was provided through 10 study patients undergoing pregnancy within the context of study GS-US-412-5624 (PURPOSE 1), who received injections in the thigh. Among these 10 participants, injection site reactions (ISRs) were reported in 5 (15.6%) participants (11 events [16.9%]); all ISRs were Grade 1.

In summary, no new safety concerns were identified in association with injection in alternative injection sites

Safety during oral bridging

Safety during the oral bridging phase was evaluated in the pivotal clinical studies and additional in Studies GS-US-200-4625 and GS-US-200-4334 in PWH, where an oral bridging dose of LEN was 300 mg administered once weekly (QW) starting 26 to 28 weeks after the last subcutaneous (SC) LEN injection.

In Study GS-US-200-4625, 57 participants received oral bridging with LEN, and 49.1% of participants (28 of 57 participants) had any adverse event (AE) during oral bridging. The only AEs reported in > 2 participants overall were COVID-19 (7.0%, 4 of 57 participants), cough, diarrhoea, and upper respiratory tract infection (5.3%, 3 of 57 participants each).

In Study GS-US-200-4334, 121 participants received oral bridging with LEN, and 62.8% of participants (76 of 121 participants) had any AE during oral bridging. The only AEs reported in > 5 participants overall were influenza (9 [7.4%] participants), COVID-19 (7 [5.8%] participants), nasopharyngitis (6 [5.0%] participants), and syphilis (6 [5.0%] participants). None of these were considered related to the study drug.

In Study GS-US-412-5624 (PURPOSE 1), 44 participants received oral bridging with LEN or placebo, and the only AEs reported in more than 1 participant were all in the LEN group: upper respiratory tract infection (30.0%, 3 participants) and urinary tract infection (20.0%, 2 participants). None of these were considered related to the study drug.

In Study GS-US-528-9023 (PURPOSE 2), 92 participants received oral bridging with LEN or placebo, and the only AEs reported in more than 1 participant were COVID-19 (LEN 10.3%, 4 participants; TVD 6.3%, 1 participant), dermatitis (LEN 5.1%, 2 participants; TVD 0 participants), and sinusitis (LEN 5.1%, 2 participants; TVD 0 participants). These were not considered related to the study drug.

In summary, no new safety concerns were identified during oral bridging.

6.4.3.1. Adverse drug reactions

Table 55. Summary of ADRs proposed for inclusion by the applicant in the SmPC

System Organ Class	
Injection site reactions	Very common

The MAH has proposed to include ISRs as the only ADR. Injection site reactions were the most common adverse drug reactions and are addressed in other sections above/below.

The Applicant described the approach used to determine whether LEN AEs (in particular hypersensitivity, nausea and headache) listed as ADRs for Sunlenca are to be included as ADRs in the SmPC for LEN. The methodology used considered the risk difference between the LEN and comparator groups, the temporal relationship of the events to LEN exposure, biological plausibility, medical judgement, and confounding factors. Given the confounding of other antiretrovirals in HIV-1 treatment studies for Sunlenca, data from other sources (including healthy volunteers administered placebo during Phase 1 studies) were taken into account when considering causality. This is supported.

The applicant also evaluated exposure-safety relationships for LEN for participants in the PURPOSE studies, including box plots of LEN Cmax in relation to the presence or absence of common AEs. The plots indicate no relationship between systemic exposure and presence of absence of an AE, across headache, nausea, dizziness, vomiting, diarrhoea or injection site nodule.

On the basis of the above, none of hypersensitivity, nausea and headache were considered to be ADRs for LEN in the PrEP indication.

The Applicant also provided a detailed discussion of cases of rhabdomyolysis in relation to LEN exposure. Apart from the 2 serious cases of rhabdomyolysis that were already known, no new serious cases have been reported. Further, all 6 cases reported in the LEN group in PURPOSE 1 (n = 2) and PURPOSE 2 (n = 4) were assessed as not related to study drug by the investigator. None were associated with renal events. The conclusion of the Applicant that rhabdomyolysis is not considered an ADR for LEN as the available data do not provide evidence to support a causal role for LEN can be supported.

6.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Injection site reactions

Table 56. GS-US-412-5624 (PURPOSE 1): Injection site reactions to study sc injection reported in ≥ 2% of participants who received either LEN or Placebo injection, duration (overall and by preferred term, event level) (randomised blinded phase, safety analysis set, participants with ≥ 1 sc injection)

	SC LEN (N = 2140)	SC LEN Placebo (N = 3204)
Total number of visits when SC injection was administrated	5079	7586
Total duration of any ISRs to study SC injection (days)		
N	5351	2184

	SC LEN (N = 2140)	SC LEN Placebo (N = 3204)
Mean (SD)	167 (135.0)	54 (79.1)
Median	159	16
Q1, Q3	52, 267	5, 75
Min, max	1, 679	1, 636
Total duration of any ISRs (excluding nodule and induration) to study SC injection (days)		
N	1136	1296
Mean (SD)	31 (57.4)	21 (43.1)
Median	9	7
Q1, Q3	4, 29	3, 15
Min, max	1, 435	1, 385
Duration of any ISRs to study SC injection by preferred term (days)		
Injection site nodule		
N	4056	845
Mean (SD)	206 (124.9)	107 (92.8)
Median	190	79
Q1, Q3	91, 274	44, 148
Min, max	1, 679	1, 636
Injection site pain		
N	910	984
Mean (SD)	29 (55.5)	21 (44.6)
Median	9	7
Q1, Q3	4, 25	3, 17
Min, max	1, 435	1, 385
Injection site swelling		
N	104	190
Mean (SD)	18 (31.7)	11 (24.0)
Median	8	4
Q1, Q3	4, 19	3, 8
Min, max	1, 266	1, 260

	SC LEN (N = 2140)	SC LEN Placebo (N = 3204)
Injection site induration		
N	159	43
Mean (SD)	140 (140.3)	42 (65.7)
Median	92	8
Q1, Q3	12, 219	4, 68
Min, max	1, 632	1, 276
Injection site pruritus		
N	50	39
Mean (SD)	45 (55.7)	24 (35.5)
Median	29	10
Q1, Q3	6, 65	5, 28
Min, max	1, 268	1, 192

AE = adverse event; eCRF = electronic case report form; HLT = high-level term; ISR = injection site reaction; LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; SD = standard deviation
Duration (days) = stop date − onset date + 1. For ongoing ISRs, stop date was imputed as last study date or data cut date, whichever was earlier.
Treatment-emergent ISRs to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Each SC dose consisted of 2 SC injections into the abdomen (or thighs for pregnant participants).
Events counted as: 1) for nodules and induration a) unique participants, preferred terms, and associated injection visits and locations (when available from ISR eCRF) or b) unique participants, AE reported terms, and AE onset dates (when ISR eCRF unavailable) or 2) for other ISRs, unique participants, preferred terms, and AE onset dates.
If associated injection visit was unavailable from ISR eCRF, events were assigned to latest injection visit with date on or prior to AE onset date.

In Study GS-US-412-5624 (PURPOSE 1), ISRs were reported in 68.8% of participants who received LEN, with the majority being Grade 1 or 2 in severity. The most common ISRs were injection site nodule (63.8%), injection site pain (31.3%), and injection site swelling (4.5%). Only 4 participants (0.2%) experienced Grade 3 ISRs, and none were considered serious. The incidence of ISRs decreased slightly with subsequent injections, with 56.4% of participants experiencing ISRs after the first injection, 40.3% after the second injection, and 24.7% after the third injection.

