23 June 2022
EMA/657007/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sunlenca

International non-proprietary name: lenacapavir

Procedure No. EMEA/H/C/005638/0000

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

A	alemtuzumab
ADME	absorption, distribution, metabolism, and elimination
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARAs	acid reducing agents
ART	ARV 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
BCRP	breast cancer resistance protein
BIC	bictegravir
BVY	bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®)
CCR5	chemokine receptor 5
CD4	clusters of differentiation 4
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COBI	cobicistat
CPK	creatinine phosphokinase
CSR	clinical study report
C_{trough}	concentration at the end of the dosing interval
CYP	cytochrome P450 enzyme

DDI	drug-drug interaction
DRV	darunavir
DTG	dolutegravir
DVY	emtricitabine/tenofovir alafenamide (coformulated; Descovy®)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EMA	European Medicines Agency
ETV	etravirine
EU	European Union
F	bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
Gilead	Gilead Sciences
GCP	good clinical practice
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HTE	heavily treatment-experienced
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IND	investigational new drug
INSTIs	integrase strand-transfer inhibitors
IQ	inhibitory quotient
ISR	injection site reaction
IV	intravenous
LEN	lenacapavir
LSM	least-squares mean
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable
NDA	new drug application
NRTIs	nucleoside reverse transcriptase inhibitors
NNRTIs	nonnucleoside reverse transcriptase inhibitors

OBR	optimised background regimen
OSS	overall susceptibility score
$paEC_{95}$	protein adjusted 95% effective concentration
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	per protocol
PWH	people with HIV
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
ΔΔQTc	time-matched, baseline-adjusted, placebo-corrected QTc
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RIF	rifampin
RNA	ribonucleic acid
SAEs	serious AEs
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
T_{max}	time (observed time point) of C_{max}
TQT	thorough QT
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences Ireland Unlimited Company submitted on 30 July 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sunlenca through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The applicant applied for the following indication:

"*Lenacapavir, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations (see section 5.1).*"

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision P/0005/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0005/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's requests for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance lenacapavir contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Johann Lodewijk Hillege

Table 1 Steps taken

The application was received by the EMA on	30 July 2021
The procedure started on	19 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2021
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	21 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	2 December 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 April 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 April 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 June 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lenacapavir Gilead on	23 June 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	23 June 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The therapeutic indication claimed by the applicant is:

Lenacapavir, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations (see section 5.1).

2.1.2. Epidemiology

Approximately 38 million people are infected with HIV-1 worldwide of which approximately 26 million are on ARV treatment. Around 2.2 million people are living with HIV-1 in Western and Central Europe and North America (UNAIDS 2020). In 2019, 690,000 people died from AIDS-related causes worldwide. Reliable figures for prevalence of multidrug resistant (MDR) HIV-1, i.e. resistance to antiretroviral drugs among several drug-classes, are not available. However, a subset of patients with HIV-1 that are heavily treatment-experienced (HTE) with multiple prior regimen failures and significant drug resistance have limited treatment options and may be unable to achieve durable HIV-1 viral suppression.

2.1.3. Clinical presentation, diagnosis and prognosis

HIV-1 infection is a life threatening and serious disease of major public health significance. The virus targets the immune system and infected individuals become gradually more immunodeficient. Acute HIV-1 infection usually presents with non-specific signs and symptoms (including fever, rash, sore throat, enlarged lymph nodes etc.) or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Diagnosis therefore most often occurs during the chronic infection. Without treatment, HIV infection progresses from a phase of latency, of varying length, to acquired immunodeficiency syndrome (AIDS) and subsequent death. AIDS is defined as an HIV infection with either a CD4+ T-cell count below 200 cells per microliter, or the occurrence of specific diseases associated with HIV infection. Diseases associated with late-stage HIV infection include opportunistic infections, various tumours, and unspecific symptoms such as fever, night sweats and weight loss.

2.1.4. Management

Advances in combination antiretroviral (ARV) therapy (ART) for HIV-1 have led to durable suppression of viral replication, allowing for preservation and reconstitution of immunologic function and averting disease progression to AIDS, ultimately delivering a normal quality of life and life expectancy. For most people with HIV-1, these are possible with a well-tolerated once daily therapy. While combination ART for the treatment of HIV-1 infection has largely reduced the morbidity and mortality previously associated with HIV 1 disease, a subset of patients continues to experience virologic and immunologic failure. There remains an unmet medical need for new therapies for individuals failing currently available therapies because of multidrug resistance (MDR).

2.2. About the product

Lenacapavir is a selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (CA) subunits. Lenacapavir inhibits HIV-1 replication by interfering with multiple, essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA, virus assembly and release, and capsid core formation.

Lenacapavir is an antiviral for systemic use, direct acting antivirals, other antivirals (ATC code J05AX31).

The recommended treatment regimen in adults consists of oral loading with lenacapavir tablets followed by once every 6 months maintenance dosing (subcutaneous injections). On treatment Day 1 and Day 2, the recommended dose of lenacapavir is 600 mg per day taken orally. On treatment Day 8, the recommended dose is 300 mg taken orally. Then, on treatment Day 15, the recommended dose is 927 mg administered by subcutaneous injection. This is followed by 927 mg of lenacapavir administered by subcutaneous injection once every 6 months.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment (AA). The product was considered to be of major public health interest. However, the dossier that would be available at the time of submission was not considered mature enough for accelerated assessment. The fact that several pieces of information could only be provided by the company after the first round of assessment is problematic as the AA timelines simply do not allow for a thorough assessment of a significant body of new information. For this reason, the CHMP did not agree with the request for an AA.

2.4. Quality aspects

2.4.1. 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 active substance. Lenacapavir sodium is also referred as LEN.

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 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous (SC) injection (22-gauge, 12.7 mm).

Film-coated tablets:

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

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 child-resistant clear PVC/aluminium/paperboard blister. The blister is packaged with silica gel desiccant in a flexible laminated pouch.

2.4.2. 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:

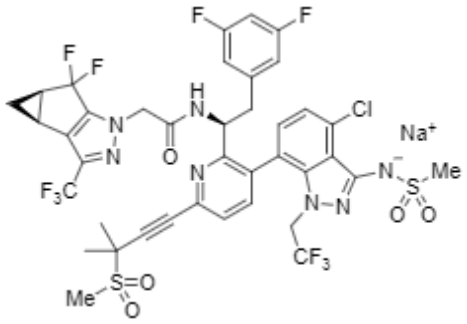


Figure 1 Active substance structure

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. The configuration of all three stereocentres have been found to be stable during the manufacturing process, i.e., unable to racemise or epimerise. Also, due to constraints in the cyclopropyl ring making trans-configuration impossible, enantiomeric purity is ensured by the combined control strategy at the level of starting materials and synthetic process.

Several crystalline forms of lenacapavir, including solvates and non-solvates, as well as an amorphous form were identified during development. Lenacapavir is isolated as a single crystalline polymorph, which is consistently obtained by the proposed synthetic method. The crystalline form of lenacapavir sodium was selected based on the following aspects:

- Reproducible crystallisation, not dependant on scale;
- Impurity purging during the isolation;
- Suitable biopharmaceutical properties.

Isolation of crystalline lenacapavir sodium 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, also the particle size of the active substance is not considered critical.

Manufacture, characterisation and process controls

Lenacapavir sodium is synthesised from well-defined starting materials with acceptable specifications and in a sufficient number of steps to demonstrate control over the formation, fate and purge of impurities.

In response to a Major Objection (MO), one of the initially proposed starting materials was redefined during the procedure.

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 now considered satisfactory.

The characterisation of the active substance and its impurities are 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. The calculation of toxicological qualification of specified impurities has been updated during the procedure as requested and the relevant part of the quality dossier have been updated accordingly.

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 the solution (visual), water content (Ph. Eur.), sodium content (LC), assay (LC), impurity content (LC), residual solvents (GC), organic volatile impurities (GC), bacterial endotoxin (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.

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 (10 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 the active substance from the proposed manufacturer stored in the approved packaging configuration. Stability data has been provided for up to 36 months under long term conditions (30ºC / 75 % RH) and for up to 6 months under accelerated conditions (40ºC / 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 on stress conditions (exposure to heat (solid and in solution), acid, base, oxidative agents (H2O2, AIBN, Cu2+, Fe3+), and light) 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.

2.4.3. Finished medicinal product (solution for injection)

Description of the product and Pharmaceutical development

Lenacapavir injection, 309 mg/mL corresponding to 464 mg in 1.5 mL, is a sterile, preservative-free, clear, yellow to brown solution for subcutaneous 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 overall goal of lenacapavir pharmaceutical development was to develop a formulation suitable for SC injection that would provide a clinically relevant steady-state and minimise 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 ionisation 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 13 mm non-vented vial access device with Luer lock fitting 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

The manufacturing process consists of 6 main steps: dissolution and mixing, bioburden reduction via filtration, filtration/filling/stoppering/sealing, moist heat terminal sterilisation, 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 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 considerations 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 on a maximum daily dose of 650 mg lenacapavir is in accordance with ICH Q3B. Both a 650 mg and 927 mg maximum daily dose will give the same reporting, identification and qualification limit for the finished product.

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

Each unspecified degradation product is controlled at 0.2%, the ICH Q3B identification threshold.

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. 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.

To address a MO, 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 test for container closure integrity had been validated. The same reference standards used in the active substance are used for the lenacapavir solution for injection.

Batch analysis results are provided for 10 batches, two of which full scale, 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 (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 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, samples from a development batch were 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 the finished product at -20°C, and 50°C/ambient humidity in, as well as at 5°C/ambient humidity in, glass 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 2 years with the following storage conditions: "This medicinal product does not require any special temperature storage conditions. Sensitive to light. Store in the original package. Store the vials in the outer carton in order to protect the solution 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 (section 6.3) are acceptable.

Adventitious agents

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

2.4.4. 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 with respect to dose. 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. Formulation of lenacapavir sodium as an amorphous spray-dried dispersion (SDD) was determined to be the most appropriate strategy to improve its PK performance.

Lenacapavir-sodium is spray-dried with two excipients to form lenacapavir SDD as a finished product intermediate. Lenacapavir SDD, together with the remaining excipients, is further processed 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 exceptions 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.

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 which has shown no tendency for crystallisation or phase transition in any development or clinical batches manufactured to date. Pharmaceutical development of the finished product contains QbD elements.

Lenacapavir solubility, dissolution robustness, and discriminating capability in different media led to selection of the dissolution method. In response to a MO, the composition of the medium, the test conditions and the dissolution criteria have been fully justified. The discriminatory power of the dissolution method has been demonstrated. The primary blister, packaged with silica gel desiccant in a flexible laminated pouch, has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of the lenacapavir tablets consists of several main steps starting with spray-drying the lenacapavir sodium with two excipients into lenacopavir SDD, a finished product intermediate. Lenacapavir SDD is then granulated with the remaining excipients. The resulting granules are lubricated and compressed into lenacapavir tablets, which are then film-coated. 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 include 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.).

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 considerations when establishing the acceptance criteria. A number of degradation products are controlled as specified degradation products in the specification for lenacapavir tablets.

A reporting limit of 0.1%, an identification limit of 0.2% and a qualification limit of 0.2% calculated on a maximum daily dose of 650 mg lenacapavir is in accordance with ICH Q3B. Both a 650 mg and 927 mg maximum daily dose will give the same reporting, identification and qualification limit for the finished product.

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

Each unspecified degradation product is controlled at 0.2%, the ICH Q3B identification threshold.

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. Based on the risk assessment, 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.

To address a MO, a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) 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 in the lenacapavir tablets.

Batch analysis results are provided for eight production scale 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 seven commercial scale batches of finished product stored for up to 12 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 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. All results were within the specification limits, but small trends were seen with decrease in water content and dissolution. The tablets are stable.

In addition, samples from a development batch were 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 showed a higher water content on the test sample due to exposure to the study condition without protection, but still within the specification. The data confirm that lenacapavir tablets are not photolabile.

Stress studies were conducted on one pilot batch of the finished product for up to 1 month at -20°C and up to 2 weeks at 50°C. Lenacapavir tablets were stable when stored in an open dish at 30°C/75% RH for up to 1 month. Lenacapavir tablets were stable when stored in an open dish at 30°C/75% RH for up to 1 month. All results were within the specification limits

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 2 years with the following storage conditions: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture" as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.4.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance. A verification protocol for the design spaces has been provided. In response to a MO, starting material selection was re-defined and accepted for the manufacture of lenacapavir active substance. In response to a MO, the suitability and discriminatory power of the QC dissolution test for the lenacapavir film-coated tablets has been demonstrated. The nitrosamine risk assessment has been updated following a MO raised for each pharmaceutical form of the finished product and it is now satisfactory. 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.

2.4.6. 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.

2.4.7. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

See in Clinical pharmacology.

2.5.2.2. Secondary pharmacodynamic studies

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 lenacapavir resulting in 50% cell death (CC_{50}-values) varied from 26 µM to more than the maximum concentrations tested, i.e. > 50 µM, and the corresponding selectivity indexes (CC_{50}/EC_{50} 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.

Lenacapavir (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.

2.5.2.3. Safety pharmacology programme

Lenacapavir was tested in a battery of safety pharmacology assays investigating effects on cardiovascular, central nervous system (CNS)/neurobehaviour 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 QT_C 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 lenacapavir 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 lenacapavir. Due to the low free plasma concentrations of lenacapavir (free Cmax 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 lenacapavir is available, the lack of a hERG study is however considered acceptable. Taken together, lenacapavir does not appear to have a potential for adverse cardiovascular effects.

Subcutaneous administration of lenacapavir to rats in a 6-week GLP SC toxicity study showed effects on behavioural endpoints in a functional observation battery 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 subcutaneous dosing regimen.

Subcutaneous single dose administration of lenacapavir 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 lenacapavir-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.

In conclusion, no safety issues were identified for the cardiovascular system in the non-clinical safety pharmacology assessments. There are no margins to the clinical exposure after the 6-months clinical oral and subcutaneous dosing regimen. Only minor effects were seen for the respiratory endpoints which are likely toxicologically non-relevant. For behavioural changes, see non-clinical discussion.

No safety concerns related to CNS, CV or respiratory function were found in the assessment of the clinical studies for lenacapavir (see clinical assessment below).

2.5.2.4. Pharmacodynamic drug interactions

See in Clinical Pharmacology

2.5.3. Pharmacokinetics

Studies have been performed to characterise the absorption, distribution, metabolism, and excretion (ADME) of lenacapavir, using the intended clinical route of administration (oral and subcutaneous [SC]), and the species selected for non-clinical safety testing, i.e. rats and dogs as the main non-clinical species but also rabbits and monkeys.

Methods of analysis

Lenacapavir 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 [^{14}C]-lenacapavir in rats and dogs was assessed by liquid scintillation counting (LSC), quantitative whole-body autoradiography (QWBA) and/or profiling by LC-^{14}C-HRMS. Lenacapavir in bile, faeces and urine from rats and dogs was quantified by a LC-MS/MS method.

Absorption

Lenacapavir showed low forward and high reverse permeability through monolayers of Caco-2 with evidence of efflux transport.

Single dose pharmacokinetics of lenacapavir 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 V_{ss} (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 $t_{½}$. The mean plasma elimination half-life was estimated to 38 hours in rat and 30 hours in dog.

As lenacapavir 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:lenacapavir:water [Solution Formulation B]) with various concentrations of lenacapavir 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 $t_{1/2}$ ranged from 219 to 403 hours in rats and from 66 to 525 hours in dogs, which are substantially longer than the mean $t_{1/2}$ 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 AUC_{inf} 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 lenacapavir from Solution Formulation A was somewhat more sustained than from the aqueous suspension. Administration of lenacapavir sodium salt resulted in comparable mean AUC_{inf} 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 lenacapavir 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. See toxicokinetics in the section for Toxicology.

Distribution

Tissue distribution in albino and pigmented rats following a single IV administration of 3 mg/kg was evaluated by QWBA. The pattern of [^{14}C]-lenacapavir-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 [^{14}C]-lenacapavir-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 lenacapavir 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.

Lenacapavir (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 lenacapavir 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 lenacapavir to pass the placenta or to be excreted into milk is not known. This is reflected in SmPC section 5.3.

Metabolism

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

In vitro

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

Lenacapavir 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 [^{14}C]-lenacapavir 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 [^{14}C]-lenacapavir, respectively, or of dogs following a single oral administration of 2 mg/kg [^{14}C]-lenacapavir. Unchanged lenacapavir (as atropisomers 1 and 2 combined) represented a predominant part (approximately 99%) of the total radioactivity in plasma of rats and dogs. Lenacapavir 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.

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 [^{14}C]-lenacapavir 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 [^{14}C]-lenacapavir-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 P-gp and BCRP inhibitor to rats suggest that intestinal secretion of lenacapavir 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.

2.5.4. Toxicology

The toxicological programme is intended to represent a proposed clinical regimen of one initial combination of a 600 mg oral tablet dose and a 927 mg SC injection dose on day 1 (d1), followed by a 600 mg tablet on d2 and subsequently a 927 mg SC injection every 26 weeks. The SC injections generate a depot that nominally allows the interval of 26w between injections. 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 generated more or less the same toxicity findings. Oral exposure did not generate any toxicity (repeat-dose toxicity or in DART-EFD).

2.5.4.1. Single dose toxicity and Repeat dose toxicity

Mortality: No rats or dogs died prematurely after a single lenacapavir IV infusion or after oral exposure. No rats died/were terminated after SC exposure whereas some dogs (n=3) were died/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 gall-bladder 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 lenacapavir 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 (see also Pharmacology in section 3.3.2).

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:

#Mouse: 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.

#Rat: 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 ~21-36% 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).

#Dog: In male and females 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 also 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 effect 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 lenacapavir can generate hepatobiliary toxicity in rats, dogs and possibly mice if achieving sufficient systemic exposure. 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 lenacapavir inhibition of dog Bile Salt Export Pump (BSEP) protein transporter (IC_{50} 0.12uM) (see Discussion below).

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 $AUC_{0\text{-}336h}$ 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}). *See Non-Clinical Discussion*.

2.5.4.2. Genotoxicity and Carcinogenicity

Lenacapavir 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 $AUC_{0\text{-}336h}$ 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 $AUC_{0\text{-}672h}$ 569000-616000 ng x h/mL, $AUC_{0\text{-}2184h}$ 640000-987000 ng x h/mL, and C_{max} 1470-2350 ng/mL).

The single dose dose-range finding study for a transgenic rasH2 carcinogenicity study was conducted (doses between 30 and 300 mg/kg, one dose followed by 13w observation). There were no signs of neoplasia or pre-neoplasia. Pivotal carcinogenicity studies are planned to be submitted and formally assessed post-approval. See also *Discussion*.

2.5.4.3. Reproductive and developmental toxicity

A standard Developmental and Reproductive Toxicity (DART) test set was conducted for lenacapavir. 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 $AUC_{0\text{-}672h}$ of 231000 ng x h/mL an Cmax of 587 ng/mL, and a human exposure margin of 0.83x (unadjusted $AUC_{0\text{-}672h}$) and 5.4x (adjusted $AUC_{0\text{-}672h}$).

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 $AUC_{0\text{-}24h}$ of 22000 ng x h/mL, a C_{max} of 1210 ng/mL, and a human safety margin of 0.08x (unadjusted $AUC_{0\text{-}24h}$) and 14.4x (adjusted $AUC_{0\text{-}24h}$).