Of the total 10,158 SC LEN injections administered, 4056 injection site nodule events (39.9%) were reported. Of the total 15,171 placebo injections administered, 845 injection site nodule events (5.6%) were reported. At Day 1 (SC Injection 1), injection site nodules were reported in 56.4% of participants who received LEN (202 had 1 nodule per participant and 998 had 2 nodules per participant) and 13.3% of participants who received placebo injections (238 had 1 nodule per participant and 187 had 2 nodules per participant). Injection site nodule events decreased with subsequent injections in both the LEN and placebo groups.

The median (Q1, Q3) longest nodule diameter for any event was 2.0 (1.5, 3.0) cm in participants who received LEN and 1.0 (0.5, 1.5) cm in participants who received placebo injections.

The percentages of participants with ongoing or resolved injection site nodules after Day 1 (SC Injection 1) were as follows:

- LEN: ongoing 35.0%; resolved 21.4%
- Placebo: ongoing 2.3%; resolved 11.0%

The percentages of participants with ongoing or resolved injection site indurations after Day 1 (SC Injection 1) were as follows:

- LEN: ongoing 0.5%; resolved 2.6%
- Placebo: ongoing < 0.1%; resolved 0.6%

Table 57. GS-US-528-9023 (PURPOSE 2): Injection site reactions to study sc injection by preferred term, severity, and injection reported in ≥ 2% of participants who received either LEN or placebo injection (participant level) (randomised blinded phase, safety analysis set, participants with ≥ 1 sc injection)

Preferred Term Severity	SC LEN (N = 2183)	SC LEN Placebo (N = 1088)
Number of participants received at least one injection	2183	1088
Number (%) of participants with any:		
Serious ISRs to study SC injection	0	0
ISRs to study SC injection leading to premature discontinuation of study drug	26 (1.2%)	3 (0.3%)
ISRs to study SC injection leading to premature discontinuation of study	2 (< 0.1%)	1 (< 0.1%)
Number (%) of participants with ISRs to study SC injection	1816 (83.2%)	756 (69.5%)
Grade 1	1441 (66.0%)	594 (54.6%)
Grade 2	361 (16.5%)	161 (14.8%)
Grade 3	14 (0.6%)	1 (< 0.1%)
Injection site pain	1231 (56.4%)	581 (53.4%)
Grade 1	992 (45.4%)	484 (44.5%)
Grade 2	235 (10.8%)	96 (8.8%)
Grade 3	4 (0.2%)	1 (< 0.1%)
Injection site nodule	1383 (63.4%)	427 (39.2%)
Grade 1	1276 (58.5%)	402 (36.9%)
Grade 2	107 (4.9%)	25 (2.3%)
Injection site erythema	377 (17.3%)	211 (19.4%)
Grade 1	325 (14.9%)	146 (13.4%)
Grade 2	49 (2.2%)	65 (6.0%)
Grade 3	3 (0.1%)	0
Injection site induration	342 (15.7%)	110 (10.1%)
Grade 1	295 (13.5%)	87 (8.0%)
Grade 2	47 (2.2%)	23 (2.1%)

Preferred Term Severity	SC LEN (N = 2183)	SC LEN Placebo (N = 1088)
Injection site swelling	149 (6.8%)	104 (9.6%)
Grade 1	143 (6.6%)	84 (7.7%)
Grade 2	6 (0.3%)	20 (1.8%)
Injection site bruising	67 (3.1%)	42 (3.9%)
Grade 1	61 (2.8%)	41 (3.8%)
Grade 2	6 (0.3%)	1 (< 0.1%)
Injection site pruritus	74 (3.4%)	30 (2.8%)
Grade 1	67 (3.1%)	30 (2.8%)
Grade 2	7 (0.3%)	0
Injection site warmth	51 (2.3%)	24 (2.2%)
Grade 1	50 (2.3%)	24 (2.2%)
Grade 2	1 (< 0.1%)	0
Number of participants received injection at Day 1/SC Injection 1	2183	1088
Number (%) of participants with ISRs to study SC injection following Day 1 SC injection	1616 (74.0%)	628 (57.7%)
Grade 1	1367 (62.6%)	522 (48.0%)
Grade 2	240 (11.0%)	106 (9.7%)
Grade 3	9 (0.4%)	0
Injection site nodule	1218 (55.8%)	336 (30.9%)
Grade 1	1139 (52.2%)	317 (29.1%)
Grade 2	79 (3.6%)	19 (1.7%)
Injection site pain	926 (42.4%)	453 (41.6%)
Grade 1	785 (36.0%)	391 (35.9%)
Grade 2	139 (6.4%)	62 (5.7%)
Grade 3	2 (< 0.1%)	0
Injection site erythema	248 (11.4%)	151 (13.9%)
Grade 1	221 (10.1%)	117 (10.8%)
Grade 2	24 (1.1%)	34 (3.1%)
Grade 3	3 (0.1%)	0
Injection site induration	267 (12.2%)	92 (8.5%)
Grade 1	231 (10.6%)	77 (7.1%)
Grade 2	36 (1.6%)	15 (1.4%)
Injection site swelling	83 (3.8%)	62 (5.7%)
Grade 1	83 (3.8%)	52 (4.8%)
Grade 2	0	10 (0.9%)

Preferred Term Severity	SC LEN (N = 2183)	SC LEN Placebo (N = 1088)
Injection site warmth	35 (1.6%)	22 (2.0%)
Grade 1	34 (1.6%)	22 (2.0%)
Grade 2	1 (< 0.1%)	0
Number of participants received injection at Week 26/SC Injection 2	1859	946
Number (%) of participants with ISRs to study SC injection following Week 26 SC injection	1292 (69.5%)	468 (49.5%)
Grade 1	1140 (61.3%)	389 (41.1%)
Grade 2	149 (8.0%)	79 (8.4%)
Grade 3	3 (0.2%)	0
Injection site nodule	942 (50.7%)	222 (23.5%)
Grade 1	909 (48.9%)	214 (22.6%)
Grade 2	33 (1.8%)	8 (0.8%)
Injection site pain	746 (40.1%)	344 (36.4%)
Grade 1	642 (34.5%)	297 (31.4%)
Grade 2	103 (5.5%)	47 (5.0%)
Grade 3	1 (< 0.1%)	0
Injection site erythema	195 (10.5%)	119 (12.6%)
Grade 1	174 (9.4%)	82 (8.7%)
Grade 2	21 (1.1%)	37 (3.9%)
Injection site induration	174 (9.4%)	62 (6.6%)
Grade 1	161 (8.7%)	53 (5.6%)
Grade 2	13 (0.7%)	9 (1.0%)
Injection site swelling	58 (3.1%)	50 (5.3%)
Grade 1	56 (3.0%)	41 (4.3%)
Grade 2	2 (0.1%)	9 (1.0%)
Number of participants received injection at Week 52/SC Injection 3	744	379
Number (%) of participants with ISRs to study SC injection following Week 52 SC injection	433 (58.2%)	155 (40.9%)
Grade 1	396 (53.2%)	130 (34.3%)
Grade 2	35 (4.7%)	24 (6.3%)
Grade 3	2 (0.3%)	1 (0.3%)
Injection site nodule	300 (40.3%)	59 (15.6%)
Grade 1	293 (39.4%)	58 (15.3%)
Grade 2	7 (0.9%)	1 (0.3%)
Injection site pain	238 (32.0%)	112 (29.6%)
Grade 1	210 (28.2%)	97 (25.6%)
Grade 2	27 (3.6%)	14 (3.7%)
Grade 3	1 (0.1%)	1 (0.3%)

Preferred Term Severity	SC LEN (N = 2183)	SC LEN Placebo (N = 1088)
Injection site erythema	74 (9.9%)	41 (10.8%)
Grade 1	67 (9.0%)	35 (9.2%)
Grade 2	7 (0.9%)	6 (1.6%)
Injection site swelling	30 (4.0%)	14 (3.7%)
Grade 1	26 (3.5%)	11 (2.9%)
Grade 2	4 (0.5%)	3 (0.8%)
Injection site induration	28 (3.8%)	7 (1.8%)
Grade 1	27 (3.6%)	5 (1.3%)
Grade 2	1 (0.1%)	2 (0.5%)

AE = adverse event; eCRF = electronic case report form; HLT = high-level term; ISR = injection site reaction; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; SC = subcutaneous
Adverse events were coded according to MedDRA Version 27.0.
Treatment-emergent ISRs to study SC injection (related to study drug/procedure, HLT = injection site reactions) began on or after first SC LEN or placebo injection date.
Denominators for percentages are the total number of participants by visit and overall for the respective summaries.
Multiple ISRs were counted only once per participant for the highest severity grade for each preferred term.
Injection visits assigned to latest SC injection visit with date on or prior to the AE onset date, except for injection site nodules or induration (when collected from ISR eCRF).
Preferred terms were presented by descending order of the total frequencies.

Of the total 10,094 SC LEN injections administered, 4797 injection site nodule events (47.5%) were reported. Of the total 5145 placebo injections administered, 1085 injection site nodule events (21.1%) were reported. At Day 1 (SC Injection 1), injection site nodules were reported in 55.8% of participants who received LEN (6.9% had 1 nodule per participant and 48.8% had 2 nodules per participant) and 30.9% of participants who received placebo injections (9.3% had 1 nodule per participant and 21.6% had 2 nodules per participant). The incidence of injection site nodule events decreased with subsequent injections in both the LEN and placebo groups.

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

The percentages of participants with ongoing or resolved injection site nodules after Day 1 (SC Injection 1) were as follows:

- LEN: ongoing 31.7%; resolved 24.0%
- Placebo: ongoing 4.0%; resolved 26.9%

The percentages of participants with ongoing or resolved injection site indurations after Day 1 (SC Injection 1) were as follows:

- LEN: ongoing 4.2%; resolved 8.1%
- Placebo: ongoing 0.5%; resolved 8.0%

Updated data on ISRs with a data cut date of 04 December 2024 for PURPOSE 1 (compared to 08 May 2024 for the marketing authorisation application [MAA]) and 03 January 2025 for PURPOSE 2 (compared to 05

August 2024 for the MAA), provided on request, indicated a numerically similar incidence of ISRs, including noduli and indurations, in both studies as compared with the earlier (original) dataset.

The applicant provided *post hoc* exploratory, linear regression analyses of nodule change during follow up (not shown here), which support a downward trend in nodule size but do not provide a basis to predict complete nodule resolution. In fact, the presented data contradict the underlying assumption that nodule resolution follows a uniform, linear pattern. Resolution rates vary between cohorts and time points.

In addition, limited biopsy data (not shown here) from 6 patients in PURPOSE 1 and 4 patients in PURPOSE 2 demonstrate granulomatous inflammation and foreign body reactions at injection sites, indicating that nodule resolution is affected by biological factors other than the resorption of a subcutaneous drug depot.

Serious AEs

Study GS-US-412-5624 (PURPOSE 1)

Serious AEs were reported as follows during the Randomized Blinded Phase: LEN 2.8%, 59 participants; TVD 3.3%, 35 participants.

The following SAEs were reported in ≥ 0.1% of participants in either study drug group:

- LEN: spontaneous abortion (0.7%, 15 participants) and fetal death, malaria, and overdose (each 0.1%, 3 participants)
- TVD: spontaneous abortion (0.8%, 9 participants), asthma (0.4%, 4 participants), and gastritis, humerus fracture, lower limb fracture, and obstructed labor (each 0.2%, 2 participants)

Study GS-US-528-9023 (PURPOSE 2)

Serious AEs were reported as follows during the Randomized Blinded Phase: LEN 3.3%, 71 participants; TVD 4.0%, 43 participants (GS US 528 9023 Interim Week 52 CSR, Section 11.5).

The following SAEs were reported in ≥ 0.1% of participants in either study drug group:

- LEN: appendicitis and suicide attempt (each 0.3%, 7 participants) and suicidal ideation, depression, hepatitis A, and abscess limb (each 0.1%, 3 participants)
- TVD: appendicitis (0.6%, 6 participants), suicidal ideation (0.4%, 4 participants), suicide attempt (0.3%, 3 participants), and major depression and anxiety (each 0.2%, 2 participants)

6.4.4.1. Deaths

Study GS-US-412-5624 (PURPOSE 1)

No deaths were reported in the LEN or TVD group during the Randomized Blinded Phase. Six deaths were reported in the DVY group, as follows: haemorrhage due to road traffic accident, asphyxia secondary to strangulation, nonaccidental-burns, ischemic cardiomyopathy, knife stab to chest, and advanced ovarian cancer (each 1 participant). None of these AEs leading to death were considered by the investigator to be related to study drugs.

Study GS-US-528-9023 (PURPOSE 2)

Five treatment-emergent deaths were reported during the Randomized Blinded Phase (LEN 4 participants; TVD 1 participant), as follows: car collision, cerebrovascular accident and pulmonary thromboembolism, death caused by suicide, and sudden death without a defined cause in which the participant was found dead (1 participant each in the LEN group) and death due to an undetermined cause in which the participant was found dead (1 participant in the TVD group) In addition, 1 non–treatment-emergent death due to intracranial haemorrhage was reported in the TVD group; the participant's last dose was 128 days preceding the death.

None of the AEs leading to death were considered by the investigator to be related to study drugs.

6.4.4.2. Discontinuation of study drugs due to adverse events

Study GS-US-412-5624 (PURPOSE 1)

Adverse events that led to discontinuation of study drugs during the Randomized Blinded Phase were reported as follows: LEN 0.4%, 9 participants; TVD 0 participants. The only AE leading to discontinuation of study drugs that was reported in ≥ 0.1% of participants in the LEN group was injection site nodule (0.2%, 4 participants)

Study GS-US-528-9023 (PURPOSE 2)

Adverse events that led to discontinuation of study drugs during the Randomized Blinded Phase were reported as follows: LEN 1.5%, 32 participants; TVD 0.9%, 10 participants. The AEs leading to discontinuation of study drugs that were reported in ≥ 0.1% of participants in the LEN group were injection site nodule (0.8%, 17 participants) injection site pain (0.4%, 8 participants).