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 non-pivotal rabbit study gave a 5 mg/kg $AUC_{0\text{-}24h}$ of 26600 ng x h/mL and C_{max} 7120 ng/mL (with unadjusted $AUC_{0\text{-}24h}$ margin of 0.1x and adjusted $AUC_{0\text{-}24h}$ margin 17.4x) and a 20 mg/kg $AUC_{0\text{-}24h}$ of 178000 ng x h/mL and Cmax 45700 ng/mL (unadjusted $AUC_{0\text{-}24h}$ margin of 0.64x, adjusted $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}192h}$ of 54800 ng x h/mL, an C_{max} of 412 ng/mL, and a human safety margin of 0.20x (unadjusted $AUC_{0\text{-}192h}$) or 4.5x (adjusted $AUC_{0\text{-}192h}$). The systemic exposure for 300 mg/kg between rat dams and PND10 offspring was ~5-6x more in mother compared to pups.

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 lenacapavir 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 are unclear.

2.5.4.4. Toxicokinetic data

For animal-to-human exposure margins, a clinical $C_{maxd1\text{-}w26}$ is 136.2 ng/mL and $AUC_{d1\text{-}w26}$ 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 $AUC_{0\text{-}336h}$ 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 proposed 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 $AUC_{0\text{-}672h}$ 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). In a similar rat study for impurity qualification (single SC dose followed by 13w recovery), the NOAEL of 100 mg/kg corresponding to an average $AUC_{0\text{-}672h}$ 569000-616000 ngxh/mL, $AUC_{0\text{-}2184h}$ 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 $AUC_{0\text{-}672h}$) or 13.1x-14.4x (adjusted $AUC_{0\text{-}672h}$).

#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 $AUC_{0\text{-}168.5h}$ 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 172-541h (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.

The applicant mainly uses a time-adjusted AUC (human: 26w) for safety margin calculations (presumably e.g., 13 x $AUC_{0\text{-}336h}$ or 6.5 x $AUC_{0\text{-}672h}$). 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) and possibly developmental/reproductive toxicity.

2.5.4.5. Local Tolerance

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 lenacapavir-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).

In-vivo studies – Rat: In a rat acute toxicity study (single exposure 3-30 mg/kg IV infusion over 30 min, lenacapavir 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 lenacapavir 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.

2.5.4.6. Other toxicity studies

Antigenicity: A total set of four skin sensitisation tests were conducted. Out of those, lenacapavir sodium 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 lenacapavir in dimethylforamamide applied to mice.

Phototoxicity: A phototoxicity assessment of lenacapavir sodium 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), lenacapavir is unlikely to have a phototoxic potential.

2.5.4.7. 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.

See discussion below on additional impurity concerns.

2.5.5. Ecotoxicity/environmental risk assessment

Lenacapavir is a small molecular weight chemical with a molecular weight of 990.3 g/mol. The water solubility of lenacapavir 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 D_{ow} values of 5.9 (pH 5), 5.3 (pH 7) and 3.6 (pH 9). As such, there may be an increased likelihood of bioaccumulation. With regard to environmental exposure, the average daily exposure across a year is estimated to be 8.37 mg/day (total exposure of 927mg+600mg = 1527 mg on d1 followed by 600mg on d2 and 927 mg on d184, divided by 365d). Based on a Fpen of 0.01, the phase I default PECsw is 0.042ug/L (action limit >0.01 ug/L).

Based on an OECD TG301B study, lenacapavir is not readily biodegradable in sewage sludge. Lenacapavir had no acute (3h) toxicity effect on sludge microorganisms (NOEC 1000 mg/L). Aquatic toxicity assessment with algae did not identify any toxicity after 72h exposure but it was found that the lenacapavir concentration in the solution with algae decreased to 36% of initial at the end of the test – indicating that the presence of algae affects lenacapavir levels (giving a measured time-weighted average NOEC of 2.7 ug/L). Preliminary assessment shows that lenacapavir affects Daphnia (OECD TG211) with a NOEC of 3.1 ug/L, fish (OECD TG210) with a NOEC of 2.1 ug/L, sediment-dwellers (OECD TG218) with a NOEC of 108 mg/kg and EC10 at 465 mg/kg dwt, and that it is highly adsorbed to sludge (Kd > 10000 L/kg) – making a terrestrial Phase IIB assessment necessary.

Several ecotoxicological studies are missing and are planned to be submitted before end of 2022 (see also Discussion below). While some of these studies have been submitted after the first round (see below in table) within the MAA procedure, a full ERA assessment has to wait until all studies have been submitted. As such, the available information does not allow to conclude definitively on the potential risk of lenacapavir to the environment.

Table 1 Summary of main study results

Substance (INN/Invented Name): Lenacapavir (GS-6207)					
CAS-number (if available): 2189684-45-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD TG123	Log D_{ow} (pH 5 and pH7) >4.5			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log *D*	5.9 (pH 5) 5.3 (pH 7) 3.6 (pH 9)			B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound has to be assessed for PBT properties.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
Default Phase I PECsw	0.042	µg/L			> 0.01 threshold (Y)
Other concerns (e.g., chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD TG106	*Sludge* *K_{d1} = 43160 L/kg* *K_{d2} = 40326 L/kg* *K_{oc1} = 128452 L/kg* K_{oc2} = 113277 L/kg *Soil* K_{d1} = 2216 L/kg K_{d2} = 1540 L/kg K_{d3} = 2225 L/kg K_{oc1} = 137618 L/kg K_{oc2} = 236953 L/kg K_{oc3} = 125003 L/kg			Submitted in round 2* Indicates high/very adsorption to sludge and moderate to high adsorption to soil.
Ready Biodegradability Test	OECD TG301B	8-10% < 60% Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not planned unless necessary for PBT.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata, 72h exposure*	OECD TG201	Measur. NOEC	2.7	ug/L	*Raphidocelis subcapitata* *Degradation or adsorption of test substance to algae, reducing concentration over time to 36%, giving a*

					time-weighted average measured NOEC
Daphnia sp. Reproduction Test	OECD TG211	NOEC LOEC	3.1 >3.1	µg/L µg/L	Submitted in round 2* **NOEC is a time weighted average value.**
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC LOEC	2.1 3.8	µg/L µg/L	Submitted in round 2*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC EC50	1000 >1000	mg/L mg/L	
Phase IIb Studies					
Bioaccumulation	OECD TG305	BCF		L/kg	Ongoing %lipids: Remains to be submitted. **OC**
Aerobic and anaerobic transformation in soil	OECD TG307	DT50 $\%CO_2$			Remains to be submitted. **OC**
Soil Microorganisms: Nitrogen Transformation Test	OECD TG216	%effect		mg/kg	Remains to be submitted. **OC**
Terrestrial Plants, Growth Test/*Species*	OECD TG208	NOEC		mg/kg	Remains to be submitted. **OC**
Earthworm, Acute Toxicity Tests	OECD TG207	NOEC		mg/kg	Remains to be submitted. **OC**
Collembola, Reproduction Test	OECD TG232	NOEC		mg/kg	Remains to be submitted. **OC**
Sediment-dwelling organism	OECD TG218	NOEC LOEC EC10	108 225 465	mg/kg	Submitted in round 2* Unit is mg/kg dwt

* A full ERA assessment of the new studies and the conclusions of the ERA after round 1 has to wait until all studies have been submitted.

2.5.6. Discussion on non-clinical aspects

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Lencapavir to the environment.

The applicant commits to perform the following studies as follow-up measure:

Phase II studies remain to be submitted but available data indicates the need for a full Phase II ERA (Phase IIA and IIB). The applicant is committed to providing those studies when completed.

Pharmacokinetic aspects

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 Tl_{ast} (72h). The oral bioavailability (Fpo) originally listed as about 22% based on calculations using AUC_{inf} was not considered accurately determined given the incomplete curves with respect to the long elimination time of the drug (>30 h) and a Tlast of 72 h. Oral bioavailability of about 15% in rats and 22% in dogs estimated based on AUC_{last}, i.e. $AUC_{0\text{-}72h}$, 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 IC_{50} 0.12uM). Liver effects were indeed seen at doses that resulted in C_{max} and C_{ave} 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. 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 Cmax 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 lenacapavir generally generated long-lasting local effects of oedema, granulomatous inflammation, and necrosis in all animal models (the last 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. 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. 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 and do not necessitate a mention in SmPC 5.3.

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).

Lenacapavir has not demonstrated any genotoxicity signals. No carcinogenicity studies have been submitted except a dose-range finding transgenic RasH2 study (which did not find any signs of neoplasia). A 6-month transgenic mouse (TgRasH2) and a 2-year rat carcinogenicity studies with lenacapavir are stated to be in progress becoming available between end of 2021 and early 2023). As the intended patient population allows the option of post-approval submission, and there are no clear warnings signals for oncogenicity, the post-approval submission approach is acceptable.

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 463.5 mg per injection site is considered the largest dose – which is only relevant for the local tissue sound the depot, this dose will be used as the maximum dose for impurity calculations (instead of the proposed systemic exposure estimate based on the oral dose plus some minor addition from the depot dose [600mg+50mg]).

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.

SmPC

Regarding non-clinical SmPC text, the applicant has proposed a SmPC 4.6 text stating that animal studies do not indicate direct or indirect harmful effects with respect to fertility parameters, pregnancy, foetal development, parturition or postnatal development. The proposed SmPC text also notes that after administration to rats during pregnancy, lenacapavir was detected at low levels in the plasma of nursing rat pups, without effects on these nursing pups. There are no indications of adverse effects on lenacapavir on male or female rat fertility. It is agreed that the there is an absence of adverse DART signals.

Environmental risk assessment

Most Phase II studies remain to be submitted but available data indicates the need for a full Phase II ERA (Phase IIA and IIB). The applicant is committed to providing those studies before end 2022. It can be noted that unless found necessary based on PBT considerations, no OECD TG308 will be conducted (in line with the recommendations of the Draft CHMP ERA guideline from 2018). For the PECsw calculation, prevalence data for adults (15-49 years; 0.8% in 2020 according to UNAIDS) is used as the European worst-case scenario. As a result of the missing studies, the available data do not allow to conclude definitively on the potential risk of lenacapavir to the environment.

2.5.7. Conclusion on the non-clinical aspects

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

The CHMP considers the following measure necessary to address the non-clinical issues:

Phase II studies remain to be submitted but available data indicates the need for a full Phase II ERA (Phase IIA and IIB). The applicant is committed to providing those studies when completed (REC).

2.6. Clinical aspects

2.6.1. Introduction

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.

- **Tabular overview of clinical studies**

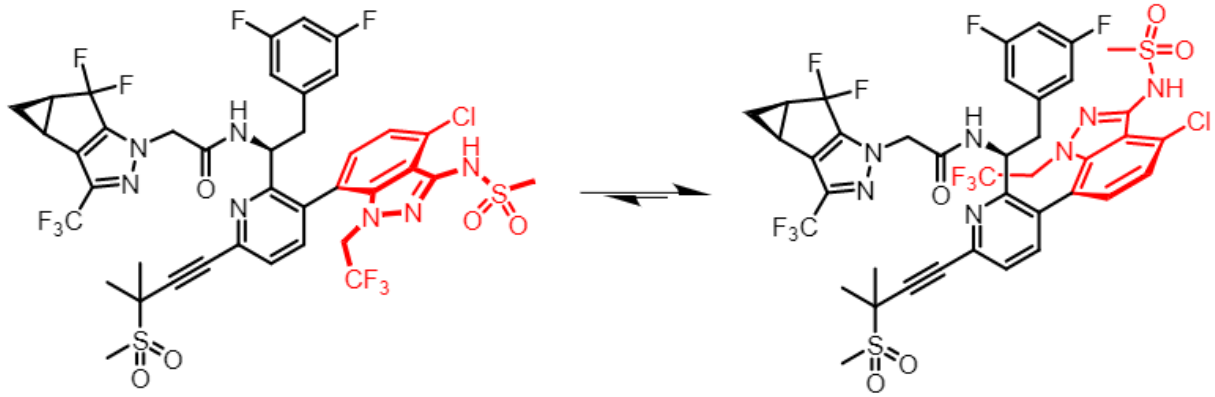
Study Number	Study Description	Test Treatment(s)		
		Dosage Form	Dose	n[a]
GS-US-200-4070	Phase 1 placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC LEN in healthy participants	LEN FA 100-mg/mL suspension	30 mg 100 mg 300 mg 450 mg	32
GS-US-200-4071	Phase 1 single- and multiple-dose study evaluating the safety, tolerability, and PK of various LEN oral formulations and the effect of food on the PK of LEN oral tablets in healthy participants	LEN FA 50-mg/mL capsules	30 mg 100 mg 300 mg	88
		LEN FA 100-mg/mL capsules	75 mg 300 mg	
		LEN 50-mg tablet	50 mg	
		LEN 300-mg tablet	300 mg 900 mg 1800 mg	
GS-US-200-4072	Phase 1b randomized, double-blind, placebo-controlled monotherapy study in PWH (Part A)	LEN FA 100-mg/mL injectable suspension	20 mg 50 mg 150 mg 450 mg 750 mg	29
GS-US-200-4329	Phase 1 mass-balance study to evaluate the PK, metabolism, and excretion of a single intravenous dose of radiolabeled [^{14}C]-LEN in healthy participants	LEN 3-mg/mL solution	10 mg	18
		[^{14}C]LEN 3-mg/mL[c] solution (~30 µCi/mL)	20 mg	
GS-US-200-4330	Phase 1 study to evaluate the PK of single-dose LEN in participants with normal and severe renal impairment	LEN 300-mg tablet	300 mg	20
GS-US-200-4331	Phase 1 study to evaluate the PK of single-dose LEN in participants with normal or impaired hepatic function	LEN 300-mg tablet	300 mg	20
GS-US-200-4332	Phase 1 study to evaluate the effect of LEN on QT/QTc interval in healthy participants	LEN 300-mg tablet Moxifloxacin 400-mg tablet	600 mg	97

Study Number	Study Description	Test Treatment(s)		
		Dosage Form	Dose	n[a]
GS-US-200-4333	Phase 1 study to evaluate the effect of transporters and cytochrome P450 enzyme inhibitors on the PK and safety of LEN in healthy participants	LEN 300-mg tablet LEN 50-mg capsule	300 mg	291
		COBI 150-mg tablet	150 mg	
		DRV/COBI 800/150-mg tablet	800/150 mg	
		VORI 200-mg tablet	200 mg 400 mg	
		ATV/COBI 300/150-mg tablet	300/150 mg	
		RIF 300-mg tablet	600 mg	
		EFV 600-mg tablet	600 mg	
		FAM 40-mg tablet	40 mg	
		PIT 2-mg tablet	2 mg	
		ROS 5-mg tablet	5 mg	
		TAF 25-mg tablet	25 mg	
		MDZ 2-mg/mL oral syrup	2.5 mg	
GS-US-200-4538	Phase 1 placebo-controlled, single ascending dose study to evaluate the safety, tolerability, and PK of SC solutions of LEN in healthy participants	LEN SC Formulation 1 (300 mg/mL, FA)	300 mg	100
		LEN SC Formulation 2 (309 mg/mL, NaS)	309 mg 927 mg	
		LEN SC Formulation 3 (155 mg/mL, NaS)	309 mg 927 mg	
		LEN SC Formulation 4 (300 mg/mL, NaSP)	900 mg	
		LEN SC Formulation 6 (75 mg/mL, NaSP)	75 mg 225 mg	
		LEN SC Formulation 7 (50 mg/mL, NaSP)	50 mg	
GS-US-200-5709	Phase 1 study to evaluate the safety, tolerability, and PK of multiple-dose oral and/or SC LEN in healthy participants	LEN 300-mg tablet	300 mg 600 mg	60
		LEN SC (309 mg/mL, NaS)	927 mg	
GS-US-200-4334	Phase 2 randomized, open-label, active-controlled study evaluating the safety and efficacy of LEN in combination with other antiretroviral agents in PWH	LEN 300-mg tablet	50 mg 300 mg 900 mg	182
		LEN 50-mg tablet		
		LEN SC (309 mg/mL, NaS)	927 mg	
		DVY™ 200/25-mg tablet	200/25 mg	
		TAF 25-mg tablet	25 mg	
		BIC 75-mg tablet	75 mg	
GS-US-200-4625	Phase 2/3 randomized, placebo-controlled study to evaluate the safety and efficacy of LEN in combination with an optimized background regimen in heavily treatment-experienced PWH with multidrug resistance	LEN 300-mg tablet	300 mg 600 mg	72
		LEN SC (309 mg/mL, NaS)	927 mg	

2.6.2. Clinical pharmacology

Pharmacokinetics

Lenacapavir (LEN; GS-6207) is a novel, 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).



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 were developed: 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 2/3 study.

The proposed indication is: *in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.*

On treatment Day 1 and Day 2, the recommended dose of Lenacapavir is 600 mg per day taken orally. On treatment Day 8, the recommended dose is 300 mg taken orally. Then, on treatment Day 15, the recommended dose is 927 mg administered by subcutaneous injection. This is followed by 927 mg of Tradename administered by subcutaneous injection once every 6 months.

Methods

Bioanalysis

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.

Pharmacokinetic data analysis

A non-compartmental analysis and a population PK (popPK) analysis were used.

The popPK analyses (CTRA-2021-1054 LEN PopPK) were performed using Nonlinear mixed effects modelling and the first order conditional estimation method with interaction. PK data from the oral

tablets, and LEN sodium salt solutions (150 and 300 mg/mL) from five Phase 1 studies (GS-US-200-4071, GS-US-200-4329, GS-US-200-4333, GS-US-200-4538, and GS-US-200-5709), 1 Phase 2 study (GS-US-200-4334), and 1 Phase 2/3 study (GS-US-200-4625) were included in the analysis. The PopPK model was used to simulate individual PK and the impact of delayed maintenance SC doses based on varying lenacapavir treatment adherence.

The popPK analysis dataset included 7053 samples from 384 participants with at least 1 measurable concentration. A total of 198 samples (2.8%) were BLQ and were excluded from the analysis. No information was missing for available PK samples or continuous covariate data. There were no outliers identified in the dataset.

The following covariates were evaluated for their ability to explain variability in the popPK model parameters: booster effects (tenofovir alafenamide [TAF], emtricitabine/tenofovir alafenamide [F/TAF], bictegravir/emtricitabine/tenofovir alafenamide [B/F/TAF], bictegravir, TAF + F/TAF, F/TAF + bictegravir, cobicistat [COBI], ritonavir, darunavir, all other ARVs), baseline body weight (WT), body surface area, age, sex, race, ethnicity, dose, healthy status (HIV, HV), food, formulation (tablet, sodium salt solution 300 mg/mL, sodium salt solution 150 mg/mL, intravenous solution) and baseline estimated glomerular filtration rate (mL/min). Correlations between the PK parameters and the covariates were explored graphically, followed by linear regression or analysis of variance testing. These analyses were conducted on individual specific random effects for the PK parameters. Covariates that showed a statistically significant ($P < 0.01$) effect and that could be meaningfully explained from both a clinical and scientific perspective were examined further. To identify potentially significant covariate effects, covariates were added to each of the PK parameters (univariate testing) in the popPK analysis. Covariates that yielded a significant decrease in −2 times the log likelihood function and resulted in a significant decrease in the log likelihood ratio test were retained for further analysis. A stepwise forward addition ($P < 0.01$) and backward elimination ($P < 0.001$) strategy was then used to identify the final popPK model.