Table 58. Adverse events leading to drug discontinuation in >1 patient

Preferred term	Study GS-US-412-5624 (PURPOSE 1)	Study GS-US-528-9023 (PURPOSE 2)
Injection site nodule	4 participants (0.2%)	17 participants (0.8%)
Injection site pain	0 participants	8 participants (0.4%)
Injection site induration	0 participants	2 participants (0.1%)
Injection site ulcer	0 participants	2 participants (0.1%)
Total AEs leading to discontinuation	9 participants (0.4%)	32 participants (1.5%)

6.4.5. Safety in special populations

Safety in adolescents

Safety analyses for adolescents were summarized (participants aged < 18 years versus ≥ 18 years for Studies GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2). Note that the adolescent population (16 to < 18 years of age) comprises mainly of Study GS-US-412-5624 (PURPOSE 1) participants as this population only included 4 participants from Study GS-US-528-9023 (PURPOSE 2).

Table 59. AEs in adolescents and adults

Age group	> 18 years	<18 years
ISR	injection site nodule (63.5%, 1323 participants)	injection site nodule (75.0%, 42 participants)
	injection site pain (31.2%, 651 participants)	injection site pain (32.1%, 18 participants)
		injection site induration (3.6%, 2 participants)
	injection site swelling (4.5%, 94 participants	injection site swelling (3.6%, 2 participants)
Non-ISRs		urinary tract infection (14.7%, 306 participants)
	genitourinary chlamydia infection (12.5%, 7 participants),	genitourinary chlamydia infection (14.1%, 293 participants)
	headache (16.1%, 9 participants),	headache (13.2%, 276 participants)
	genitourinary tract gonococcal infection (8.9%, 5 participants)	

One SAE (pyelonephritis) was reported. The SAE was not considered related to the study drug. No deaths in the subgroup were reported. There were no clinically relevant changes from baseline in median eGFRCG in the adolescent group.

The available data suggests that the safety profile is qualitatively similar to that in adults, with no new safety concerns identified. The small sample size limits the ability to detect rare adverse events, but there is no known biological basis to anticipate a substantially different safety profile compared to adults.

The participants in the studies reflect the anticipated target group for PrEP, and there are limited data available in elderly patients. However, no specific safety concerns for these groups are anticipated based on the available nonclinical data and known pharmacokinetic profile of lenacapavir.

No patients had hepatic or renal impairment at baseline in the pivotal clinical studies. Two Phase 1 single-dose studies have previously assessed the pharmacokinetics of lenacapavir in participants with moderate hepatic impairment or severe renal impairment and adequate information is offered to prescribers in statements proposed by the Applicant for the SmPC.

Safety during pregnancy and lactation

GS-US-412-5624 (PURPOSE 1)

Available PK data for LEN during and after pregnancy and in breastmilk and breastfed infants is presented in 6.2.2.9. Special populations above.

At a cut-off date of 04 December 2024 (compared to 08 May 2024 for the MAA), of the 297 confirmed pregnancies in the LEN group that were reported during the RBP of PURPOSE 1, a total of 208 pregnancies were completed, 88 were ongoing and 1 had a pregnancy status categorized as unknown. A total of 130 completed uninterrupted pregnancies (which included 2 twin gestations) resulted in 106 healthy offspring, including 2 completed uninterrupted pregnancies whose outcomes were categorized as unknown. This represents just 4 additional outcomes for completed uninterrupted pregnancies since the original dataset submitted for the MAA.

Similarly, 90 pregnancies have been reported in the open-label extension phase of PURPOSE 1, although it is unclear how many are ongoing past the first trimester. Twelve pregnancies were reported as completed, all of which ended in induced or spontaneous abortion. Data from 76 pregnancies are pending. Thus, no new birth outcomes for completed uninterrupted pregnancies could be presented from the OL phase since the original dataset submitted for the MAA.

Overall, rates of adverse pregnancy outcomes, such as spontaneous abortions, stillbirths, and congenital anomalies following exposure to LEN were similar to both active comparator and background rates, at both interim and updated cut-off dates.

The Applicant provided a granular analysis of 89 cases of infants exposed to LEN through breastfeeding, reported during PURPOSE 1. 20 cases reported at least one AE, and two fatalities were reported. Both infant deaths were determined to be unrelated to LEN exposure and may reflect the comparatively high background rates of infant mortality in the target population.

Most AEs occurred prior to the initiation of breastfeeding, and LEN exposure started in utero for most infants. There were no indications that any of the reported AEs could be considered related to LEN exposure from breast milk. However, the duration and extent of breastfeeding, and timing of the first maternal LEN dose in relation to lactation initiation, varied and the actual systemic exposure of these infants is not known. This limits interpretation of the observed AE data.

The most up to date analyses of PK data from 98 mother-infant pairs showed a very low infant-to-mother plasma ratio for LEN, although outliers with ratios up to 0.65 were observed (see Pharmacokinetics).

Post-marketing data

A cumulative search of the Gilead global safety database returned 366 cases (from 369 pregnancies) of maternal exposure to LEN, 89 cases of the use of LEN in lactating women, 3 cases of partner exposed

pregnancies, and no cases of potential infertility. The majority of these data (342 of 366 reports of maternal exposure and all the lactation reports) were received from Study GS-US-412-5624 (PURPOSE 1).
As requested, the applicant has presented separate summary and assessment of 8 post-marketing cases of LEN-exposed pregnancy and/or lactation that were not collected within the scope of the pivotal clinical studies. Among the 8 pregnancy cases, there were no reports of maternal pregnancy-related AEs or abnormal pregnancy outcomes. There were no reports of fetal or congenital anomalies, and no AEs reported in the offspring. These cases do not provide any data inconsistent with the available pregnancy data from PURPOSE 1.

6.4.6. Immunological events

Not applicable

6.4.7. Safety related to drug-drug interactions and other interactions

There are no safety data of concern relating to drug-drug interactions.

6.4.8. Vital signs and laboratory findings

Overall, no clinically relevant changes from baseline in fasting glucose or the fasting lipid parameters of total cholesterol, LDL cholesterol, HDL cholesterol, or total cholesterol to HDL ratio were shown at Week 52 in either study.

Grade 3 or above abnormalities regarding triglycerides were more frequent in patients treated with lenacapavir (Sunlenca) (11/353 (3.1%)) vs. in patients receiving placebo (0/49 (0%). The applicant provided detailed data regarding this issue per request, concluding that the incidence of Grade 3 and 4 elevations in triglycerides was low, and these events were transient in nature with ongoing LEN exposure. This is suggestive of other causes being the driver of the observed increases.

The proportion of participants with each graded individual laboratory abnormality was generally similar between the 2 study drug groups.

There were no clinically relevant changes from baseline in serum creatinine and eGFRCG within the LEN or TVD group in either study. The proportions of participants who had graded proteinuria by dipstick was slightly lower in the LEN group compared to (LEN 23.6% and TVD 27.0%, P = 0.0284) There were no Hy's Law cases in either study. Liver-related laboratory evaluations were generally similar between the two study drug groups. Urine creatinine was similar between LEN and TVD groups at each time point through Week 52.

There were no clinically relevant changes from baseline within or between the study drug groups, or difference in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, body temperature, and waist circumference in either study. There were no clinically significant changes in weight.

TVD (mainly emtricitabine) is associated with hepatobiliary disorders, mainly elevated AST, elevated ALT and hyperbilirubinaemia. Toxicology studies indicate that lenacapavir can generate hepatobiliary toxicity in

rats, dogs and possibly mice if achieving sufficient systemic exposure. The applicant provided a discussion regarding the potential relatedness of several events to the drug LEN, including: AST increased, hyperbilirubinaemia, creatine kinase increased and creatine increase. On the basis of lack of association between LEN exposure and such laboratory abnormalities in studies, infrequent occurrence of Grade 3 and 4 events, with improvements or resolutions upon continued LEN exposure and a similar or lower incidence of events in LEN groups compared to placebo groups in the Sunlenca ISS, none of these were considered to be ADRs for LEN.

Post-marketing data

As of 16 August 2024, the cumulative post-marketing exposure to Lenacapavir (Sunlenca®) was estimated to be 1781 PY based on sales data.

A small number of serious cases of injection site necrosis have been reported in the post-marketing setting following improper administration (intradermal injection) of LEN. This has been addressed in a separate procedure (EMEA/H/C/005638/II/0025) in which the Sunlenca SmPC was updated to emphasise the importance of correct injection technique.

A small number of post-marketing pregnancies exposed to LEN have been reported and are presented further under 6.4.5. Safety in special populations above.

6.4.9. Overall discussion and conclusions on clinical safety

6.4.9.1. Discussion

Safety database and ADR methodology

The safety profile of LEN was evaluated in two Phase 3 studies, GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2), which enrolled a total of 8,660 participants. Supplementary safety data from LEN for patients living with multi-drug-resistant HIV was also provided.

Safety data for up to 12-months of exposure are available for 4323 patients across the two pivotal studies, The majority of participants received 2 (Day 1 and month 6) injections. Data regarding exposure beyond 12 months are not available. The median follow-up time for adverse effects in the main studies is approximately 40 weeks.

Adverse events and Adverse Drug Reactions

Injection site reactions

ISRs were the most common adverse event reported. Most ISRs were Grade 1 or 2 in severity.

In Study GS-US-412-5624 (PURPOSE 1), the frequency of injection site nodules decreased from 56.4% to 24.7% from the first to the third injection, respectively. Similarly, in Study GS-US-528-9023 (PURPOSE 2), the frequency of injection site nodules decreased from 55.8% to 40.3% from the first to the third injection. No clear patterns regarding ISRs were reported throughout subgroups of sex, gender, race, ethnicity or BMI.

Notably, at the end of the submitted observation period 35.5% of patients on LEN in PURPOSE 1 and 35.9% of patients on LEN in PURPOSE 2 had non-resolved noduli or indurations. The corresponding numbers for the placebo group were 2.3% and 4.5%.

Long-term consequences of ISRs, such as the potential for scarring or permanent skin damage are still not fully characterised. The impact of non-resolving nodules and indurations is not fully understood. The Applicant was not able to provide any patient reported outcomes or other data on patient experience of non-resolving ISRs.

Updated data on ISRs were provided on request with a data cut date of 04 December 2024 for PURPOSE 1 (compared to 08 May 2024 for the marketing authorisation application [MAA]) and 03 January 2025 for PURPOSE 2 (compared to 05 August 2024 for the MAA). These data indicated a numerically similar incidence of ISRs, including noduli and indurations, in both studies as compared with the earlier (original) dataset. The ADR is described in section 4.8 of the SmPC.

Overall, chronic inflammation impacts nodule persistence, and some nodules may remain indefinitely. In addition, local chronic inflammatory reaction has the theoretical potential to contribute to carcinogenesis. No known neoplasms have been associated with systemic lenacapavir administration at any dose. Information regarding the non-resolution of certain noduli is included as a warning in SmPC section 4.4.

Systemic adverse events

In terms of systemic AEs, the most common events reported in the LEN group were headache (13.3% in GS-US-412-5624 and 10.8% in GS-US-528-9023), nausea (4.8% in GS-US-412-5624 and 7.4% in GS-US-528-9023), and diarrhoea (2.0% in GS-US-412-5624 and 2.6% in GS-US-528-9023).

In the TVD group, the most common systemic AEs were headache (14.5% in GS-US-412-5624 and 14.5% in GS-US-528-9023), nausea (13.3% in GS-US-412-5624 and 12.8% in GS-US-528-9023), and diarrhoea (10.0% in GS-US-412-5624 and 9.9% in GS-US-528-9023)

There were no deaths considered related to the study drug or comparators. Two deaths without defined cause were reported in breast-fed infants of mothers in the LEN arm. The narrative information is limited, and no causal inferences can be drawn.

Safety in special populations and situations

The patient safety database encompasses the anticipated patient target group at risk for HIV infection. However, data is limited or missing for special populations, including the elderly and adolescents under 18 years of age. Subgroup analyses did not indicate any clinically significant differences in relation to BMI, weight, race or ethnicity. Clinical data from elderly patients, as well as patients with hepatic or renal disorders, is limited, but no notable differences in safety profile warranting mention in the proposed SmPC are anticipated.

In terms of safety in adolescents, the available data suggests that the safety profile is qualitatively similar to that in adults, with no new safety concerns identified. The small sample size limits the ability to detect rare adverse events, but there is no known biological basis to anticipate a substantially different safety profile compared to adults. The available data do not raise specific safety concerns for this population.

During the oral bridging period in Studies GS-US-200-4334 and GS-US-200-4625, LEN was well tolerated. The combined sample size during oral bridging is limited, and only very common adverse drug reactions can

be expected to be detected. No new safety concerns are expected during oral bridging, and none were identified.

No new safety concerns were identified in alternative injection sites.

Pregnancy and lactation

Lenacapavir is a direct-acting antiretroviral with a viral rather than host target. Preclinical studies do not suggest any harmful effects in pregnancy or lactation.

Although the cumulative data from GS-US-412-5624 (PURPOSE 1) contains 369 pregnancies, at the updated data cut-off date of 04 December 2024 the outcome is unknown for 38%, and 17% resulted in induced abortion. The frequency of pregnancy complications, spontaneous abortions, malformations and still-births was reported as comparable to calculated background incidence, although the available data is not powered to detect rare events.

The EMA guideline anticipates outcome data from >300 pregnancies past the first trimester as the basis for safety recommendations in the SmPC. In the absence of comprehensive clinical data, appropriate caution regarding use of lenacapavir in pregnancy and lactation is warranted. However, with the outcome of 88 + 76 ongoing pregnancies exposed to LEN still pending, there is a commitment to collect and analyse more data. Additionally, it is noted that participants in the planned studies PURPOSE 3 (cis gender women, USA) and PURPOSE 4 (people who inject drugs, USA) will have the same approach as for PURPOSE 1, permitting participants to continue on study medication should they become pregnant during the course of the study, which will generate further prospective pregnancy outcome data for LEN. Based on the above, lenacapavir use may be considered during pregnancy if the expected benefit outweighs the potential risk to the foetus.

A total of 89 cases of exposure of an infant to LEN via a lactating mother were reported during PURPOSE 1 to date and related AEs were summarised in the dossier, and a separate summary of 8 post-marketing cases that were not included within the scope of the pivotal clinical studies. Most AEs occurred prior to the initiation of breastfeeding, and LEN exposure started in utero for most infants. There were no indications that any of the reported AEs could be considered related to LEN exposure from breast milk. However, the duration and extent of breastfeeding, and timing of the first maternal LEN dose in relation to lactation initiation, varied and the actual systemic exposure of these infants is not known. This limits interpretation of the observed AE data.