The final model was a 2-compartment model with first-order absorption after oral administration, parallel direct (first-order) and transit compartment absorption after SC administration, and first-order elimination from the central compartment.

The covariate model resulting from the stepwise covariate analysis was found to be unstable with terminated minimisation. A number of attempts were made to increase model stability. The final PK parameter estimates are shown in the **Table *2*** below.

Table 2 Comparison of Lenacapavir Final Model Estimates and Bootstrap results

Parameter	Final PopPK Model Estimate [RSE][a]	Bootstrap Final Model Median Estimate [2.5th; 97.5thPercentiles]
θ_1: Clearance (L/h)	4.05 [15%]	4 [3.15; 4.97]
θ_2: Central volume (L)	68 [7%]	67.8 [60.8; 78.1]
θ_4: Peripheral volume (L)	908 [16%]	906 [677; 1190]
θ_5: Intercompartment clearance (L/h)	41.2 [6%]	41 [37.2; 46.4]
θ_3: PO absorption rate constant, k_a (1/h)	0.0287 [11%]	0.0288 [0.0233; 0.0368]
θ_6: SC transit absorption rate constant, k_{tr} (1/h)	0.00201 [3%]	0.00201 [0.0019; 0.00215]
θ_7: SC direct absorption rate constant, k_{dir} (1/h)	0.000376 [8%]	0.000373 [0.000305; 0.000441]
θ_9: PO bioavailability relative to IV, F_{po}	0.0624 [15%]	0.0617 [0.0472; 0.0797]
θ_{11}: Dose effect on PO bioavailability	−0.412 [13%]	−0.414 [−0.505; −0.299]
θ_{19}: Booster effect on PO bioavailability	0.587 [32%]	0.57 [0.262; 1.03]
θ_8: SC fraction for direct absorption	0.42 [5%]	0.422 [0.381; 0.477]
θ_{10}: SC bioavailability relative to IV, F_{sc}	1.03 [16%]	1.02 [0.801; 1.27]
θ_{12}: Dose effect on CL	0.0864 [44%]	0.0841 [0.0226; 0.157]
θ_{13}: Healthy volunteer effect on CL	0.304 [29%]	0.306 [0.157; 0.45]
θ_{14}: Weight effect on CL and Q	0.75 [Fixed]	Fixed
θ_{15}: Weight effect on V_c and V_p	1 [Fixed]	Fixed
θ_{16}: Healthy volunteer effect on V_p	1.33 [18%]	1.31 [0.949; 1.81]
θ_{17}: Age effect on CL	−0.238 [39%]	−0.234 [−0.41; −0.0578]
θ_{18}: Female effect on CL	−0.204 [24%]	−0.201 [−0.286; −0.103]
θ_{20}: SC 150 mg/mL effect on V_p	−0.794 [6%]	−0.791 [−0.889; −0.651]
θ_{21}: SC 150 mg/mL effect on k_{tr}	0.435 [27%]	0.432 [0.18; 0.687]
ω_{11}: IIV on CL (%CV)	44 [9%]	42.8 [38.7; 47.3]
ω_{33}: IIV on V_p (%CV)	85 [11%]	84.2 [75.7; 93.8]
ω_{44}: IIV on k_{tr} (%CV)	32 [18%]	32.3 [25.5; 38.9]
ω_{55}: IIV on k_a (%CV)	78 [9%]	77.9 [71.3; 85.2]
ω_{77}: IIV on F_{sc} (%CV)	39 [21%]	39.1 [29.6; 46.9]
σ_1: Residual proportional variability (%CV)	27 [4%]	27.2 [26.2; 28.3]
σ_2: Residual additive (ng/mL)	0.025 [Fixed]	Fixed

%CV = percentage coefficient of variation; IIV = interindividual variability; IV = intravenous; PO = oral; PopPK = population pharmacokinetic; RSE = relative standard error; SC = subcutaneous; SE = standard error
a RSE is defined as the SE divided by the θ × 100%.
Source: lena-gof-final-20210414.R

A sensitivity analysis was performed to determine the impact of relevant covariates on lenacapavir exposure based on the Phase 2/3 posology. Lenacapavir exposures (AUC_{tau}, C_{max}, and C_{trough}) were simulated using the Bayesian post hoc PK parameters. For the oral portion, the COBI/RTV booster effects were the most influential covariates with an increase in lenacapavir exposures of 58.8%

(**Figure *2***). These were followed by WT effects with a percent change in lenacapavir exposures ranging from approximately −32.3% to +23.5% (relative to the median exposures) for participants with extreme covariate values (ie, 5th and 95th WT percentiles), respectively.

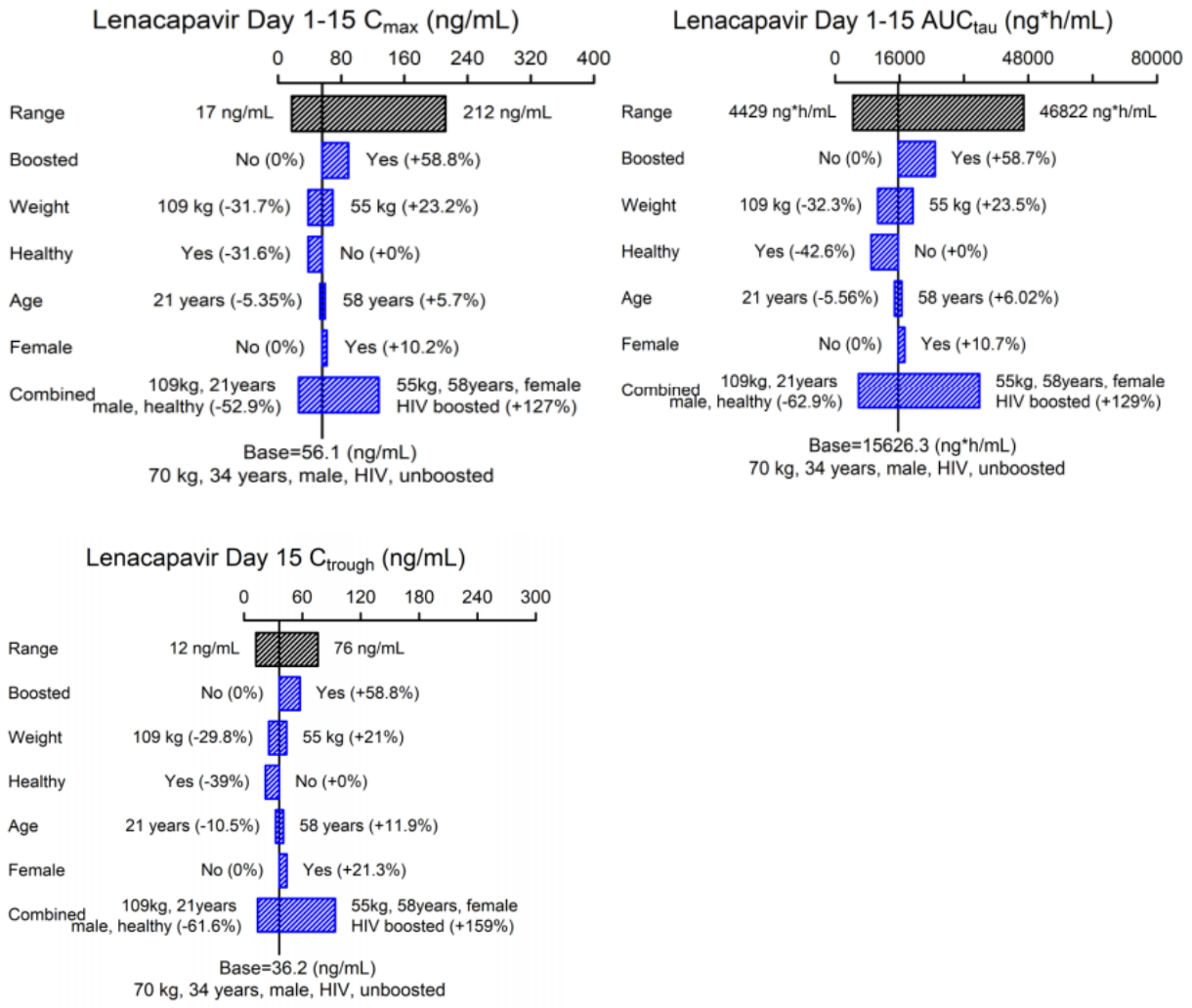


Figure 3 Sensitivity Plot Comparing the Effect of Covariates on Lenacapavir AUC_{tau}, C_{max}, and C_{trough} on Days 1 to 15 (Oral Loading Portion) based on the Phase 2/3 posology

Base, as represented by the black vertical line and values, refers to the median post hoc AUCtau, Cmax, and Ctrough on Days 1 to 15 of lenacapavir. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire analyzed population. Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. The upper and lower values for each covariate capture 90% of the plausible range in the population. Source: Figure 8 in CTRA-2021-1054 LEN PopPK

For exposure associated with the SC administration on Day 15, age, weight, and healthy volunteers were the most influential covariates with changes in lenacapavir exposures of approximately 50% for all 3 covariates. Sex was a minimally influential covariate (**Figure *3***).

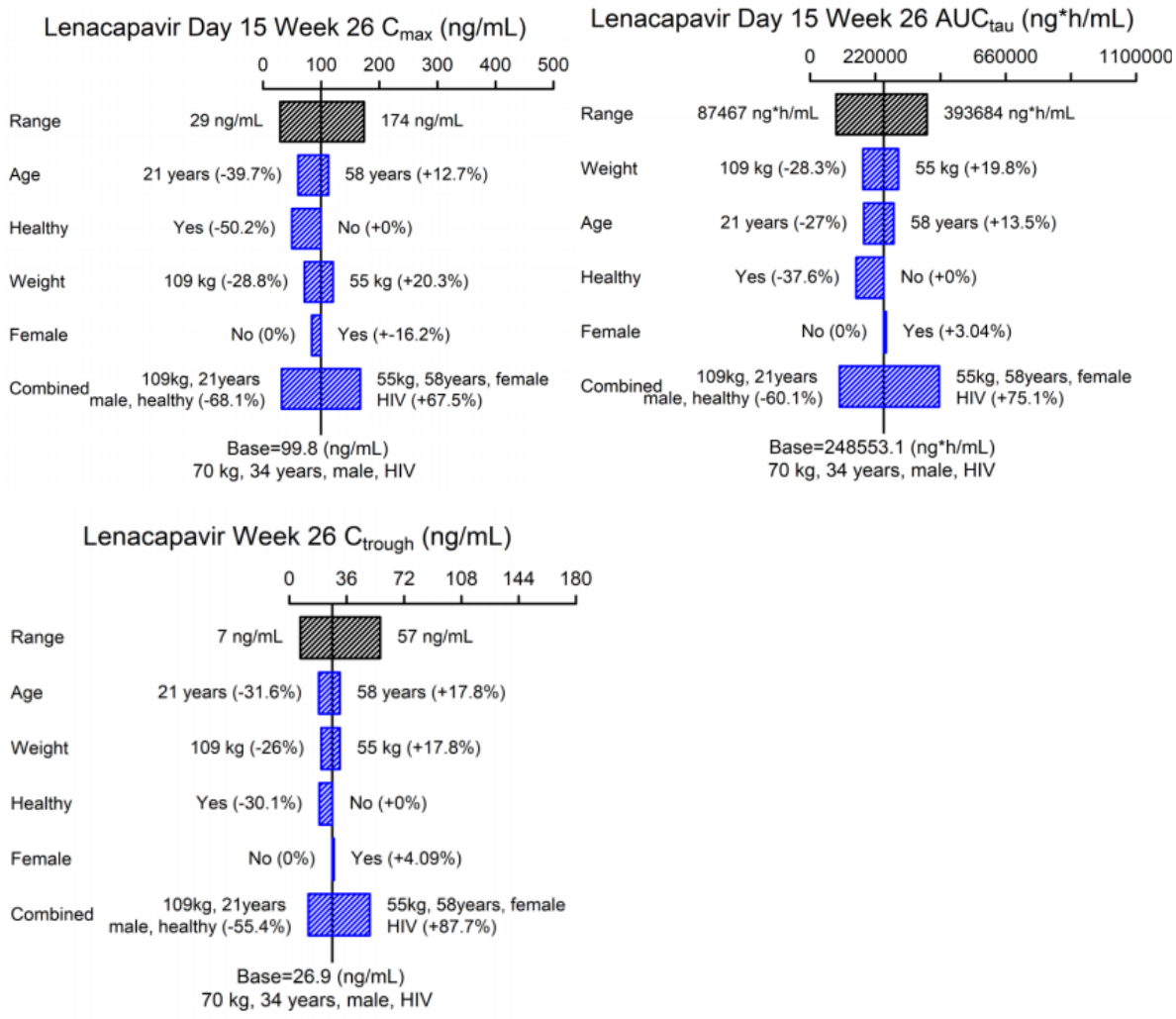


Figure 4 Sensitivity Plot for AUCtau, Cmax, and Ctrough Day 15-Week 26 (SC Administration)

Base, as represented by the black vertical line and values, refers to the median post hoc AUCtau, Cmax, and Ctrough on Day 15 Week 26 of lenacapavir. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the entire analyzed population. Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. The upper and lower values for each covariate capture 90% of the plausible range in the population. Source: Figure 8 in CTRA-2021-1054 LEN popPK

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 SC 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).

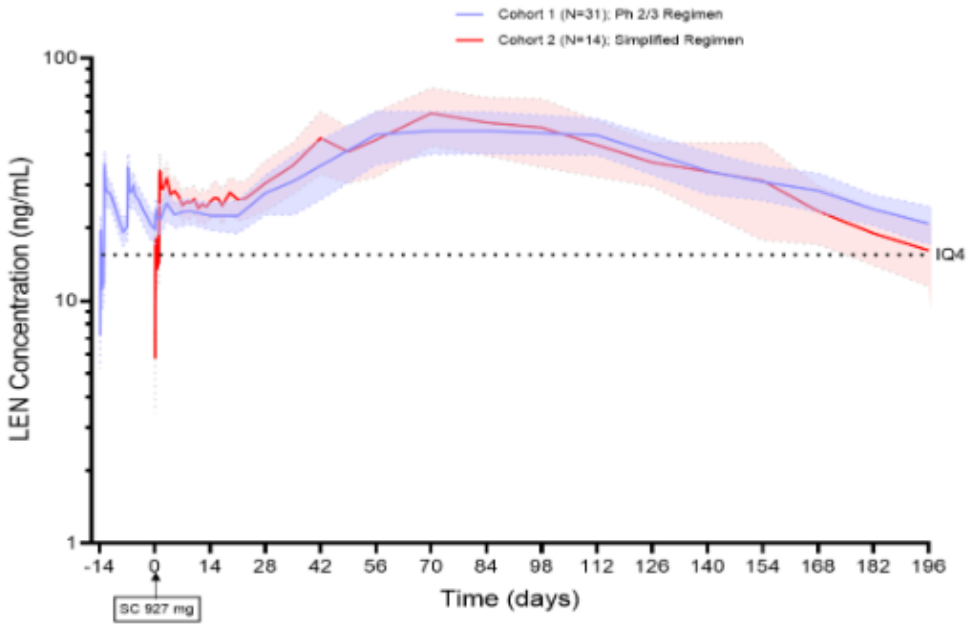
Bioavailability

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 oral bioavailability was approximately 10% following administration of LEN 300 mg. LEN seemed to be completely absorbed after SC administration (F_{sc} approximately 100%).

Based on population PK modelling, the oral bioavailability for LEN 600 mg tablets was estimated to approximately 6%, whereas the SC bioavailability was estimated to approximately 100% in patients with HIV.

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

Interim data from the study in healthy volunteers comparing the Phase 2/3 regimen with the simplified regimen (oral LEN 600 mg and SC LEN injection 927 mg on Day 1, oral LEN 600 mg on Day 2 followed by SC LEN injection 927 mg every 6 months thereafter) is included in figure below (study GS-US-200-5709).



*Blue and pink shaded areas represent 90% confidence interval band for the mean profile for Cohort 1 and Cohort 2, respectively; Horizontal dotted line shows IQ4 of 15.5 ng/mL. On X-axis, values -14 to 0 represent 14-day oral lead-in period for Cohort 1

Figure 5 Mean (90%CI) lenacapavir plasma concentration/time profiles with the phase 2/3 and the simplified posology.

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.

No food effect was observed in the population pharmacokinetic analysis.

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

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.

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 (Vz/F) were 19 240 L (65%) and 51 077 (65%), respectively (study GS-US-200-4071).

The mean (CV%) Vz/F was 11675 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 IV 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).

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 1986L. Based on popPK analysis the CL was estimated to 4.05 L/h for a typical 70-kg patient with HIV.

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). The mean apparent CL was approximately 4.3 L/h.

In the mass balance study GS-US-200-4329, lenacapavir was primarily eliminated in the faeces via biliary excretion mediated by PgP (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 postdose, with levels of radioactivity being below the limit of quantitation by 576-600h in urine and 2784-2808h in faeces.

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-$C_9H_9NO_3$ 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-CO_2 adduct (M46), each of which accounted for < 2% of the dose. The proposed biotransformation pathways are summarised in the figure below.

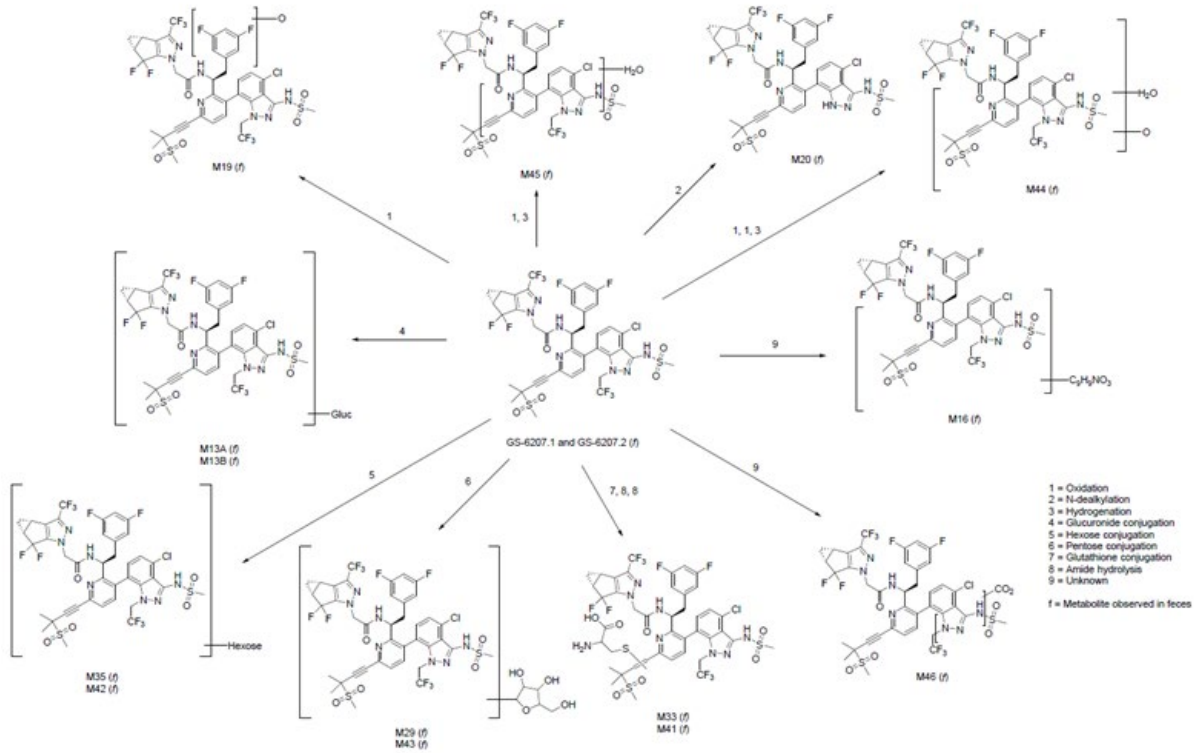


Figure 6 Proposed Major Biotransformation and Excretion Pathway for Lenacapavir in Humans. Source: GS US 200-4329 CSR

Dose proportionality, time dependencies and variability

Dose proportionality has not been studied after repeated SC administration.

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).

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).

Using the developed popPK model, 2 SC doses at Day 1 and week 26 were simulated. The accumulation ratio was derived using the AUC Day 1 to Week 26 and the AUC Weeks 26 to 52. The median (5^{th} and 95^{th} percentiles) of the resulting accumulation ratio is 1.17 (1.09 to 1.51). Steady state was estimated to be reached after/at the third SC dose. This range was confirmed by new data from study GS-US-200-4625 (see table below), where C_{trough} at Week 52 (40.8 ng/mL, 51.0%CV) was 1.14-fold higher compared with Week 26 (35.9 ng/mL, 57.1%CV). Comparable accumulation was observed in study GS-US-200-4334.

Table 3 GS-US-200-4625: Plasma Pharmacokinetic Parameters of LEN Following Oral 600 mg Daily Dosing (Days 1 and 2) and 300 mg (Day 8), With SC LEN Injection Every 26 Weeks Starting From Day 15 (Day 1 SC)

PK Parameter Mean (%CV)	Day 2[a] (N = 70)	Day 8[a] (N = 72)	Day 15[a] (N = 72)	Week 26 (N = 69)	Week 52 (N = 37)
C_{trough}[b] (ng/mL)	55.0 (116)	61.0 (70.9)	50.5 (66.1)	35.9 (57.1)	40.8 (51.0)
Lower 90% CI of C_{trough}[b] (ng/mL)	42.3	52.5	44.0	31.8	35.0

%CV = percentage coefficient of variation; CI = confidence interval; LEN = lenacapavir (GS-6207); PK = pharmacokinetic; SC = subcutaneous
For Cohort 1B, Days 16 and 22 reflect Days 2 and 8 respectively, relative to the start of oral LEN.
a An SC dose was administered on Day 15 of the dosing regimen.
b C_{trough} and pre-dose concentration used interchangeably to show the last concentration prior to the next dose
Source: GS-US-200-4625 Week 52 PK analysis report (m 5.3.5.1)

In the popPK analysis, the inter-individual variability (CV%) was estimated to 44% for CL, 85% for V_p, 78% for Ka, 32% for Ktr and 39% for Fsc. Intra-individual (inter-occasion) variability was not included in the analysis. Intra-subject variability was not evaluated.

Target population

The intended commercial formulations are evaluated in the ongoing Phase 2 and 2/3 studies (studies GS-US-200-4334 and GS-US-200-4625) and are included in the popPK analysis. In these studies, lenacapavir was administered as 3-day loading regimen comprising single oral doses of LEN 600 mg, 600 mg, and 300 mg on Days 1, 2, and 8, respectively, followed by a SC maintenance dose of 927 mg administered once every 6 months, starting on Day 15. Mean LEN concentrations above IQ4 (15.5 ng/mL) were observed 2 days after start of LEN treatment and were maintained throughout the

duration of the PK follow-up (study GS-US-200-4334). The mean (CV%) C_{max} and AUC_{tau}, between Day 1 to week 26, were estimated to 93.1 ng/mL (62%) and 218 712 ng*h/L (48%), respectively. In study GS-US-200-4625, the mean (CV%) C_{max} and AUC_{tau}, between Day 1 to week 26, were estimated to 136 ng/mL (75%) and 277 903 ng*h/L (47%), respectively.

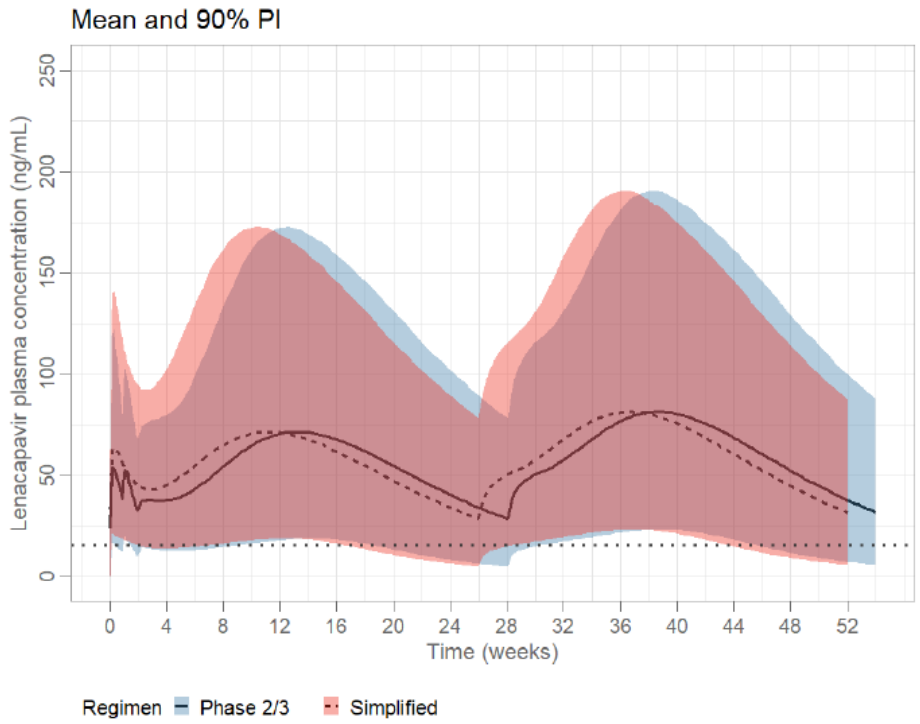
Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 29% to 84% higher in heavily treatment experienced patients with HIV-1 infection as compared to subjects without HIV-1 infection based on population pharmacokinetics analysis.

A new simplified posology is proposed and entails oral LEN 600 mg and SC LEN injection 927 mg on Day 1, oral LEN 600 mg on Day 2 followed by SC LEN injection 927 mg every 6 months thereafter. This new posology has only been studied in healthy subjects.

Both the original and the simplified dosing regimens were selected to target an exposure 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). The target of IQ4 is supported by the results of the dose ranging proof-of-concept study (study GS-US-200-4072).

The final model parameter estimates for lenacapavir were used to generate distributions of PK parameters based on IIV. The simulations were then conducted in R, with 100 repetitions for each patient (for a total of approximately 40,000 virtual patients). AUC_{tau}, C_{max}, and C_{tau} were calculated using the simulated individual PK profiles. Patient demographics were taken from the analysis dataset.

Simulated concentration-time profiles following the Phase 2/3 regimen and the simplified posology in adults PWH are shown below, whereas PK parameters for the phase 2/3 posology are shown in the table above. The mean C_{trough} of LEN following administration of LEN to PWH in the Phase 2/3 study at Day 15 and at Week 26 was 32.7 ng/mL and 29.3 ng/mL, respectively, resulting in an IQ of 8.4-fold and 7.6-fold above the $paEC_{95}$ (3.87 ng/mL) against WT HIV-1 virus.



IQ4 = inhibitory quotient 4; PI = prediction interval
The solid black line and blue shaded area represent the simulated mean and 90% PI lenacapavir concentrations in adult patients with HIV receiving the Phase 2/3 dosing regimen. The dashed black line and red shaded area represent the simulated mean and 90% CI lenacapavir concentrations in adult patients with HIV receiving the simplified dosing regimen. The horizontal dotted line represents the IQ4 threshold at 15.5 ng/mL.
Source: lena-pksim-20210416-regcomp-v2. R

Figure 7 Simulated Lenacapavir Concentration-Time Profile in Adult People With HIV Who Received the Phase 2/3 or the Simplified Dosing Regimen (Presented Versus IQ4 Threshold)

Table 4 Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration

	Day 1 and 2: 600 mg (oral), Day 8: 300 mg (oral), Day 16 927 mg (SC)		
Parameter Mean (%CV)[a]	**Day 1 to Day 15**	**Day 15 to end of month 6**	**Steady state**
C_{max} (ng/ mL)	69.6 (56)	87 (71.8)	97.2 (70.3)
AUC_{tau} (h•ng/mL)	15,600 (52.9)	250,000 (66.6)	300,000 (68.5)
C_{trough} (ng/mL)	35.9 (56.8)	32.7 (88)	36.2 (90.6)

CV = coefficient of variation; SC = subcutaneous
[a] Simulated exposures utilizing population PK analysis.

Simulations were performed to support the proposed dosing window, using the Phase 2/3 dose regimen. By following the missed dose recommendations as outlined for tablets, the simulations showed that the pharmacokinetic exposures are predicted to be within a reasonable range during days

1-15 following treatment initiation. Following SC administration of LEN every 6 month, the mean (90% CI) C_{trough} was 29.2 ng/mL (24.6, 32.5 ng/mL). If the maintenance SC dose is delayed by 2 weeks (ie, Week 28), mean (90% CI) LEN concentrations were predicted to be 24.5 (20.4, 27.3) ng/mL. If the maintenance SC dose is administered 2 weeks earlier (ie, Week 24) than the planned 26-week (6 months) dosing interval, LEN trough concentrations were predicted to be 34.6 (29.4, 38.5) ng/mL.

In the ongoing Phase 2 and Phase 2/3 studies, SC LEN doses are administered within 24 to 28 weeks from the previous SC LEN dose as per protocol. For participants who are not dosed within the 28-week window and continued in the studies, the oral LEN lead-in regimen is restarted prior to subsequent SC LEN administration (oral LEN 600 mg daily for 2 days followed by oral LEN 300 mg 6 days later, with SC LEN injection 927 mg restarting 1 week later).

Special populations

Population PK analysis that included mild and moderate renal impaired participants (N = 40, CLcr range 46.8 to 86.9 mL/min) did not identify renal function as a covariate on LEN exposure (CTRA-2021-1054 LEN PopPK).

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.

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.

Based on the popPK analysis, sex was identified as a statistically significant covariate for LEN PK. 298 males and 86 females were included in the analysis. The AUC was up to 11% higher in females than in males, C_{max} was higher or lower depending on the route of administration. Dose adjustment is not required as the exposure difference is not considered clinically meaningful.

Based on the popPK analysis, no effect of race or ethnicity was identified. 218 white, 146 black, 14 Asian and 6 others were included in the analysis.

Body weight was identified as a statistically significant covariate for LEN PK based on population PK analysis. The exposure decreased with increasing body weight. Participants weighing 41 to 164 kg were included. In a sensitivity analysis, the maximum percent change in LEN exposure was -32.3% to +23.5% (relative to the median exposures) for participants in the weight range 55 to 106 kg (5^{th} and 95^{th} WT percentiles). The impact of WT on the exposure was evaluated in studies GS-US-200-4625 and GS-US-200-4334. The exposures across body weight quartiles showed that there were no clinically relevant differences in the overall range and distribution of AUC and C_{max} for the dosing regimen. While C_{trough} was lower (39%) in quartile 4, it was well above the IQ4, suggesting no dose adjustment is warranted based on body weight.

Based on popPK analysis, age was identified as a statistically significant covariate on the PK of LEN. The exposure was higher in older subjects. Subjects aged 18 to 78 years were included in the analysis. In a sensitivity analysis, the maximum percent change in LEN exposure was -39.7% to 17.8% (relative

to the median exposures) for participants in the age range 21 to 58 years (5th and 95th age percentiles).

Table 5 Number of Participants 65 Years and Older Included in Clinical Studies GS US 200 4625 and GS-US-200-4334

	Age 65 to 74 Years (Number of Participants/Total Number)	Age 75 to 84 Years (Number of Participants/Total Number)	Age ≥ 85 Years (Number of Participants/Total Number)
Study GS-US-200-4625[b]	5[c]/72	1/72	0/72
Study GS-US-200-4334[d]	1/183	0/183	0/183

a Participants above 65 years of age were only enrolled in Studies GS-US-200-4625 and GS-US-200-4334. No other PK studies (including GS-US-200-4538, GS-US-200-5709, GS-US-200-4071, GS-US-200-4072, GS-US-200-4333, GS-US-200-4332) had participants above 65 years of age.
a Study GS-US-200-4625 includes all enrolled participants.
b PK data are available from 4 participants.
c Study GS-US-200-4334 includes all enrolled participants.

Use of LEN in paediatric participants has not been evaluated in clinical studies at this time. No adolescents have been enrolled in the LEN clinical development programme.

Pharmacokinetic interaction 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).

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 AUCinf 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.

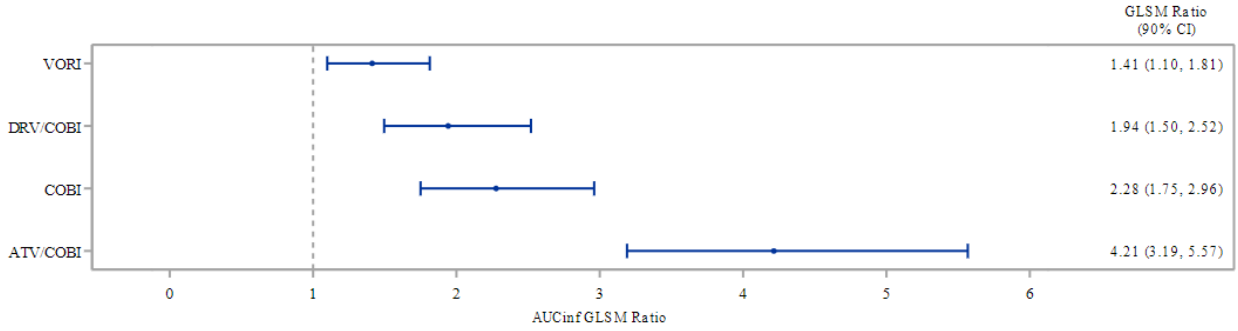
Coadministration of a single-dose LEN with the potent CYP3A4 inhibitor (VORI) under fasting conditions resulted in a 41% increase in AUC_{inf}, with no change in C_{max}.

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.

This figure presents a Forest plot of geometric mean ratios for AUCinf for LEN as a victim of inhibition by each inhibitor (COBI, DRV/COBI, VORI, and ATV/COBI) (Study GS-US-200-4333).



ATV = atazanavir; COBI = cobicistat; DRV = darunavir; GLSM = geometric least-squares mean; LEN = lenacapavir; PK = pharmacokinetic; VORI = voriconazole

Figure 8 GS-US-200-4333: Forest Plot of Geometric Mean Ratios for AUCinf for LEN as a Victim of Inhibition in Cohorts 2, 3, 5, and 7 (LEN PK Analysis Set)

Effect of lenacapavir on other medicines

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. Characterisation 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.

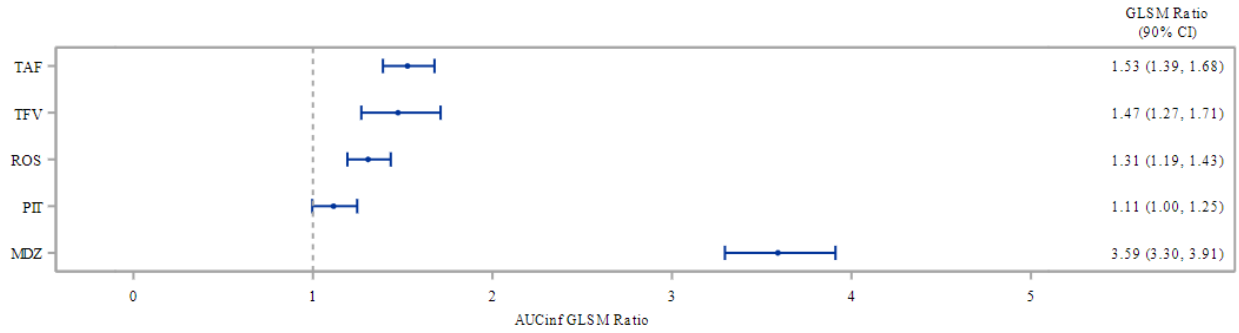
Coadministration of single-dose PIT (an OATP substrate) both simultaneously with LEN and staggered from LEN did not result in changes in PIT AUC_{inf} and C_{max}.

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.

This figure presents a Forest plot of geometric mean ratios for AUC_{inf} for LEN as a perpetrator for each probe substrate (PIT, ROS, TAF, and MDZ) in Cohort 11.



GLSM = geometric least-squares mean; LEN = lenacapavir; MDZ = midazolam; PIT = pitavastatin; PK = pharmacokinetic; ROS = rosuvastatin; TAF = tenofovir alafenamide; TFV = tenofovir

Figure 9 GS-US-200-4333: Forest Plot of Geometric Mean Ratios for AUCinf for LEN as a Perpetrator of Drug Interactions in Cohort 11 (LEN PK Analysis Set)

Exposure relevant for safety evaluation

Based on the initial population pharmacokinetic simulations, the mean (CV%) $AUC_{Day1\text{-}week\ 26}$ and $C_{max,Day\ 1\text{-}Week26}$ were 234295 ng*h/mL (65%) and 97.1 ng/mL (62%) using the simplified posology. These were used for the calculation of cutoffs for interactions.

At steady state with the simplified regimen, the mean (CV%) popPK simulated AUC_{tau} was 271687 ng*h/mL (70%), C_{max} 88.4 ng/mL (72%) and C_{trough} 32.3 ng/mL (94%).

The relevant PK parameters for the phase 2/3 posology are summarised in Table 4.

2.6.2.1. Pharmacodynamics

Mechanism of action

Biophysical Characterisation of LEN Binding to Recombinant HIV-1 Capsid Protein

Protein x-ray crystallography results indicated that LEN binds at the interface formed between two adjacent CA monomers within a CA hexamer, such that up to six molecules of LEN can bind to each CA hexamer. The central amide and pyridine ring make hydrogen bonds with Asn57 within the N-terminal domain (NTD) of one monomer, whereas the indazole and sulfonamide groups of LEN make hydrogen bonds with Gln179 and Asn183 within the C-terminal domain (CTD) of the neighboring monomer. 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-organised CA tubes assembled in the absence of LEN.

Inhibition of HIV-1 Early- and Late-Stage Replication Steps by LEN in MT- 2 Cells

LEN targets both an early and late stage capsid-mediated event essential for HIV-1 replication. LEN was also capable of irreversibly inactivating fully infectious cell-free HIV-1 virions with a mean virucidal EC_{50} of 25 nM.

Table 6 Antiviral Activity of LEN at Distinct Stages of HIV-1 Replication Cycle in MT-2 Cells

Compound[1]	EC_{50} (nM)[2]			
	Complete Replication Cycle (WT HIV-1)	Target Cell Infection (Early-Stage)	Virus Production and Maturation (Late-Stage)	Complete Replication Cycle (HIV-1 CA-M66I)
LEN	0.025 ± 0.003	0.023 ± 0.008	0.439 ± 0.181	> 50
RAL	1.7 ± 0.1	1.9 ± 0.8	> 1,000	1.8 ± 0.4
ATV	2.0 ± 1.0	> 1,000	2.3 ± 0.9	4.1 ± 0.8

1 ATV = atazanavir; RAL = raltegravir
2 EC_{50} and CC_{50} values represent mean (± SD) obtained from 3 independent experiments (Data from PC-200-2021).