The most up to date analyses of PK data from 98 mother-infant pairs (a notably larger dataset versus the original submission) showed a low infant-to-mother plasma ratio for LEN, although outliers with ratios up to 0.65 were observed (see Pharmacokinetics).

Based on the above, breastfeeding may be considered despite lenacapavir use if the expected benefit outweighs the potential risk to the child.

6.4.10. Product information

Please see the SmPC.

6.4.11. Conclusion

6.4.11.1.1. Overall assessment of available safety data

The safety profile of lenacapavir is compatible with a drug with an exogenous (viral) target and few if any systemic secondary pharmacological effects, as would be necessary for uptake as PrEP. The main safety issue is ISR's. While these are generally mild to moderate in severity, non-resolution of induration and noduli over extended observation times has previously been raised as a concern for Sunlenca and is a concern for this product as well. Appropriate information in the SmPC and PIL has been instituted.

Permissive labelling statements on use in pregnancy and lactation takes into consideration the non-human target of the active substance, absence of relevant preclinical safety signals and sufficiently reassuring clinical safety data in pregnancy and lactation.

6.4.11.1.2. Adverse drug reactions in the SmPC

The ADRs proposed for inclusion in the SmPC are described in section 6.4.3.1 above. The MAH has proposed to include ISRs as the only ADR and this is supported.

6.4.11.2. Conclusions on clinical safety

The overall safety profile of LEN as HIV-1 PrEP seems to be favourable. The main safety concern is slow- or non-resolving noduli. A warning on this in section 4.4 of the SmPC has been implemented.

7. Risk management plan

7.1. Safety specification

7.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP (version 1.0):

Table 60. Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in pregnancy and lactation Long term safety information

7.1.2. Discussion on proposed safety specification

Safety in pregnancy and lactation is listed as an area of missing information and this is appropriate. The pregnancy registry used for Sunlenca is proposed to be included in the LEN PrEP RMP and this is supported. Further updates regarding ongoing pregnancies from PURPOSE 1 are pending, and the applicant has committed to registration of additional pregnancy outcomes in further planned studies.

The applicant agreed with the CHMP requirement that long term safety should be listed as Missing information in the RMP.

7.2. Pharmacovigilance plan

7.2.1. Proposed pharmacovigilance plan.

The applicant has not proposed other routine Pharmacovigilance activities beyond adverse drug reactions reporting and signal detection.

In addition, the applicant has proposed the following additional pharmacovigilance activities:

Table 61. 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				
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)

7.2.2. Discussion on the Pharmacovigilance Plan

7.2.2.1. Routine pharmacovigilance activities

The routine pharmacovigilance activities proposed by the applicant are considered sufficient.

7.2.2.2. Additional pharmacovigilance activities

The additional pharmacovigilance activity proposed by the applicant to address the missing information "safety in pregnancy and lactation" is considered sufficient. The interim reports of the ongoing Antiretroviral Pregnancy Registry (APR) will be submitted in the scope of the PSURs, which is acceptable.

7.3. Plans for post-authorisation efficacy studies

Not applicable, as the applicant does not propose any PAES.

7.4. Risk minimisation measures

7.4.1. Proposed risk minimisation measures

Table 62. Planned routine risk minimisation measures

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

7.4.2. Discussion on the risk minimisation measures

7.4.2.1. Routine risk minimisation measures

The routine risk minimisation measures as proposed by the applicant are sufficient.

7.4.2.2. Additional risk minimisation measures

The applicant did not propose any additional risk minimisation measures, which is acceptable.

7.4.2.3. Patients engagement on the risk minimisation activities

Not applicable.

7.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes are acceptable.

7.6. PRAC outcome

Not applicable

7.7. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

The Applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

8. Pharmacovigilance

8.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

8.2. Periodic Safety Update Reports submission requirements

The scientific opinion holder shall submit periodic safety update reports for this product in alignment with the requirements for the centrally authorised product as set out in the list of Union reference dates (EURD list) and any subsequent updates published on the European medicines web-portal.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

9. Product information

9.1. Summary of Product Characteristics (SmPC)

9.1.1. SmPC section 4.1 justification

The approved indication is aligned with the population studied in the pivotal clinical trial(s). The wording, though not identical, covers the same use as products approved for PrEP such as Apretude and Truvada.

9.1.2. SmPC section 5.1 justification

The primary analyses of the main trials (GS-US-412-5624 and GS-US-528-9023) were deleted from SmPC section 5.1. These analyses, which compare the HIV-1 incidence in the LEN arm to an estimated background HIV-1 incidence, are not robust enough to demonstrate the efficacy of LEN as PrEP. The only efficacy results that should be presented in 5.1 are the type-I-error-controlled secondary analyses of HIV-1 incidence in the LEN and TVD arms.

9.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

10. Benefit-risk assessment

10.1. Therapeutic context

10.1.1. Disease or condition, proposed therapeutic indication

The final indication is:

Solution for injection:

Lenacapavir Gilead injection is 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 (see sections 4.2, 4.4 and 5.1).

Film-coated tablets:

Lenacapavir Gilead tablet is 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 for:

- *oral loading*
- *oral bridging*

(see sections 4.2, 4.4 and 5.1).

10.1.2. Available therapies and unmet medical need

For a detailed description, please see section 3.1 of this document.

HIV-1 infection is a disease of major public health concern. While the number of new HIV infections globally has continued to decline, it is estimated that approximately 1.3 million new HIV infections still occur each year, despite efforts to improve HIV testing, treatment, and prevention, and the increased availability of pre-exposure prophylaxis (PrEP).

There are currently two available PrEP options in the EU. Daily oral emtricitabine/tenofovir disoproxil fumarate (F/TDF; Truvada®; TVD) which is approved for adults and adolescents. TVD is recommended by the World Health Organization (WHO) as part of the HIV-1 prevention standard of care. Cabotegravir (CAB; Apretude®), is administered by intramuscular injection every 2 months. It is approved for adults and adolescents and provides an alternative option for HIV-1 prevention that does not depend on adherence to a daily oral regimen.

The dapivirine vaginal ring received a positive scientific opinion from the European Medicines Agency under

the "EU-Medicines for all" procedure and is recommended by WHO as an additional HIV-1 prevention option for CGW aged ≥ 18 years.

In the EU/EEA, sex between men remains one of the most common modes of HIV transmission. Globally, cisgender women and girls are a high-priority population for PrEP. Adolescents represent an additional special population with disproportionate HIV incidence and an unmet need for additional PrEP options.

Lenacapavir (LEN) is a first-in-class selective inhibitor of HIV-1 capsid function. Lenacapavir (Sunlenca) is approved for treatment of multi-resistant HIV-1 and the Applicant is now seeking approval of lenacapavir as PrEP.

10.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 6.3.2 of this document.

The primary efficacy and safety data supporting the use of LEN for PrEP are based on the interim analyses of the ongoing pivotal Phase 3 Studies GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2).

GS-US-412-5624

This study recruited cisgender adolescent girls and young women (AGYW) ⩾ 16 to ⩽ 25 years of age, who have sex with cisgender males. Participants were to have unknown HIV-1 status at screening and no prior HIV-1 testing within the last 3 months. Pregnant and breastfeeding women were excluded from entering the study. However, women who became pregnant during the study had the option to remain on study drug.