Inhibition of Proper Capsid Core Formation and HIV-1 Assembly by LEN

The morphology of capsid structures was examined in ultrathin-sectioned HIV-1 (strain IIIB). Virions produced in the presence of LEN contained predominantly malformed capsid cores in which the nucleic acids were either regionally or diffusely confined within the irregularly shaped capsid core. This morphology was distinct from virus produced in the presence of an HIV-PI (ATV), which lacked any capsid-like structure. Virus produced in the presence of LEN or ATV was non-infectious when diluted below the EC_{50} concentration of each compound.

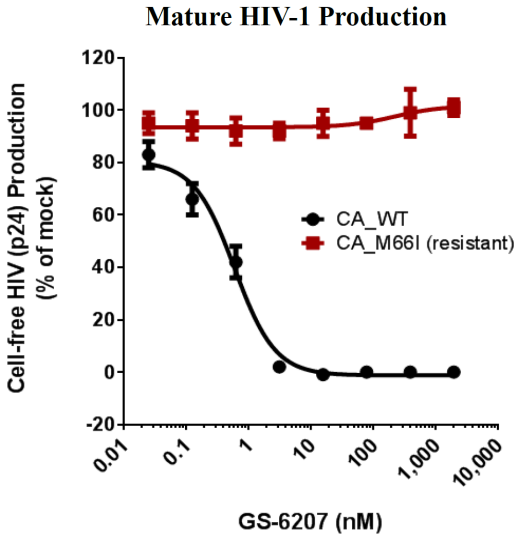
Virus production

Virus-producing HEK293T cells showed a dose-dependent reduction in the amount of mature HIV-1 released into the cell culture supernatant in the presence of LEN, with an EC_{50} of 0.305 nM.

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.

LEN did not inhibit Gag polyprotein cleavage in virus-producing cells but significantly reduce intracellular capsid (p24), and to a lesser extent, Gag (p55) levels by a mechanism that required LEN binding to the capsid domain of these viral proteins as these effects were abrogated with the capsid M66I resistant HIV-1 mutant.

Figure 10 Effect of LEN on the Production of Mature Extracellular WT and LEN-Resistant HIV-1 in HEK293T Cells[1]



[1] Extracellular p24 levels represent the mean (± SD) obtained from 2 independent experiments

Effects of LEN on Reverse Transcription, Integration of Viral DNA and Accumulation of 2-LTR Circles

Lenacapavir showed no effect on HIV-1 entry into PBMCs using a quantitative virus entry reporter assay, indicating that LEN targets a post-entry process essential for HIV-1 replication. Time-of-drug-addition assays demonstrated that LEN inhibits HIV-1 infection after reverse transcription but before provirus integration. LEN reduced the accumulation of 2-LTR circles rather than increasing these products of abortive integration, as observed with DTG, which suggests that LEN inhibits the active transport of viral pre-integration complexes into the host cell nucleus.

The nuclear translocation of intact capsids containing viral DNA is mediated in part by various host nuclear import factors (eg, CPSF6, NUP158, NUP358) that interact with HIV-1 capsid via the same binding site as that of the LEN molecule {Bhattacharya 2014, Matreyek 2013, Price 2012, Price 2014}. It is expected that LEN competes with these host cell factors for binding to HIV-1 capsid protein and thereby interferes with capsid-mediated nuclear import of pre-integration complexes, an essential step in the formation of an integrated provirus. Alternatively, this nuclear import block could originate, at least in part, from increased steric hindrance following LEN-mediated stabilisation of CA oligomers within capsids docked at nuclear pore complexes.

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 with EC_{50} =0.19 nM. Lenacapavir showed a Hill slope of 3.5 yielding an EC_{95} value of 0.23 nM.

Taking into account the human serum shift determined by equilibrium dialysis LEN exhibited a plasma protein binding-adjusted EC_{95} ($paEC_{95}$) value of 4 nM, which was used for the estimation of clinical inhibitory quotient (IQ) for the projected trough concentration of LEN in humans (15.5 ng/ml se PK AR).

Table 7 EC_{50}, Hill Slope and EC_{95} 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.

Table 8 Activity of LEN in Primary Human Target Cells

	EC_{50} (nM)[2]	
Compound[1]	$CD4^+$ T-Lymphocytes	Monocyte-Derived Macrophages
LEN	0.06 ± 0.02	0.03 ± 0.01
EFV	1.23 ± 1.1	0.29 ± 0.22
DTG	0.96 ± 0.38	1.87 ± 0.31
ATV	6.88 ± 5.69	8.31 ± 4.99

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

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 EC_{50} value of 0.05 nM. Lenacapavir also showed antiviral activity against HIV-2 but was 15- to 25-fold less active relative to HIV-1 isolates.

Table 9 Antiviral Activity of GS-6207 Against HIV Clinical Isolates in Human PBMCs

Virus Isolate	HIV-1 Subtype	EC_{50} (nM)		
		GS-6207	DTG	AZT
HIV-1 92UG031	A	0.04	0.63	51.6
HIV-1 92UG037	A	0.07	0.47	21.7
HIV-1 89BZ_167	B	0.08	1.18	10.1
HIV-1 90US_873	B	0.04	0.82	13.2
HIV-1 91US001	B	0.03	0.53	20.3
HIV-1 91US004	B	0.04	0.40	19.7
HIV-1 96TH_NP1538	B	0.05	0.40	4.10
HIV-1 BaL	B	0.04	0.40	43.2
HIV-1 JR-CSF	B	0.04	0.41	4.53
HIV-1 YU-2	B	0.04	ND	1.32
HIV-1 92BR025	C	0.05	0.91	16.9
HIV-1 98US_MSC5016	C	0.10	0.77	37.8
HIV-1 92UG001	D	0.02	1.09	7.29
HIV-1 98UG_57128	D	0.03	0.70	6.61
HIV-1 CMU02	E	0.05	0.81	8.31
HIV-1 CMU08	E	0.05	0.96	34.1
HIV-1 93BR020	F	0.05	0.38	25.1
HIV-1 JV1083	G	0.16	0.93	20.5
HIV-1 YBF30	Group N	0.02	0.54	8.96
HIV-1 BCF01	Group O	0.04	0.64	10.5
HIV-1 90TH_CM235	CRF01_AE	0.04	1.02	10.7
HIV-1 01CM008BBY	CRF02_AG	0.05	1.04	8.21
HIV-1 91DJ263	CRF02_AG	0.04	0.45	34.9
HIV-2 CBL-20	N/A	0.57	0.36	14.3
HIV-2 CDC310319	N/A	1.02	1.81	28.8

a EC_{50} values represent the mean of triplicate runs; ND = not determined

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 harbouring HIV protease inhibitor (PI) resistance mutations. Overall, LEN showed antiviral activity against all HIV-1 isolates evaluated, regardless of subtype or presence of drug resistance mutations.

Table 10 Antiviral Potency of LEN and Control Compounds Against Wild-Type HIV-1 Clinical Isolates in HEK293T Cells

Compound	IC_{50}, nM (n = 37)	
	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)

Additionally, 3 PI-resistant isolates were analysed. There was no change in susceptibility to LEN for the 3 PI-resistant isolates compared to wild-type isolates. In comparison, PIs ATV, DRV, and LPV exhibited 3.4 – 16.8-fold reduced susceptibility for viruses containing PI resistance mutations relative to wild-type, as expected.

Table 11 Summary of Antiviral Potency of LEN and Control Compounds Against PI-Resistant HIV-1 Clinical Isolates in HEK293T Cells

Compound	IC_{50}, nM (n = 3)[a]	
	Geometric Mean	Range
LEN	0.204	0.124 - 0.297
ATV	26.7	10.4 - 150
DRV	5.14	0.845 - 26.5
LPV	191	87.7 - 871

ATV = atazanavir; DRV = darunavir; LEN = lenacapavir; LPV = lopinavir; PI = protease inhibitor

a Genotypes of PI-resistant clinical isolates (Mutations in italicized type represent key resistance mutations): **Isolate 20-141494**: *L10V*, I15V, *K20R*, M36I, R41R/K, *M46I*, *I54V*, K55K/R, R57K, *I62V*, *L63P*, *A71V*, *L76V*, *V82I/T*, *I93L*; **Isolate 20-141498**: *L10I*, T12N, K14R, *L24I*, *M46I*, *I54V*, *L63P*, *I64V*, *V82A*: **Isolate 20-141517**: *L10I*, *V11V/I*, *I13V*, I15V, *K20R*, V32I, *L33F*, E35D, *M36I*, N37D, *F53L*, *D60E*, *L63P*, H69Q, *A71V*, *V82A*, *I84V*, L89F, *L90M*, *I93L*

There were no notable differences observed in the mean LEN IC_{50} values for any of the HIV-1 subtypes evaluated. Notably, the range of means across subtypes was narrow (0.166 – 0.297 nM), with less than 2-fold difference in potency across subtypes.

Table 12 Comparison of LEN Antiviral Activity Across HIV-1 Subtypes

HIV-1 Subtype	A	A1	AE	AG	B	BF	C	D	G	H
Geometric Mean IC_{50}, nM[a]	0.252	0.266	0.234	0.274	0.228	0.194	0.273	0.166	0.297	0.201
n	2	2	6	3	12	1	5	4	3	2

a Geometric mean IC_{50} values include wild-type and drug-resistant clinical isolates

Activity of LEN at Different multiplicities of infection (MOIs)

The in vitro antiviral activity of LEN was determined against HIV-1 (NL4-3 strain) and compared with TAF, EFV, DTG, and DRV in a human T-cell line infected with a wide range of MOIs. Lenacapavir demonstrated antiviral activity at all tested MOIs (MOI ranged from 0.01 – 1.25) and similar to other antiretroviral drugs, the in vitro antiviral activity of LEN is affected by the level of infection.

Table 13- Activity of LEN in a Human T-Cell Line at Different MOIs

HIV-1 Infection Condition	EC_{50} (nM)[1]				
MOI	LEN	TAF	EFV	DTG	DRV
0.01	0.028 ± 0.013	10.0 ± 4.5	0.69 ± 0.30	0.31 ± 0.13	1.36 ± 1.46
0.05	0.050 ± 0.016	12.8 ± 7.9	1.15 ± 0.34	0.50 ± 0.22	1.33 ± 0.70
0.25	0.152 ± 0.074	50.5 ± 48.5	2.79 ± 1.73	1.57 ± 1.10	2.67 ± 2.42
1.25	0.455 ± 0.168	61.1 ± 25.0	6.26 ± 1.22	2.46 ± 1.01	3.84 ± 1.60

DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; MOI = multiplicity of infection; TAF = tenofovir alafenamide;
1 EC_{50} values represent the mean (± SD) obtained from 4 independent experiments (Data from PC-200-2031).

LEN Cross-Resistance

Activity of LEN in HIV-1 Mutants Resistant to the 4 Main Drug 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 14 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

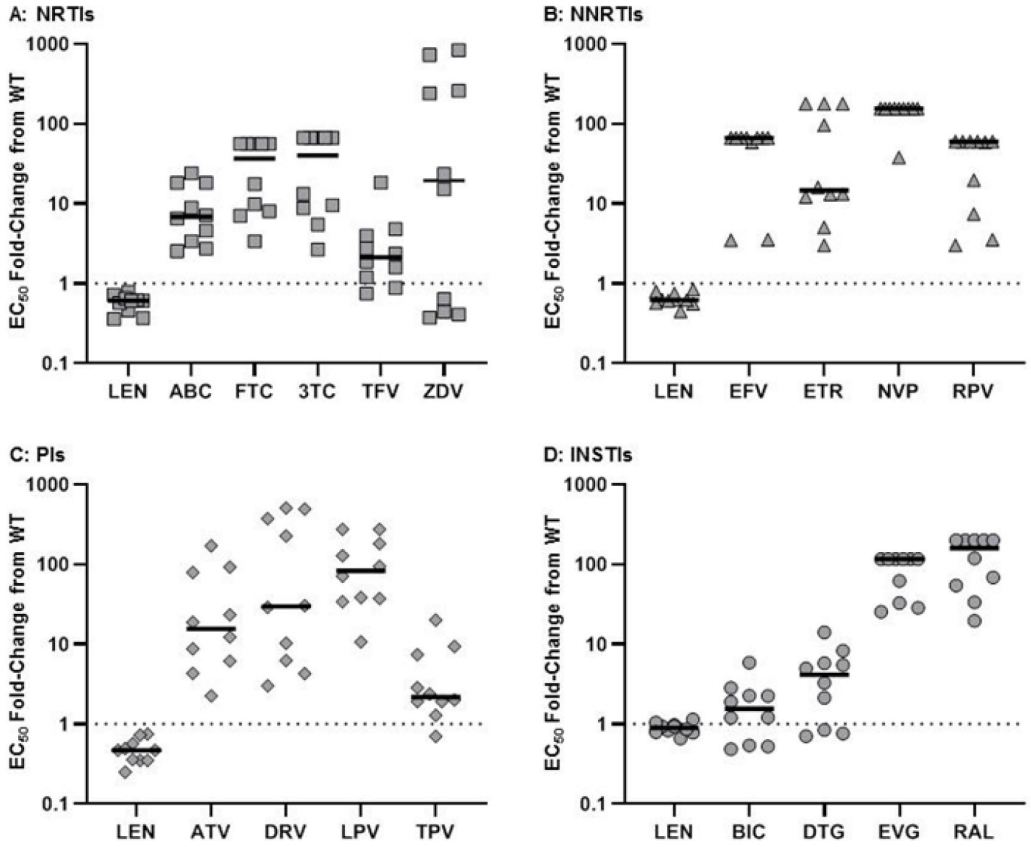


Figure 11 Relative Drug Susceptibilities in HIV-1 Clinical Isolates with Resistance Mutations to the 4 Main ARV Drug Classes

Horizontal lines indicate median values.

Activity of LEN in HIV-1 Clinical Isolates Containing Gag-Protease Sequences From ARV-Experienced and ARV-Naïve People with HIV

The antiviral potency of LEN was tested against a panel of treatment-experienced (TE) and treatment-naïve (TN) HIV-1 patient isolates that contained naturally occurring gag polymorphisms. Fifty-one patient-derived isolates comprising 36 TE and 15 TN HIV-1 sequences were cloned into pXXLAI, and their drug susceptibilities to LEN, protease inhibitors (DRV, ATV), and maturation inhibitors (BVM, GSK-3532795) were measured in a multicycle HIV-1 assay conducted in MT-2 cells.

In both TN and TE isolates, LEN exhibited similar potency (average EC_{50} of 0.088, and 0.089 nM, respectively) with minimal variability across all isolates (Table below), that was similar to the wild-type potency (EC_{50}: 0.095 nM). Overall, these data indicate that the antiviral activity of LEN was not affected by the presence of naturally occurring pre-existing gag polymorphisms, or the presence of PI-resistance mutations, or the degree of treatment experience of the patients.

Table 15 Relative Drug Susceptibilities in Treatment-Experienced and Treatment-Naïve HIV-1 Isolates

Isolate Type	Mean Drug Susceptibilities (EC_{50} Fold-Change from Wild-Type, range)					
	LEN (CAI)	DRV (PI)	ATV (PI)	BVM (MI)	GSK-795* (MI)	TAF (NRTI)
TE (n=36)	0.9 0.4 – 1.8	21 0.5 – >112	35 0.5 – >66	40 0.5 – >64	94 0.5 – >333	0.8 0.3 – 1.4
TN (n=15)	0.9 0.6 – 1.6	1.0 0.5 – 1.8	1.0 0.5 – 1.9	42 1.7 – >64	72 1.1 – >333	0.9 0.5 – 1.5

CAI: capsid inhibitor; MI: maturation inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; TE: treatment-experienced isolates; TN: treatment-naïve isolates. (Data from PC-200-2036)

Activity of LEN in HIV-1 Site-Directed Mutants and Clinical Isolates Containing Gag Cleavage Site Mutations

The antiviral potency of LEN was tested against a panel of site-directed mutant viruses (SDM; n=19) and 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 43 mutants with a mean fold-change in EC_{50} of 1.0 relative to the wild type virus (SDM: 1.1-fold, TE: 1.0-fold).

In contrast, the presence of GCSMs in some SDMs was associated with low-level resistance to PIs and low- to high-level resistance to MIs, while 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 in the SDM and TE isolates tested.

Table 16 Relative Drug Susceptibilities in HIV-1 Site-Directed Mutants and Treatment-Experienced Isolates Harboring Gag Cleavage Site Mutations

Isolate Type	Mean Drug Susceptibilities (EC_{50} Fold-Change from Wild-Type, range)					
	LEN (CAI)	DRV (PI)	ATV (PI)	BVM (MI)	GSK-795* (MI)	TAF (NRTI)
SDM (n=19)	1.1 0.7 – 1.9	1.2 0.5 – 2.3	1.8 0.4 – 3.6	>12 0.3 – >64	31 0.7 – 267	0.9 0.5 – 1.4
TE With GCSM (n=24)	1.0 0.4 – 1.8	>22 0.5 – >112	>36 0.7 – >66	>40 0.5 – >64	>85 0.5 – >333	0.8 0.3 – 1.4

* GSK-795: GSK-3532795/BMS-955176
CAI: capsid inhibitor; GCSM: gag cleavage site mutations; MI: maturation inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; SDM: site-directed mutants; TE: treatment-experienced isolates. (Data from PC-200-2037)

LEN Resistance

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 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 17 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).

Resistance experiments were also performed at clinically relevant fixed drug concentrations in MT-2 cells and in human PBMCs. In MT-2 cells infected with clonal HIV-1 strain HXB2D, LEN was tested at concentrations corresponding to tissue culture equivalent IQs of 4, 8, 16, 24, and 40, with an IQ of 1 defined as a concentration corresponding to the EC_{95} for LEN (0.23 nM).

The rate and frequency of viral breakthrough for fixed LEN concentrations was compared to that of four clinically approved antiretroviral inhibitors (emtricitabine [FTC], EFV, rilpivirine [RPV], and ATV), with each used at a fixed drug concentration equal to their respective tissue culture equivalent (ie, adjusted for protein binding) of the clinical plasma trough concentration (C_{min}) {Mulato 2016}. At a fixed concentration of 0.92 nM LEN (IQ of 4), a replicating virus emerged in 3 of 8 independent infected samples tested and each isolate encoded the capsid N74D mutation previously identified at low LEN concentrations in the dose escalation selections. No breakthrough virus emerged at any of the higher test concentrations of LEN. In comparison, parallel selections with FTC resulted in rapid emergence of the clinically relevant M184I/V reverse transcriptase (RT) variants in 7 of 8 infected samples, whereas a breakthrough of the Y181I RT variant was observed in the presence of RPV in 1 of 8 infected samples tested. Selections with fixed C_{min} concentrations of EFV, ATV and DTG each did not lead to any breakthrough of drug-resistant HIV-1 variants. These data suggest a high barrier to in vitro resistance emergence for LEN at concentrations above an IQ of 4.