Patients were randomised in a 2:2:1 ratio (no stratification) to receive either LEN (n=2134), DVY (n=2136), or TVD (n=1068), respectively. The participants were to continue in the Randomised Blinded Phase until all randomised participants have completed at least 52 weeks of follow-up in the study.

Participants in the LEN group received SC LEN injections administered on Day 1 and every 6 months (26 ± 2 weeks). On Day 1 and Day 2 they also received oral LEN 600 mg (2 x 300-mg tablets) which is required for pharmacokinetic loading. Moreover, daily oral TVD or DVY placebo-to-match was taken.

In the TVD or DVY groups participants took daily oral TVD or DVY as well as placebo SC LEN injections every 6 months and on Days 1 and 2 oral loading placebo-to-match LEN (2 tablets).

The primary efficacy evaluation was the comparison of the HIV-1 incidence in the LEN group during the study versus the bHIV incidence. The main secondary efficacy evaluation was the comparison of HIV-1 incidence in the LEN group versus the TVD group.

GS-US-528-9023

This study recruited cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender nonbinary (GNB) ⩾ 16 years old who have receptive anal sex with partners assigned male at birth. Participants were to have unknown HIV-1 status at screening and no prior HIV-1 testing within the last 3 months.

Patients were randomised in a 2:1 ratio (no stratification) to receive either LEN (n=2179) or TVD

(n=1086). The participants were to continue in the Randomised Blinded Phase until all randomised participants have completed at least 52 weeks of follow-up in the study.

Study drug was administered as in GS-US-412-5624, described above, except there was no DVY group in this study.

The primary efficacy evaluation was the comparison of the HIV-1 incidence in the LEN group during the study versus the estimated bHIV incidence. The main secondary efficacy evaluation was the comparison of HIV-1 incidence in the LEN group versus the TVD group.

10.3. Favourable effects

GS-US-412-5624

There were no HIV-1 infections in the LEN group prior to the primary efficacy data cut, while the estimated bHIV incidence was 2.407 infections per 100 PY. Thus, the primary analysis showed that HIV-1 incidence in LEN is significantly lower than estimated bHIV (H01, P-value <0.0001), and sequential testing of following endpoints were performed.

The fifth key alpha-controlled statistical hypothesis (H05) was the rate difference for the HIV-1 incidence (LEN vs TVD). The rate difference was −1.685 (95% CI: −2.737 to −0.939; P < 0.0001).

The sixth key alpha-controlled statistical hypothesis (H06) was then tested. Using the rate ratio method LEN was demonstrated to be superior to TVD (rate ratio: 0.000; 95% CI: 0.000 to 0.101; P < 0.0001). The analysis of LEN versus TVD was statistically significant.

Adherence to LEN injections was high with on-time injection for 91.1 % of participants at Week 26 and 93.5% of participants at Week 52. Adherence to TVD (based on TFV-DP in red blood cells from dried blood spots) was low and consistent with dosing < 2 days per week.

GS-US-528-9023

In the LEN group there were 0.103 infections per 100 PY which was significantly lower than the estimated bHIV incidence of 2.374 infections per 100 PY (H01; rate ratio: 0.043; 95% CI: 0.010 to 0.182; P < 0.0001). The primary endpoint was met, and sequential testing of following endpoints was performed.

The third key alpha-controlled statistical hypothesis (H03) was the rate difference for the HIV-1 incidence in LEN group versus the TVD group (−0.828; 95% CI: −1.669 to −0.255; P < 0.0001).

The fourth key alpha-controlled statistical hypothesis (H04) was then tested. Using the rate ratio method LEN was demonstrated to be superior to TVD (rate ratio:0.111; 95% CI: 0.024 to 0.513; P = 0.00245).

Of the participants in the LEN group, 87.2% received the Week 26 SC LEN injection within 28 weeks of the first injection, and 92.7% received the Week 52 SC LEN injection within 28 weeks of the previous injection. With respect to adherence, the TFV-DP in red blood cells from dried blood spot samples indicated dosing $\geqslant$ 4 days per week.

10.3.1. Uncertainties and limitations about favourable effects

In both GS-US-412-5624 and GS-US-528-9023 the primary analysis was a comparison of the HIV-1 incidence in the lenacapavir arm to the bHIV incidence rate.

The bHIV incidence was estimated in the screened population using recency assay results from samples that were positive for HIV-1 infection incorporated into a recent infection testing algorithm (RITA). This method has not previously supported claims for a PrEP product.

The validity of the RITA-based method relies on the assumption that HIV-1 status was completely random at screening, meaning that those who were HIV-1 negative (and who were therefore randomised) would subsequently contract HIV-1 at the same rate as the entire screened population (including those HIV positive) had historically done. This assumption is untenable because the rate may well have been higher in those who were HIV-1 positive (that is, in those who had previously contracted HIV-1). If so, the bHIV incidence would be overestimated, which would lead to an overestimation of the efficacy of lenacapavir. Such a bias is not acceptable to support efficacy or labelling claims. Therefore, the primary analysis is not included in the SmPC section 5.1.

The efficacy of LEN is still considered established because the trial had a statistically significant and multiplicity-controlled secondary analysis showing that LEN is superior to TVD in the prevention of HIV-1.

The number of breakthrough infections on LEN was too small to reliably investigate baseline factors that could be related to failure and development of potential resistance mutations in circulating viruses. No data are available at present. The Applicant is planning to conduct a non-interventional study of LEN for PrEP in a real-world setting. Details of this study will be provided when available (**REC**).

10.4. Unfavourable effects

The safety database includes >4300 patients who received the to-be-marketed dose of lenacapavir across studies GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2).

In Study GS-US-412-5624, the median exposure time to study drugs during was 42.6 weeks (range: 38.1, 53.4) for LEN and 41.4 weeks (range: 38.1, 53.3) for TVD.

In Study GS-US-528-9023, the median exposure time was 39.3 weeks (range: 28.4, 54.1) for LEN and 39.3 weeks (range: 28.3, 55.1) for TVD. TVD: 41.4 (38.1, 53.3) weeks

The most common adverse events (AEs) reported were injection site reactions (ISRs), with a significantly higher incidence in the LEN group compared to the TVD group in both studies.

In Study GS-US-412-5624, ISRs were reported in 68.8% of participants in the LEN group, compared to 34.8% in the TVD group. The most common ISRs in the LEN group were injection site nodules (63.8%), followed by injection site pain (31.3%).

In Study GS-US-528-9023, ISRs were reported in 83.2% of participants in the LEN group, compared to 69.5% in the TVD group. The most common ISRs in the LEN group were injection site nodules (63.4%), followed by injection site pain (56.4%).

At the end of the submitted observation period 35.5% of patients on LEN in PURPOSE 1 and 35.9% of

patients on LEN in PURPOSE 2 had non-resolved noduli or indurations. The corresponding numbers for the placebo group were 2.3% and 4.5%

In terms of systemic AEs, the most common events reported in the LEN group were headache (13.3% in GS-US-412-5624 and 10.8% in GS-US-528-9023), nausea (4.8% in GS-US-412-5624 and 7.4% in GS-US-528-9023), and diarrhoea (2.0% in GS-US-412-5624 and 2.6% in GS-US-528-9023).