Breakthrough studies were also performed at clinically relevant fixed drug concentrations in human PBMCs using six different patient-derived HIV-1 isolates and resulted in the emergence of a greater diversity of HIV-1 variants as compared to the experiments performed in MT-2 cells infected with a clonal HIV-1 isolate. At an IQ of 4, LEN showed a breakthrough frequency lower than FTC and comparable to RPV. The frequency of viral breakthrough in the presence of LEN was substantially reduced (approximately 6-fold) in the presence of a two-fold higher drug concentration corresponding to an IQ of 8. These findings suggest that the C_{min} for LEN (corresponding to an IQ > 6 or a 6x $paEC_{95}$

> 24.8 nM) is expected to provide sufficient barrier to drug resistance development, comparable to other antiretrovirals presently used in the clinic.

Table 18 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).

The in vitro data demonstrates that a substantial reduction in the frequency of viral breakthrough in the presence of LEN is reached between 0.92 nM and 1.9 nM (corresponding to IQ4 and IQ8). The $paEC_{95}$ was estimated to 4nM in MT-4 cells as mentioned above. The dosing regimens were selected to target an exposure 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 $paEC_{95}$ (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). The mean C_{trough} of LEN following administration to PWH in the Phase 2/3 study at Day 15 and at Week 26 was 48.6 (52%) ng/mL and 35.1 (59%) ng/mL, respectively, resulting in an IQ of 12.6-fold and 9.1-fold above the $paEC_{95}$ (3.87 ng/mL=4nM) against WT HIV-1 virus.

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.

Table 19 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

Activity of LEN Against LEN-Resistant Site-Directed HIV-1 Capsid Mutants in PhenoSense Gag-Pro Single Cycle Antiviral Assay in HEK293T cells

Susceptibility to LEN of in vitro selected LEN-resistant SDMs (n=12) was tested in the single cycle antiviral assay from Monogram Biosciences. Replication capacity and LEN susceptibility data of the SDMs in the PhenoSense assay displayed similar trends compared to the data obtained in the MT-2 single cycle assay. The susceptibility of these 12 SDMs to LEN ranged from 3.8- to >2757-fold relative to the WT, whereas each SDM remained fully susceptible to the PIs ATV and DRV. These data indicate a lack of cross-resistance of LEN-resistant mutants to the protease inhibitor class.

Table 20 Replication Capacity and Drug Susceptibilities of LEN-Resistance Associated Mutations in the PhenoSense Assay

HIV-1 Capsid Genotype	Replication Capacity (% of WT)	Relative Drug Susceptibilities (fold change from WT control)		
		LEN	ATV	DRV
L56I	3.6%	204	1.5	1.6
M66I	1.5%	>2757	0.9	1.3
Q67H	58.0%	4.8	1.2	0.9
Q67Y	10.0%	24	1.4	1.2
K70N	1.2%	N/A		
N74D	N/A	16	0.9	1.1
A105E	32.0%	4.0	1.1	1.7
T107N	32.0%	3.8	1.2	1.5
M66I+Q67H	N/A	1594	1.2	1.2
Q67H+N74D	N/A	>2757	1.0	1.1
Q67H+N74S	15.0%	20	1.1	1.5
Q67H+T107N	N/A	87	1.2	1.2
Median Fold Change		24	1.2	1.2

ATV: atazanavir; DRV: darunavir; LEN: lenacapavir; N/A: not available; WT: wild-type. (Data from PC-200-2046)

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

The antiviral potency of LEN, PIs, and MIs was tested in a multicycle (MC) HIV-1 antiviral assay in MT-2 cells against a panel of replication-competent site-directed mutant viruses (SDM; n = 12) containing resistance mutations to LEN or a structurally similar analogue of LEN. Close to half of these SDMs (5 of 12; L56I, M66I, K70N, A105E, and M66I+Q67H) did not show adequate infectivity in this MC antiviral assay and thus their drug susceptibility could not be evaluated. These 5 mutants also displayed reduced replication capacity in single-cycle (SC) antiviral assays conducted separately. For the remaining 7 mutant viruses, relative susceptibility to LEN ranged from 4.1- to 306-fold change (mean: 52.4-fold) in these mutants compared to the wild type in the MC assay. No cross-resistance with protease inhibitors or maturation inhibitors was noted with these LEN-resistant mutants.

Table 21 Relative Drug Susceptibilities of LEN-Resistant Site-Directed HIV-1 Capsid Mutants in MT-2 Multicycle Antiviral Assay

Average EC_{50} Fold Change Compared to WT Control[a]									
Mutant ID	CA Mutations	CAI	PI				MI		NRTI Control
		LEN	DRV	ATV	NFV	SQV	BVM	GSK-795[b]	TAF
114	Q67H	5.7	1.4	1.7	1.2	1.3	1.1	1.2	1.5
115	Q67Y	10.3	1.1	1.4	0.9	1.6	0.7	0.9	1.5
117	N74D	14.3	1.1	0.8	0.4	0.8	0.7	0.9	1.6
120	T107N	4.1	1.1	1.0	0.7	0.8	1.3	1.1	0.9
122	Q67H+N74D	306	1.1	0.9	0.9	1.3	0.6	1.1	1.2
123	Q67H+N74S	8.4	2.1	1.9	1.9	1.7	1.0	1.6	1.3
124	Q67H+T107N	18.2	1.2	0.8	0.7	0.9	0.5	0.8	0.7
Mean Fold Change		52.4	1.3	1.2	1.0	1.2	0.8	1.1	1.2

a Average of at least 3 independent experiments
b GSK-795: GSK-3532795/BMS-955176
CA: capsid; CAI: capsid inhibitor; MI: maturation inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; WT: wild-type. (Data from PC-200-2045)

No cross-resistance with PIs was observed with LEN resistant mutants. The applicant claims the slight reduction in PI susceptibility (mean FC of 1.9 for DRV, ATV, NFV, and SQV) observed for the Q67H+N74S mutant was likely associated to methodological issues related to artificially high MOI.

Replication Capacity of WT and LEN Resistant HIV-1 Mutants in Primary Target Cells

The in vitro replication capacity of WT HIV-1 and LEN resistance associated HIV-1 variants was investigated in primary human CD4+ T cells and in monocyte-derived macrophages. Except for the Q67H variant that confers low level resistance to LEN, the six other capsid mutants tested (ie, L56I, M66I, N74D, Q67H+N74D, Q67H+T107N, N74D+T107N) displayed substantially diminished replication capacity in both CD4+ T-lymphocytes (0.03-28% of WT virus) and macrophages (1.9-72% of WT virus) for the duration of the experiment (19 days). The replicative fitness of these mutants was not significantly restored in the presence of LEN in either cell type. Replication capacity (RC) data available from 3 mutants (L56I, M66I, and Q67H) in both MC and SC assays indicated the same rank order, with M66I RC of 1.5% and 0.4%, L56I RC of 3.6% and 3.0%, and Q67H RC of 58% and 100%, respectively. These data indicate that the in vitro replication capacity of the majority of the capsid HIV-1 mutants tested, including those conferring moderate to high-level LEN resistance, is severely compromised relative to the WT virus in two primary human target cell types of HIV-1 infection.

Table 22 Effect of GS-6207 on the Replication of WT and GS-6207 Resistant HIV-1 Variants in Primary Human Target Cells

HIV-1 Capsid Genotype	Infectivity (% of WT)[a]									
	Primary CD4+ T Lymphocytes					Monocyte-Derived Macrophages				
	Day 2	Day 5	Day 11	Day 19		Day 2	Day 5	Day 11	Day 19	
± GS-6207	-	-	-	-	+	-	-	-	-	+
WT	100	100	100	100	-	100	100	100	100	-
L56I	201	14	3.9	3.0	4.3*	50	57	48	44	67*
M66I	40	2.4	0.6	0.4	1.8*	20	22	17	16	16
Q67H	49	41	87	100	80	61	63	60	60	54
N74D	7.4	0.6	0.6	1.2	4.3*	6.1	4.0	3.0	2.6	2.1
Q67H/N74D	3.1	0.1	0.03	0.03	0.5*	4.5	3.0	2.2	1.9	1.1
Q67H/T107N	226	28	22	28	62*	153	102	79	72	57
N74D/T107N	40	2.5	0.8	0.7	2.4*	25	18	13	10	10

a Representative time points post-infection (in days) are shown for each cell type. Samples showing ≤ 50% infectivity are colored red. Asterisks (*) denote samples in which viral outgrowth was partially rescued in the presence of a fixed concentration of GS-6207 for the duration of the 19 day outgrowth experiment, with maximal representative effect denoted for day 19 timepoint among six GS-6207 concentrations tested. GS-6207 concentrations evaluated were 0.04 nM, 0.016 nM, 0.65 nM, 2.5 nM, and 10 nM, corresponding to 1.3, 5.2, 21, 83, and 330-fold the WT HIV-1 single-cycle EC_{50} for GS-6207. The percentage of mutant virus replication in the presence of GS-6207 is expressed relative to that of the WT virus in the absence of the compound.

L56I and M66I as well as double mutants M66I+Q67H, Q67H+N74D, Q67H+T107N, N74D+T107N all conferred high level LEN resistance based on in vitro data (58- to >3,226-fold). Except for the single mutation Q67H (with low level LEN resistance) and double mutation Q67H+T107N (high level LEN resistance) the other mutants tested showed substantially reduced replication capacity/infectivity compared to wildtype virus in both primary human CD4+ T cells and monocyte-derived macrophages. The Q67H+T107N mutations do not seem to substantially reduce the fitness of the virus in monocyte-derived macrophages and in addition results in high level LEN resistance, which could have clinical implications if selected for in vivo. However, the maintained susceptibility of PIs or MIs indicate that these LEN-resistant mutants could be inhibited by other classes of drugs.

Bioinformatics Assessment of HIV-1 Capsid Protein Conservation and Polymorphisms in the LEN Binding Site Across HIV-1 Subtypes

A publicly available source of 10,512 HIV-1 capsid population sequences representing 8 major subtypes (A1, B, C, D, F1, G, CRF01_AE, and CRF02_AG) was used to evaluate the conservation of the CA protein and the LEN binding site. The overall sequence identity of CA protein across these 8 subtypes was found to be high (>91%). Of the 24 amino acid residues in the LEN binding site, 20 residues (83%) had a sequence conservation between 94% and 100% across all 8 subtypes, including all 7 capsid amino acid positions associated with in vitro resistance to LEN (ie, L56 [100%], M66 [100%], Q67 [99% for CRF01_AE, 100% for other subtypes], K70 [100%], N74 [100%], A105 [100%], and T107 [94-99%]). None of the T107 substitutions identified was the T107N variant that is associated with 3.8- to 4.1-fold reduced susceptibility to LEN. The remaining 4 binding site residues (S41, Q50, T54, and Y169) were mutated in >5% of patients in at least one major subtype.

SDMs with the identified substitutions were created (S41A, S41I, S41L, S41T, S41V, Q50A, Q50E, Q50G, Q50H, Q50S, Q50T, Q50Y, T54L, T54M, T54S, T54V, N57H, T107A, T107S, T107V, Y169F, L172V, Q179T, K182R) and their impact on the susceptibility to LEN was tested in the MT-4 single cycle assay. Lenacapavir susceptibility in these SDMs was within the WT range (0.7- to 2.4-fold change) for all mutants except for Q50E (3-fold from WT) and N57H (>5000-fold from WT). Notably, these two LEN resistant variants each showed reduced infectivity in MT-4 cells (20% to 30% of WT) and were detected in HIV-1 at only a low (1%) prevalence exclusively in either subtype C (Q50E) or subtype D (N57H) isolates. Deep sequence analysis of capsid from 104 patient isolates of mostly HIV-1 subtype B showed essentially similar results as the population sequence analysis. In addition, the only LEN resistance associated mutation detected by deep sequencing was the capsid T107N substitution detected in a single patient. These data indicate a high degree of sequence conservation within the LEN binding site in HIV-1 capsid, indicating a very low frequency of potentially pre-existing resistance to LEN among HIV-1 clinical isolates.

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 (EC_{50} > 29 – 50 µM).

Lenacapavir demonstrated low micromolar antiviral activity against HBV and RSV, with EC50 values and corresponding CC_{50}/EC_{50} 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.

Table 23 Antiviral Activity and Selectivity of LEN Against Non-HIV-1 Viruses

Virus	Cell Line	Positive Control[1]		LEN[1]		
		Compound	EC_{50} (nM)	EC_{50} (nM)	CC_{50} (µM)	Selectivity[2]
HCV 1b replicon	Huh7: Con1/ SG-hRLucNeo	ITMN-191	1.0 ± 0.5	> 29,000	> 44.4	>580,000
HCV 2a replicon	Huh7: JFH-1/ hRLucNeo2a	ITMN-191	21 ± 3	> 31,600	> 44.4	>632,000
HBV	HepG2-NTCP	Lamivudine	35 ± 19	1,462 ± 256	> 50	29,240
HRV-16	H1-HeLa	Rupintrivir	68 ± 22	> 50,000	> 50	>1,000,000
RSV A2	HEp-2	YM-53403	250 ± 24	8,199 ± 3,313	> 50	164,000

1 EC_{50} and CC_{50} values represent the mean (± SD) obtained from 3 independent experiments (Data from PC-200-2029).
2 Selectivity is calculated as EC_{50} against other virus divided by mean EC_{50} against 23 HIV-1 isolates in PBMCs (0.05 nM, data presented in Table 3).

In Vitro Cytotoxicity

Cytotoxicity and Selectivity of LEN in MT-4 T-Cells

The in vitro cytotoxicity of LEN was assessed in a 5-day cell viability assay in uninfected MT-4 cells. The concentration that resulted in 50% cell death (CC_{50} value) was 26.6 µM for LEN in MT-4 cells.

Table 24 Cytotoxicity and Selectivity of LEN in the MT-4 T-Cell Line

Compound[1]	MT-4 T-Cell Line	
	CC_{50} (µM)[2]	Selectivity[3]
LEN	26.6 ± 14.2	140,000
EFV	20.6 ± 4.6	14,930
DTG	15.3 ± 5.0	7,970
ATV	50.5 ± 8.1	4,720

1 EFV = efavirenz; DTG = dolutegravir; ATV = atazanavir
2 CC_{50} values represent the mean (± SD) obtained from at least 19 independent experiments (Data from m2.6.3, Section 1, PC-200-2018).
3 CC_{50}/EC_{50} ratio. Corresponding standard resolution EC_{50} values are presented in Table 1.

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 25 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 26 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 CC_{50} 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 (CC_{50}/EC_{50}) of >730,000 in each of the non-target human cell lines and primary human hepatocytes tested. Thus, the cytotoxicity of LEN in primary cells and non-target human cell lines was low.

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, concluding that LEN showed high selectivity.

Relationship between plasma concentration and effect

Exposure-effect

Plasma concentrations of LEN (phase 1b study GS-US-200-4072) were fitted to an E_{max} model to evaluate the concentration-response relationship between LEN concentration at Day 10 and the reduction from baseline in HIV-1 RNA at Day 10. E_{max} was estimated to 2.13-log_{10} copies/mL decline in HIV-1 RNA, and the 90% effective concentration (EC_{90}) value was 12.6 ng/mL.

In the ongoing Phase 2/3 study GS-US-200-4625, an exploratory analysis of the exposure-effect relationships of LEN exposures (AUC_{tau}, C_{max}, and C_{trough}) versus the primary efficacy end point (HIV-1 RNA ≥ 0.5 log10 copies/mL reduction from baseline HIV-1 RNA, at the end of Functional Monotherapy Period), was performed. The LEN exposure estimates for 24 patients were derived from the popPK analysis. Change from baseline in HIV-1 RNA at the end of functional monotherapy versus C_{trough} Day 15 are shown in the figure below.

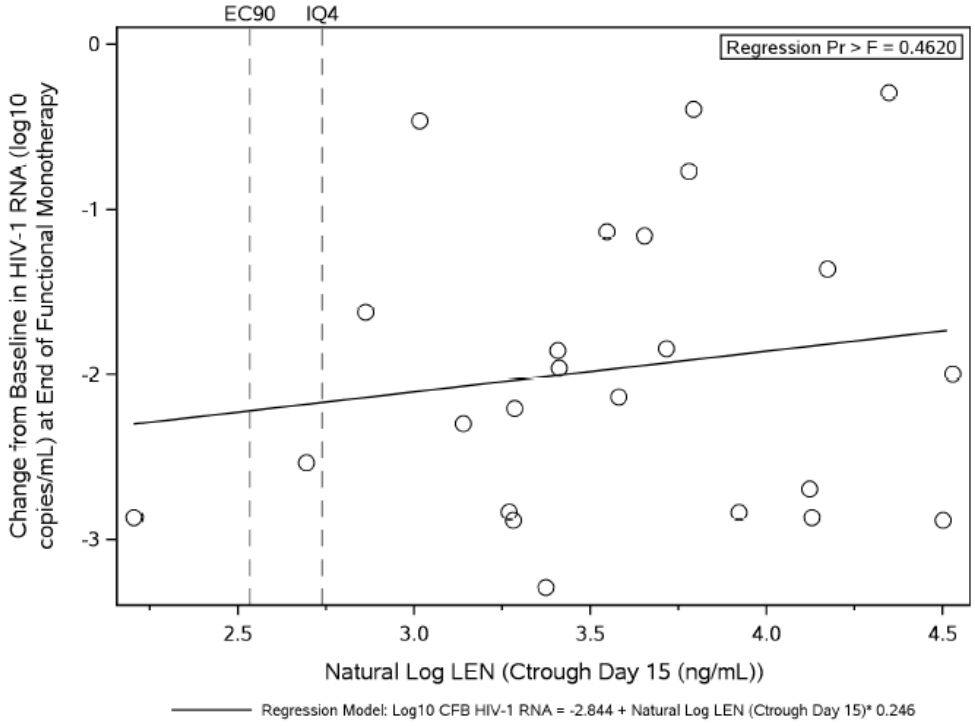


Figure 12 Linear Regression of Change from Baseline in HIV-1 RNA (log10 cp/mL) versus LEN PK Parameters

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. C_{max} of lenacapavir was approximately 2.2- and 8.8-fold higher on Study Days 6 and 12, respectively, in comparison with the therapeutic C_{max} derived from PopPK estimates from the Phase 2/3 registrational study in HTE PWH (Study GS-US-200-4625). LEN AUC_{tau} on Study Days 6 and 12 of this study was approximately 3.5- and 15.0-fold higher, respectively, relative to the Phase 2/3 therapeutic exposure estimate.

A large and unexpected imbalance in baseline QTcF between LEN and placebo treatment arms was denoted, 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-QT 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). Likewise, at the estimated therapeutic mean LEN C_{max} ranging from 111.8 to 151.6 ng/mL (dosed with or without boosters), ΔΔQTcF is predicted to be $\leq$ 1.57 msec, and the upper bound of the 2-sided 90% CI of ΔΔQTcF is below 10 msec ($\leq$ 3.84 msec).

Exposure-safety (TEAE)

Exploratory exposure-safety analyses were performed based on the most common AEs in the Phase 2 or 2/3 studies (GS-US-200-4625; GS-US-200-4334), using LEN exposure estimates derived from population PK modelling. Due to the limited data, no conclusions can be drawn.

2.6.3. Discussion on clinical pharmacology

Lenacapavir is a NCE and thus requires full documentation. An important role of PK in this submission was to support the simplified posology proposed for the oral lead in, which has not been studied in patients.

Two SmPCs are provided, one for the SC and one for the oral formulation. With regards to their PK content, these are identical apart for section 4.2 (posology & administration). Both SmPCs were updated with PK parameters derived from the pop PK analysis ($t_{1/2}$, CL, Vss/F etc) for the intended posology (i.e., the phase 2/3 posology).