In the TVD group, the most common systemic AEs were headache (14.5% in GS-US-412-5624 and 14.5% in GS-US-528-9023), nausea (13.3% in GS-US-412-5624 and 12.8% in GS-US-528-9023), and diarrhoea (10.0% in GS-US-412-5624 and 9.9% in GS-US-528-9023).

Hypersensitivity events were also reported in both groups, with a slightly higher incidence in the LEN group in Study GS-US-412-5624 (6.0% vs 5.4% in the TVD group).

9 participants in GS-US-412-5624 and 32 participants in GS-US-528-9023 discontinued the study due to AEs. Injection site nodule was the only ADR leading to drug discontinuation.

No deaths were considered related to the study drug or comparator. The only SAE reported possibly related to the study drug was spontaneous abortion (2 cases in study GS-US-412-5624).

Of the 297 confirmed pregnancies in the LEN group reported during the Randomised Blinded Phase, a total of 208 pregnancies were completed, 88 were ongoing and 1 had a pregnancy status categorized as unknown at the most recent data cut-off date. A total of 130 completed uninterrupted pregnancies (which included 2 twin gestations) resulted in 106 healthy offspring, including 2 completed uninterrupted pregnancies whose outcomes were categorized as unknown.

To date, 90 pregnancies have been reported in the open-label extension phase of PURPOSE 1 as per the latest data cut-off date. Twelve pregnancies were reported as completed, all of which ended in induced or spontaneous abortion. Data from 76 pregnancies are pending. Thus, no new birth outcomes for completed uninterrupted pregnancies could be presented from the OL phase since the original dataset submitted for the MAA.

Overall, rates of adverse pregnancy outcomes, such as spontaneous abortions, stillbirths, and congenital anomalies following exposure to LEN were similar to active comparator and background rates, at both interim and updated cut-off dates.

A total of 89 cases of exposure of an infant to LEN via a lactating mother were reported during PURPOSE 1 to date. There were no indications that any AEs reported amongst these infants should be considered related to LEN exposure from breast milk.

No new safety concerns were identified in association with injection in alternative injection sites or during oral bridging.

10.4.1. Uncertainties about unfavourable effects

The main uncertainty with regards to safety is the non-resolution of some injection site reactions also after substantial follow-up. This issue was already identified for Sunlenca and remains an outstanding issue for further follow-up for LEN. Appropriate labelling has been instituted.

The EMA guideline anticipates outcome data from >300 pregnancies past the first trimester as the basis for safety recommendations in the SmPC. In the absence of comprehensive clinical data, the label states that lenacapavir may be considered during pregnancy if the expected benefit outweighs the potential risk to the foetus.

The duration and extent of breastfeeding, and timing of the first maternal LEN dose in relation to lactation initiation, varied and the actual systemic exposure of these infants is not known. This limits interpretation of the observed AE data amongst infants exposed to LEN via breast milk. Labelling states that lenacapavir may be considered during breastfeeding if the expected benefit outweighs the potential risk to the child.

The applicant has committed to collect and present further data on pregnancy outcomes.

10.5. Effects table

Table 63. Effects table for Lenacapavir Gilead for HIV-1 pre-exposure prophylaxis

Effect (short description)	*Treatment*		*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable Effects					
Outcome	LEN	TVD	bHIV		
HIV-1 incidence (infections per 100 PY; 95% CI)	0/2134 (0.0; 0.000 to 0.190)	16 /1068; (1.685; 0.963 to 2.737)	2.407; (1.815, 3.191)	**SoE:** SE statistically significant LEN vs. TVD (HIV-1 incidence rate ratio:0.00; p-value: <0.0001) **Unc:** PE comparing LEN vs. bHIV not reliable due to overestimation of bHIV incidence.	GS-US-412-5624
HIV-1 incidence (infections per 100 PY; 95% CI)	2/2179 (0.103; 0.012 to0.373)	9/1086 (0.931;0.426 to 1.768)	2.374; 1.649 to 3.417)	**SoE:** SE statistically significant LEN vs. TVD (HIV-1 incidence rate ratio: 0.111; p-value: 0.00245) **Unc:** PE comparing LEN vs. bHIV not reliable due to overestimation of bHIV incidence.	GS-US-528-9023
Unfavourable Effects					
Adverse event	LEN (SC)	Active comparators (PO)	Placebo (SC)		
Injection site reactions (PURPOSE 1)	68.8%	N/A	34.8%	**SoE:** Consistent over studies, significant, common. **Unc:** Overlap with injection site nodule	GS-US-412-5624
Injection site nodule (PURPOSE 1)	63.8%	N/A	16.5%	**SoE:** Significant and common **Unc:** Duration unclear	GS-US-412-5624
Injection site reactions (PURPOSE 2)	83.2%	N/A	69.5%	**SoE:** Consistent over studies, significant, common. Unc: Overlap with injection site nodule	GS-US-528-9023
Injection site nodule (PURPOSE 2)	68.8%	N/A	39.2%	**SoE:** Significant and common **Unc:** Duration unclear	GS-US-528-9023

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PE: primary endpoint; SE: secondary endpoint; LEN: lenacapavir; PO: oral; SC: subcutaneous TVD: Truvada (emitricitabin/tenofivir disoproxil).

10.6. Benefit-risk assessment and discussion

10.6.1. Importance of favourable and unfavourable effects

Lenacapavir is a first-in-class selective inhibitor of HIV-1 capsid function. It inhibits HIV-1 replication by interfering with multiple steps of the viral lifecycle.

The primary analyses of HIV-1 incidence in the lenacapavir PrEP groups versus the bHIV-incidence are not considered reliable. Due to the assumption that the screening population risk would be relevant for the subpopulation excluding those testing positive, bHIV incidence may be overestimated which would favour lenacapavir in these analyses. Therefore, the primary analyses are not included in the SmPC section 5.1.

However, the efficacy of LEN is still considered established, since both trials had a statistically significant and multiplicity-controlled secondary analysis showing that LEN is superior to TVD in the prevention of HIV-1. TVD is considered an appropriate reference treatment, and these secondary analyses are the only efficacy analyses presented in the SmPC Section 5.1.

Thus, the data provided from two pivotal phase 3 trials support the efficacy of lenacapavir in preventing sexually transmitted HIV-1 infection.

Although the size of the safety database is sufficient to generally characterise the safety profile, with >4000 individuals who received at least 1 dose, follow-up is generally limited to 52 weeks. ISRs are the most significant safety concern. While generally mild to moderate and often manageable, the potential for non-resolving nodules requires adequate information to the prescriber and patient as well as monitoring.

Finally, as with all long acting injectables, individuals should be carefully selected to agree to the required dosing schedule and counselled about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection. There is a potential risk of developing resistance to lenacapavir if an individual acquires HIV-1 either before or while taking LEN or following discontinuation of LEN. This risk will be further characterised post marketing in a non-interventional study.

10.6.2. Balance of benefits and risks

The efficacy of LEN has been established. The safety profile is acceptable for the proposed use. The twice-yearly SC LEN dosing has the potential to increase adherence to PrEP. The benefit-risk balance is positive.

10.7. Benefit-risk conclusions

10.7.1. At Day 120 – Final CHMP conclusions

The overall benefit-risk balance of Lenacapavir Gilead is positive.