The upper limit of the therapeutic window was previously unclear. The applicant presented the available data with supratherapeutic exposure in human, which was from shorter studies, and extrapolation to a 6-month exposure is not warranted. Higher exposure may however be supported by preclinical data, where longer studies have been performed. The applicant does not recommend the use of lenacapavir with the strong PgP, CYP3A and UGT1A1 inhibitor atazanavir/cobicistat, which gives an AUCR of 4.2 and C_{max}R of 6.6. This is thus to be considered above the upper limit of the therapeutic window in human.

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.

Pharmacokinetic data analysis

The exclusion of < 3 % of samples with concentrations below limit of quantification (BQL) is considered acceptable. In the pcVPC plots, the simulated median seemed to be relatively close to the median of the observed data, whereas the model tended to overpredict the variability, especially in healthy volunteers. In the pcVPCs focusing only on the first days after administration, concentrations in the oral absorption phase were slightly over- and under-predicted for patients and healthy volunteers, respectively.

The goodness-of-fit plots did not indicate any major systematic bias in the observed versus individual and population predicted concentrations. No major trends were observed in the conditional weighted residuals versus population prediction concentration/time plots. Goodness-of-fit plots stratified on oral and subcutaneous administration did not reveal any apparent model misspecifications. The shrinkage of inter-individual random effects was low-to-moderate. Due to the moderate shrinkage of K_{tr} and Fsc, the individual predicted subcutaneous exposure should be interpreted with caution.

The covariates identified were dose on oral bioavailability and CL, age on CL, health status on CL and Vp, weight on CL, Q, Vc and Vp (fixed allometric exponents) and sex on CL. In addition, COBI/RTV boosters were found to affect the oral bioavailability. The clinical relevance of these covariate effects is discussed below in *Special populations*.

The exposure data from healthy volunteers dosed with the simplified posology (study GS-US-200-5709) were not included in the popPK model building. However, an external validation was performed on interim data from study GS-US-200-5709 which included the simplified posology.

The parameter uncertainty based on the bootstrap procedure had an overall low proportion of failed runs which is considered acceptable.

Absorption

It is agreed that lenacapavir is a BCV class IV compound.

T_{max} was generally reached 4 hours after oral administration of 600 mg (2 x 300 mg) LEN tablets to healthy participants (both fed and fasted conditions). Lenacapavir was slowly absorbed following subcutaneous administration of 927 mg of LEN, with t_{max} values ranging between 70 and 109 days (median 84 days). Based on comparison of exposure between studies, the oral bioavailability was estimated to be low at a dose of 300 mg (approximately 10 %), whereas LEN seemed to be completely absorbed following SC administration (bioavailability approximately 100%).

The pharmacokinetics has not been studied following SC administration at different injection sites. This is acceptable since LEN is only administered in the abdomen.

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. In addition, no food effect was identified in the popPK analysis.

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 applicant revised the text on protein binding in the SmPC to reflect the in vivo data.

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 is 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 AUC0-1176h 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. The proposed text in section 5.2 Pharmacokinetic properties/dose proportionality of the SmPC is supported.

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). However, this oral posology is not relevant for this application.

Multiple SC dose data from the phase 2 and 2/3 studies did not indicate significant accumulation nor time dependency.

Based on the popPK analysis, the inter-individual variability (CV%) in CL, V_p, K_a, Ktr and Fsc was moderate to high. No intra-individual (inter-occasion) variability was determined.

Target population

The simplified posology (this was initially the intended posology) has not been studied in PWH. Therefore, simulated concentration-time profiles based on the posology in the Phase 2/3 study (CAPELLA) were compared to profiles based on the proposed (simplified) posology. All simulations were based on a simulation dataset, which included approximately 40 000 virtual patients.

The simulations indicated a higher C_{max} and C_{trough} during the first days of treatment using the simplified dosing regimen. This was reflected also in the numerical summary of the simulated PK parameters for the Phase 2/3 and simplified regimens. The initially slightly higher C_{max} is not a concern since the level is lower than the highest C_{max} in the clinical studies in patients. The C_{trough} (weeks 26 and 52) initially seemed comparable between the two posologies and at steady-state. The simulations showed slightly higher concentrations for the simplified regimen during the first days of treatment, compared to the Phase 2/3 regimen.

Overall, the simulations indicate that the exposures, C_{max} and AUC, following the simplified posology will not exceed that for the Phase 2/3 posology. In addition, the C_{trough} (weeks 26 and 52) seemed overall comparable between the two posologies. A similar exposure was initially supported by the preliminary PK analysis in healthy volunteers (up to D15). However, CHMP considered the safety data not to be sufficiently robust to support the simplified posology (see safety section). In consequence, the studied phase 2/3 posology is the intended posology.

There are missed dose recommendations in section 4.2 of both SmPCs (SC and oral). Simulations for missed dose posologies proposed in the SmPCs concerning missed oral doses were provided both when treatment is started and re-initiated at steady state (when the SC dose is missed more than 2 weeks than intended). The missed dose recommendations for oral dosing are acceptable, however the sentence in the SmPC is clarified for ease of comprehension by the prescriber.

Different dosing windows were simulated to support the proposed dosing window (+/- 2 weeks) for SC administration for the Phase 2/3 posology. The dosing window for SC administration is considered acceptable.

Special populations

In the population PK analysis, mild and moderate renal impairment (N = 40, CLcr range 46.8 to 86.9 mL/min) was not identified as a covariate on LEN exposure. It is agreed that no dose adjustment is required. No dose adjustment is recommended for patients with severe renal impairment, this is agreed, as it falls within the therapeutic window.

In the hepatic impairment Study GS US 200 4331, the applicant claims that protein binding was similar in both groups and did not present analyses of unbound PK parameters. With 0.366 and 0.214% fu, this could mean a two-fold increased exposure, in addition to the increased total exposure already noted. 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, including the proposed text for SmPC section 5.2.

Sex was identified as a statistically significant covariate in the popPK analysis. The exposure (C_{max}, AUC) was up to 11% higher in females as compared to males. It is agreed that this effect is not considered clinically relevant. Thus, no dose adjustment is needed based on sex.

Race and ethnicity were not identified as covariates in the popPK analysis. Thus, no dose adjustment is needed based on race or ethnicity.

Body weight and age were identified as statistically significant covariate in the popPK analysis. The exposure decreased with increasing body weight. The maximum percent change in LEN exposure ranged between -32% to +24% (relative to the median exposures) for participants weighing 55 to 109 kg (5th and 95th WT percentiles). The maximum percent change in LEN exposure ranged between -39.7 to +17.8% (relative to the median exposures) for participants in the age range 21 to 58 years (5th and 95th age percentiles). The additional exploratory analysis conducted for elderly is limited by the number of subjects (n = 5). There seemed not to be any trends in the exploratory exposure-response analysis in the Phase 2/3 study, thus the absence of dose adjustment is acceptable.

The remaining SmPC text adequately reflects the available data.

Pharmacokinetic interaction studies

Calculated cut-off concentrations for evaluation of interaction potential

During the maintenance subcutaneous dosing the relevant cut-off is 50*C_{max},u:

50xC_{max}(u)[a] (µM)
0.050

a. calculated as C_{max} x fu, where C_{max} = 0.10 µM [97 ng/mL] simulated up to week 26 and human fu = 0.01. Mw=968.3 g/mol. New simulations suggest a C_{max},ss of 88.4 ng/mL, which is in the same range. Earlier conclusions are thus still valid.

During the initial oral dosing the following cut-offs are used:

50xC_{max}(u)[a] (µM)	**25xInlet C_{max}(u)[b] (µM)**	**0.1xDose/250mL[c] (µM)**
0.041	15	248

a. calculated as C_{max} x fu, where C_{max} = 0.083 µM [80 ng/mL] simulated C_{max} day 1-15 and human fu = 0.01. Mw=968.3 g/mol.
b. calculated as [fu,b × ([I]max,b + (Fa × Fg × ka × Dose/QH))]; where fu,b is calculated as [fu/(Cb/Cp)] where Cb/Cp =0.64, [I]max,b is determined as (C_{max} x Cb/Cp), ka = 0.1 min-1, dose = 600 mg/day, Fa x Fg = 1 and QH = 1600 ml/min.
c. Calculated using the clinical dose of 600 mg (on a molar basis) in a volume of 250 mL

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

All comments on the content of the table in SmPC section 4.5 were adequately adressed.

Effect of other medicines on lenacapavir

In vitro studies showed that lenacapavir is a substrate of CYP3A, P-gp and UGT1A1. Lenacapavir is thus a substrate of efflux transporters and there is no indication that lenacapavir would be present in the brain.

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 smaller effect with a 1.4-fold, 2.3-fold and 1.9-fold increase in lenacapavir AUC_{inf} when coadministered with voriconazole, cobicistat and darunavir/cobicistat, respectively. The applicant concludes that these increases in lenacapavir exposures is not clinically meaningful, and no dose adjustment or warning is suggested in the SmPC. As these increases are smaller than the AUCR of 4.2, the lack of dose adjustment 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 endorsed.

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 (28% increase in lenacapavir AUCinf). 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 IC_{50} 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.

The signals from in vitro studies to be followed up in vivo were the moderate inhibition of CYP3A4 and induction of CYP3A4 and there was also indication of interaction with OATP1B1 and OATP1B3

substrates. The in vivo study GS-US-200-4333 evaluated the drug-drug interaction potential for lenacapavir as perpetrator of CYP3A4, P-gp, BCRP and OATP.

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 AUC_{inf}. Caution is advised if lenacapavir is coadministered with sensitive CYP3A substrates that have a narrow therapeutic index.

New 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 AUC_{inf}) and BCRP transporters (as observed with coadministration of lenacapavir with rosuvastatin resulting in a 31% increase in AUC_{inf}); 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

Initially, simulated exposure during the first 6 months of treatment only were reported. Simulated steady state exposure were provided by the applicant**.**

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. In addition, LEN may compete with the host nuclear import machinery for binding to capsid and thereby interfere with nuclear transport. 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 EC_{95} value in MT-4 cells was 0.23 nM. and a plasma protein binding-adjusted EC_{95} ($_{paEC95}$) 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 (15.5 ng/ml see below).

LEN displayed antiviral activity against HIV-1 clinical isolates representing the major subtypes (Group M subtypes A, AE, AG, B, C, D, E, F, G, as well as Group N and Group O; EC_{50} ranging 0.02 – 0.16 nM) and also showed antiviral activity against two HIV-2 isolates but was 15- to 25-fold less active relative to HIV-1.

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 clevage site mutations.

L56I and M66I as well as double mutants M66I+Q67H, Q67H+N74D, Q67H+T107N, N74D+T107N all conferred high level LEN resistance based on in vitro data (58- to >3,226-fold). The Q67H+T107N do not seem to substantially reduce the fitness of the virus in monocyte-derived macrophages and in addition results in high level LEN resistance, which could have clinical implications if selected for in vivo. However, the maintained susceptilbility of PIs or MIs in these LEN-resistant mutants indicate that LEN-resistant virus could be inhibited by other classes of drugs.

The dosing regimens were selected to target an exposure 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 $paEC_{95}$ (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).

The mean (%CV) C_{trough} of LEN following administration of LEN to PWH (N = 62) in the Phase 2/3 study at Day 15 and at Week 26 was 48.6 (52%) ng/mL and 35.1 (59%) ng/mL, respectively, resulting in an IQ of 12.6-fold and 9.1-fold above the $paEC_{95}$ (3.87 ng/mL) against WT HIV-1 virus

Lenacapavir demonstrated low micromolar antiviral activity against HBV and RSV. Clinical antiviral activity against these viruses at drug exposures relevant for the inhibition of HIV is not predicted. The cytotoxicity of LEN in primary cells and non-target human cell lines was low and no significant inhibition of off targets were observed, thus, LEN showed high selectivity.

Relationship between plasma concentration and effect

This Phase 1b study GS-US-200-4072 was performed with an earlier SC formulation, and therefore the PK characteristics are not relevant for this application. However, the results from PK/PD analysis (reduction in HIV-1 RNA from baseline) are of importance to support the therapeutic plasma concentration of 15.5 ng/mL (corresponding to an IQ of 4 based on $paEC_{95}$ from MT-4 cells; 3.87 ng/mL = IQ1). The EC_{90} was estimated to 12.6 ng/mL on day 10. These results indicates that almost maximal antiviral activity is observed at IQ4 (15.5 ng/mL). Thus, the results support the target concentration of 15.5 ng/mL.

An exploratory exposure-response analysis was performed based on virologic data collected in the Phase 2/3 study, GS-US-200-4625. The results should be interpreted with caution since only a limited number of data, and one dosing regimen were included in the analysis.

Overall, based on the limited data provided, no trends in the exposure-response relationships seemed evident.

In TQT Study GS-US-200-4332, oral administration of lenacapavir 600mg bid for 8 days lead to supratherapeutic concentrations both at day 6 and 12, as compared to the phase 2/3 C_{max} and AUC. As both the C_{max} and AUC are expected to slightly decrease upon use of the simplified dose regimen, the margins may be slightly higher than noted here. A small QTc prolongation was noted in the primary analysis. The clinical relevance of this finding is likely minor, based on the high exposure achieved in the study, the size of the effect in the primary analysis and the support for the lack of effect from the average baseline post hoc analysis and the concentration-QT modelling. Nevertheless, as the TQT study did not rule out QT prolongation by LEN and as the QTc was not monitored in the target population, sensitivity analyses were requested. These sensitivity analyses reconfirmed that the estimated impact of Lenacapavir on QTc was less than 5 msec and the upper bounds of the 2-sided 90% CIs of ΔΔQTcF were below 10 msec for all time points on Study Day 6 and Study Day 12. The relationship between the predicted mean ΔΔQTcF and concentration of LEN, appears to indicate no relationship between QTc and LEN exposure. Overall, these analyses further support that it is unlikely that exposure to Lenacapavir has a clinically meaningful effect on QT/QTc prolongation.

2.6.4. Conclusions on clinical pharmacology

The PK of lenacapavir (oral and sc) is well described and there is no issue remaining.

The preclinical characterisation of antiviral activity is appropriate. The mechanism of action is novel and has been established. Activity against HIV-1 is subtype independent. There is no indication of

cross resistance with available drug classes. The intrinsic barrier to resistance is anticipated to be relatively low, as single and double mutants confer high level resistance. From a clinical perspective, no activity against co-infecting viruses such as HBV is anticipated.

2.6.5. Clinical efficacy

The primary study providing information on the efficacy and safety of LEN and supporting the proposed indication is the Phase 2/3 study in heavily treatment experienced people living with HIV-1 infection with multidrug resistance (Study GS-US-200-4625).

This initial application includes efficacy data when all participants in Cohort 1 had completed the Week 26 SC visit (i.e., 26 weeks after the first dose of SC LEN) or prematurely discontinued the study drug. In addition, interim data at week 52 has been submitted.

Supportive data for LEN are provided from a Phase 2 study in treatment-naive people with HIV-1 (Study GS-US-200-4334), the efficacy data from this study include interim data up to week 54.

Table 27 Overview of the Primary Study Supporting the Efficacy of LEN (Study GS-US-200-4625)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented
GS-US-200-4625	Phase 2/3, randomized, placebo-controlled, multicenter study	HTE PWH	**Cohort 1 (N = 36):** ***Cohort 1A (N = 24):*** • Functional Monotherapy Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + failing regimen • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR ***Cohort 1B (N = 12):*** • Functional Monotherapy Period: placebo on Days 1, 2, and 8 + failing regimen • Maintenance Period: oral LEN 600 mg on Days 15 and 16 and 300 mg on Day 22 + SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR **Cohort 2 (N = 36):** • Oral Lead-in Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + OBR • Maintenance Period: SC LEN injection 927 mg on Day 1 SC[c] and every 6 months (26 weeks) thereafter + OBR	Efficacy, PK[d], and safety

CSR = clinical study report; HTE = heavily treatment experienced; LEN = lenacapavir; OBR = optimized background regimen; PK = pharmacokinetic(s); PWH = people with HIV;

SC = subcutaneous

a Participants who were enrolled and received at least 1 dose of study drug.

b Oral LEN 300 and 600 mg were administered as 1 x 300-mg tablet and 2 x 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 x 1.5-mL injections.

c The Day 1 SC visit occurred 14 days after the first dose of oral LEN.

d Results of the PK analyses are not discussed in the text of the CSR.

Table 28 Overview of Other Data Supporting the Efficacy of LEN (Study GS-US-200-4334)

Study	Study Design	Participant Population	Number of Participants[a] by Treatment Regimen[b]	Data Presented
GS-US-200-4334	Phase 2, randomized, open-label, active-controlled, multicenter study	Treatment-naive PWH	**Treatment Group 1 (SC LEN + [DVY™ → TAF]) (N = 52):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY™ (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily TAF 25 mg **Treatment Group 2 (SC LEN + [DVY™ → BIC]) (N = 53):** • Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY™ (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks[c] + SC LEN injection 927 mg on Day 15 • Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily BIC 75 mg **Treatment Group 3 (Oral LEN + DVY™) (N = 52):** oral LEN 600 mg on Days 1 and 2 and oral daily LEN 50 mg from Day 3 onwards + oral daily DVY (F/TAF 200/25 mg) **Treatment Group 4 (BVY™) (N = 25):** oral daily BVY™ (B/F/TAF 50/200/25 mg)	Efficacy, PK, and safety

B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide; BIC = bictegravir; BVY™ = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CSR = clinical

study report; DVY™ = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); F/TAF = emtricitabine/tenofovir alafenamide; LEN = lenacapavir; PK = pharmacokinetic(s);

PWH = people with HIV; SC = subcutaneous; TAF = tenofovir alafenamide

a Participants who were randomised and received at least 1 dose of study drug.

b Oral LEN 50, 300, and 600 mg were administered as 1 x 50-mg tablet, 1 x 300-mg tablet, and 2 x 300-mg tablets, respectively, and SC LEN injection 927 mg (309 mg/mL) was administered as 2 x 1.5-mL injections.

c Participants in Treatment Groups 1 or 2 with HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 discontinued DVY at Week 28 and initiated oral daily TAF or BIC, respectively; those with values ≥ 50 copies/mL discontinued study drug at or prior to Week 28.

2.6.5.1. Dose response studies

GS-US-200-4072

This was a randomised, double-blinded, placebo-controlled, multicentre, multicohort (Phase 1b) study of LEN (Part A) and TAF (Part B) monotherapy in PWH. Part B will not be further discussed.

The primary objective of the study was to evaluate the short-term antiviral activity of lenacapavir compared to placebo, with respect to the maximum reduction of plasma HIV-1 RNA (log10 copies/mL) from Day 1 through Day 10 in adult people with HIV who were antiretroviral treatment naive or were experienced but capsid inhibitor naïve.

Eligible participants had plasma HIV-1 RNA ≥ 5000 copies/mL but ≤ 400,000 copies/mL and CD4 cell count > 200 cells/mm3; were ARV treatment naive or experienced but integrase strand-transfer inhibitor (INSTI) naive.

A single SC dose of 20, 50, 150, 450, and 750 mg of LEN suspension (100 mg/mL, not commercial formulation) or placebo was administered in the abdomen. 29 participants received a single dose of LEN (6 participants each in the LEN 20, 50, 150, and 450 mg groups and 5 participants in the LEN 750 mg group), and 10 participants received a single dose of placebo.

Efficacy Results

Overall, antiviral activity was comparable across the dose range of 50 to 750 mg. All but one (who received LEN 20 mg) of the LEN treated participant had a maximum reduction of ≥ 1 log10 copies/mL in their HIV-1 RNA through Day 10. The maximum reduction of HIV-1 RNA from Days 1 through 10 was significantly greater for each of the LEN treatment groups versus placebo. Overall, the maximal activity of lenacapavir appears similar to an integrase inhibitor.

Table 29 Efficacy Results in Study GS-US-200-4072

Efficacy End Points	LEN 20 mg (N = 6)	LEN 50 mg (N = 6)	LEN 150 mg (N = 6)	LEN 450 mg (N = 6)	LEN 750 mg (N = 5)	Placebo (N = 10)
Maximum Reduction From Baseline HIV-1 RNA (log_{10} copies/mL)						
Mean (SD)	−1.35 (0.318)	−1.79 (0.476)	−1.76 (0.203)	−2.20 (0.468)	−2.26 (0.662)	−0.17 (0.128)
Participants Achieving HIV-1 RNA < 50 copies/mL by Day 10						
< 50 copies/mL	0	1 (16.7%)	0	1 (16.7%)	1 (20.0%)	0
≥ 50 copies/mL	6 (100.0%)	5 (83.3%)	6 (100.0%)	5 (83.3%)	4 (80.0%)	10 (100.0%)
Change From Baseline in HIV-1 RNA (log_{10} copies/mL) at Day 10						
Mean (SD)	−1.29 (0.349)	−1.79 (0.476)	−1.76 (0.203)	−2.14 (0.476)	−2.26 (0.662)	−0.08 (0.180)

LEN = lenacapavir

As previously stated, the targeted therapeutic plasma concentration is 15.5 ng/mL (corresponding to an IQ of 4 based on $paEC_{95}$ from MT-4 cells; 3.87 ng/mL = IQ1). In the current study, the EC_{90} was estimated to 12.6 ng/mL on day 10.

2.6.5.2. Main studies

GS-US-200-4625 – Phase2/3 Study

Title: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination With an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance

Methods

Study GS-US-200-4625 is an ongoing Phase 2/3, randomised, placebo-controlled, multicentre study of LEN in combination with an optimised background regimen (OBR) in HTE PWH with multidrug resistance.

HIV-1 RNA results from the cohort-selection visit (14 to 30 days after the screening visit) were used to determine whether eligible participants were randomised into Cohort 1 or enrolled into Cohort 2.

Cohort 2 was established as a nonrandomised cohort to allow participants to enrol into the study when they did not meet the criteria for randomisation but were otherwise eligible. The main purpose of Cohort 2 was to remove the unintended incentive of remaining nonadherent, while ensuring the accurate identification of those who might be failing virologically due to poor adherence.

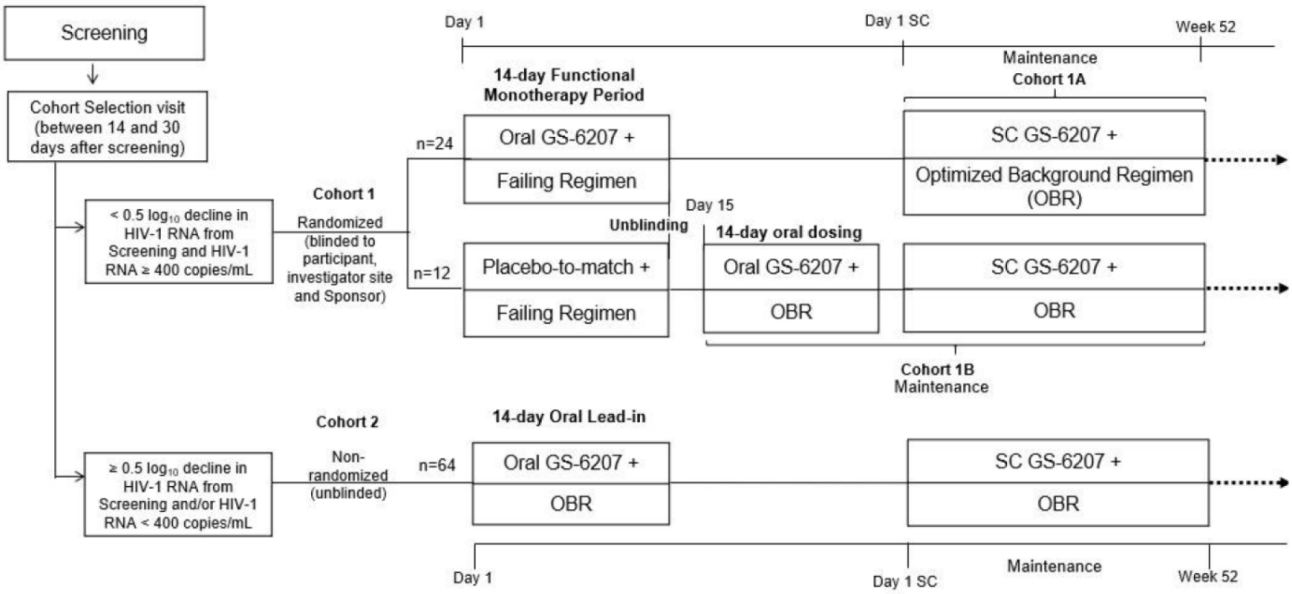


Figure 13 GS-US-200-4625: Study Design Schema

GS-6207 = lenacapavir; OBR = optimized background regimen; SC = subcutaneous

Eligible participants were enrolled into Cohort 2 if Cohort 1 was fully enrolled.

In the HTE population with a diverse underlying resistance profile, there is no standardised background regimen that can be used for all individuals. By addition of the test drug to the failing regimen during a short-term functional monotherapy period and with placebo control the assessment of viral decline can provide information on the benefit of the test drug. This approach is considered ethical and is consistent with the EMA guidelines (EMEA/CPMP/EWP/633/02 Rev. 3) and endorsed.

Study participants

Eligible participants were HTE PWH aged ≥ 18 years (all sites) or aged ≥ 12 years and weighing ≥ 35 kg (sites in North America and Dominican Republic) who were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until Day 1 (or until Day 14 for participants in Cohort 1); had plasma HIV-1 RNA ≥ 400 copies/mL at screening; had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], or integrase strand-transfer inhibitors [INSTIs]); and had ≤ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant.

Major exclusion criteria include ongoing opportunistic or other serious infection; chronic hepatitis C, untreated HBV or any of the following laboratory abnormalities:

a. Estimated glomerular filtration rate (eGFR) ≤ 50 mL/min using Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age for creatinine clearance
b. Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)
c. Direct bilirubin > 1.5 × ULN
d. Platelets < 50,000/mm3
e. Haemoglobin < 8.0 g/dL

Treatments

Cohort 1

Induction: Oral LEN (Cohort 1A, n = 24) or placebo-to-match (Cohort 1B, n = 12):

Cohort 1A: Oral LEN on Day 1 and Day 2 (600 mg) and Day 8 (300 mg) + failing regimen (FR), followed by SC LEN 927 mg + OBR on Day 15

Cohort 1B: Oral placebo-to-match on Day 1 and Day 2 and Day 8 + FR, followed by oral LEN on Day 15 and Day 16 (600 mg) and Day 22 (300 mg) along with OBR starting on Day 15; SC LEN 927 mg on Day 29

Maintenance: SC LEN 927 mg at Week 26 and every 26 weeks thereafter

Cohort 2 (Non-randomised Cohort) (n = 36):

Induction: Oral LEN (Day 1 and Day 2: 600 mg; Day 8: 300 mg), then SC LEN 927 mg (Day 15) + OBR on Day 1

Maintenance: SC LEN 927 mg at Week 26 and every 26 weeks thereafter

All treatments were given without regard to food**.**

Outcomes/endpoints

Primary endpoint

The proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period

Secondary endpoint

The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment based on the US Food and Drug Administration (FDA)–defined snapshot algorithm

Other End Points

- Incidences of treatment-emergent adverse events (TEAEs) and graded laboratory abnormalities
- The proportion of participants with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm
- The change from baseline in HIV-1 RNA (log10 copies/mL) by visit
- The change from baseline in CD4 cell count (cells/µL) by visit
- The proportion of participants with HIV-1 RNA < 50 copies/mL by visit based on Missing = Failure (M = F) and Missing = Excluded (M = E) analyses

Evaluation of the proportion of subjects with the pre-specified viral load decline (>0.5 log10 from baseline values) after 7-14 days of functional monotherapy is recognised as a valid endpoint in this patient population.

Sample size

Approximately 100 PLWH could be enrolled; 36 within cohort 1 and 64 enrolled into cohort 2. For cohort 1, a total of 36 subjects were to provide at least 90% power to detect a 60% difference between treatment groups in the proportion of subjects achieving a ≥ 0.5 log10 reduction from baseline at Day 15 of the functional monotherapy period.

For the calculation of power, it was assumed that 70% and 10% of the subjects in the LEN and the placebo group respectively, were to achieve a ≥ 0.5 log10 reduction from baseline in HIV-1 RNA using a Fisher exact test and a 2-sided type I error of 0.05. No sample size considerations have been made for cohort 2, as this cohort was not part of the primary or secondary objectives. In the current interim CSR, data from 36 subjects enrolled in cohort 2 is presented.

Randomisation and blinding (masking)

HIV-1 RNA results from a cohort selection visit were used to determine whether eligible subjects could be randomised in Cohort 1 or be enrolled in Cohort 2. Eligible subjects with both < 0.5 log10 HIV-1 RNA decline compared to the screening visit and HIV-1 RNA ≥400 copies/mL at the cohort selection visit were enrolled in Cohort 1 and were randomised 2:1 to either receive oral lenacapavir or placebo for 14 days while they continued their existing regimen using IWRS.

Enrolment into Cohort 2 occurred when Cohort 1 was fully enrolled or if a subject did not meet the criteria for randomisation in Cohort 1. In Cohort 2 there was no randomisation: all subjects enrolled were to receive oral lenacapavir for 14 days together with an optimised background regimen.

In Cohort 1, the Sponsor, subjects, and site staff were blinded to treatment assignment using lenacapavir matching placebo and were further not to know HIV-1 RNA results at Days 2 and 8. After each participant had completed the functional monotherapy period, their treatment assignment was unblinded by the investigational site using IWRS to determine their treatment regimen in the maintenance period. To mitigate the risks of inadvertently releasing the treatment information to participants who were still receiving functional monotherapy, sponsor staff was not to receive the treatment codes from IWRS until all participants in Cohort 1 had completed the functional monotherapy period. In Cohort 2, treatment was open label.

Statistical methods

The submitted statistical analysis plan (SAP, version 1.0) was based on the study protocol amendment 2 (01 September 2020) and was finalised 19 April 2021, prior to the database finalisation for the Week 26 analysis that occurred 20 April 2021. This SAP described the analysis plan for the Week 26 analysis and according to the clinical study report (CSR), there were no changes made to planned analyses after the finalisation of the SAP. Compared with the initial statistical analysis plan in the CSP, only few and minor changes had been implemented up to the primary analysis.

In addition, a Week 52 analysis was to be performed when all Cohort 1 subjects had completed Week 52 assessment or prematurely discontinued the study drug, and after all subjects in Cohort 2 had completed the Week 26 visit (ie, 26 weeks after the first dose of SC LEN) or had prematurely discontinued the study drug. This analysis has by now been performed and an updated CSR has been submitted (Addendum 1: 15 December 2021) including additional analyses through week 52 on the ongoing cohorts (cohort 1 and cohort 2). For both Cohorts 1 and 2, data collected through Week 52 (52 weeks from the first dose of SC LEN) refer to as the "Main Phase" of the study. A final analysis will be performed after all subjects have completed the study.

The SAP for the week 26 analysis was finalised after all participants were unblinded and all relevant information had been collected. A SAP for the "Data Monitoring Committee (DMC) Analysis" containing analysis methods for the primary efficacy endpoint and other endpoints to evaluate efficacy and safety of LEN compared with placebo was finalised on 30 September 2020 before the unblinding of study data on 11 November 2020. This SAP was not part of the initial submission but has been submitted.

The primary analysis was conducted after all subjects in Cohort 1 had completed the week 26 visit (i.e., 26 weeks after the first dose of SC LEN) or had prematurely discontinued study drug and included the primary analysis of the primary endpoint. There were no interim analyses planned before the analysis of the primary efficacy endpoint; therefore, no alpha level adjustment was applied to the primary efficacy endpoint.

<u>Two sets of analyses</u>

Data included in each analysis were defined as follows:

Functional monotherapy period analysis

This analysis only applied to Cohort 1 and included data collected from subjects randomised in the functional monotherapy period. This analysis was used to assess the primary efficacy endpoint and safety data collected during the blinded phase of the study. Results were summarised by treatment group. All data collected from first dose of blinded study drug up to the first dose date of the open-label study drug, defined as the earliest date of either SC LEN or open-label oral LEN, were included.

All LEN analysis

This analysis included data collected from subjects who received at least one dose of lenacapavir (i.e., oral LEN [blinded or open label] or SC LEN). Data collected on and after the first dose of lenacapavir were included. Results were summarised by cohort.

Efficacy analysis sets

The primary analysis set for efficacy analysis was the full analysis set (FAS). Two FASs were defined. For the analysis of the primary efficacy endpoint, "FAS for the Functional Monotherapy Period" included all randomised subjects who received any dose of study drug. For secondary efficacy endpoints "FAS for the Maintenance Period" was used and included all subjects who received at least one dose of SC GS-6207.

Primary analysis

The primary efficacy endpoint was the proportion of participants in Cohort 1 achieving ≥0.5 log10 reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. For subjects with missing HIV-1 RNA values the value was to be imputed using the last observation carried forward method.

The difference in proportions between the treatment arms was compared using an unconditional exact method using 2 invert 1-sided tests (Chan and Zhang 1999) with an alpha level at 0.05 to evaluate superiority. The p-value and 95% confidence interval for the point estimate of treatment difference in proportions were estimated and constructed using the above-mentioned method.

A secondary analysis of the primary efficacy endpoint was performed based on a PP analysis set.

Secondary analyses

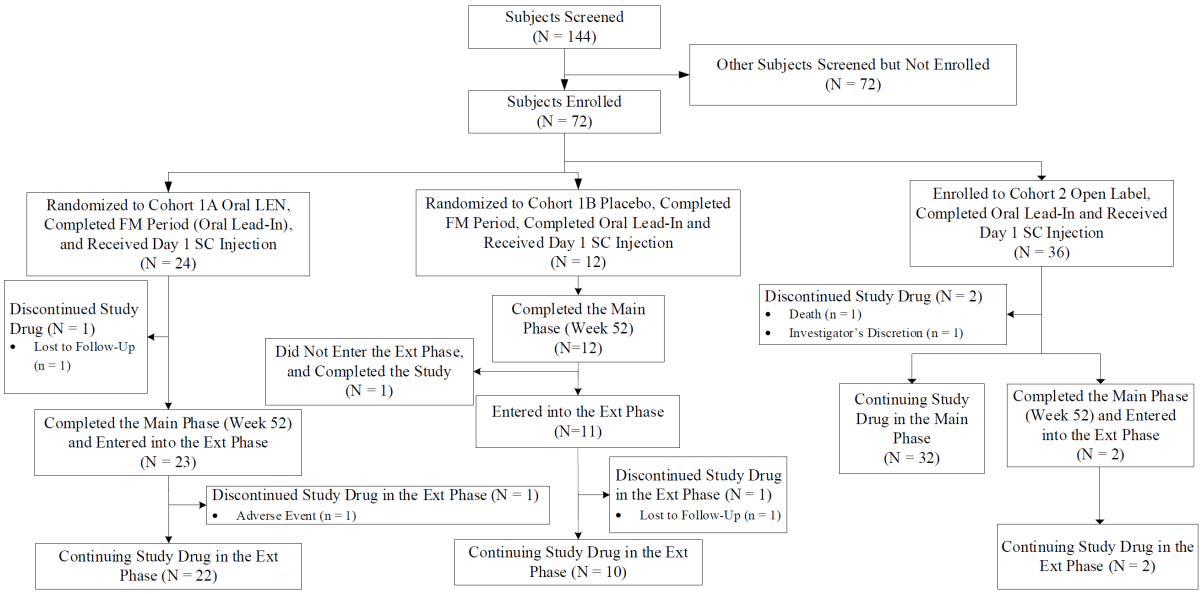
The proportion of participants in cohort 1 with HIV-1 RNA <50 copies/mL at week 26 and week 52 was summarised using the US FDA-defined snapshot algorithm. The analysis window at week 26 was defined as from study day 169 to study day 217, inclusive, where study day was calculated from the first dose of SC GS-6207. The Week 52 analysis window for snapshot algorithm is defined as from Study Day 324 to Study Day 414, inclusive. All HIV-1 RNA data collected on-treatment (i.e., including data collected up to 196 days [28 weeks] from the last dose of SC GS-6207) were to be used in the snapshot algorithm.

Subgroup analyses

Analysis of pre-defined subgroups were performed for the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 26 and week 52 as determined by the US FDA-defined snapshot algorithm. Results were to be descriptive without statistical testing; proportions have been reported with 95% CIs derived using the exact method.

Results

Participant flow



CRF = case report form; Ext = extension; FM = Functional Monotherapy; LEN = lenacapavir; SC = subcutaneous
"Main Phase" is defined as data collected through Week 52 (52 weeks from the first dose of SC LEN).
Included CRF data collected up to 28 September 2021.
One participant in Cohort 1 Placebo group who completed Week 52 visit, and decided not to receive study drug at the visit and not to enter the Extension Phase were counted as completing the Main Phase, and completing the study.

Figure 14 GS-US-200-4625: Disposition of Participants (Main Phase Only) (All Screened Participants)

Recruitment

Study Centres: 31 study centres in the United States (US) (19 centres), Thailand (4 centres), Italy (2 centres), and Dominican Republic, Spain, France, Canada, Taiwan, and South Africa (1 centre each).

Study Period:

21 November 2019 (First Participant Screened)

05 October 2020 (Last Participant Last Visit for the Primary End Point)

28 September 2021 (Last Participant last visit for the current report)

Conduct of the study

The original protocol (dated 25 September 2019) was amended twice.

Protocol Amendment 1 (18 December 2019) included no major amendment.

Protocol Amendment 2 (01 September 2020) included:

- Correction of the concentration of LEN injection from 300 mg/mL to 309 mg/mL to accurately reflect the label claim of the finished product based on improved accuracy on measurement of the product density since Protocol Amendment 1. No changes to the actual product concentration have been made. Correction of SC dose from 300 mg to 309 mg and 900 mg to 927 mg.
- Correction of suboptimal virologic response criteria to base on change in viral load from the time of initiation of LEN therapy rather than from Day 1 SC.
- Broadened the second FAS definition to include all participants who receive at least 1 dose of LEN.

- Updated the secondary analyses windows at Week 26 and Week 52 to begin from the start of LEN therapy (oral) instead of the start of LEN SC therapy.

There were no changes from planned analyses for this study.

Baseline data

Table 30 GS-US-200-4625: Demographic and Baseline Characteristics (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Age (years)						
N	24	12	36	36	72	0.2393
Mean (SD)	54 (11.3)	49 (10.9)	52 (11.2)	48 (13.7)	50 (12.6)	
Median	55	54	54	49	52	
Q1, Q3	50, 61	49, 55	49, 59	38, 60	45, 59	
Min, max	24, 71	27, 59	24, 71	23, 78	23, 78	
Sex at birth						
Male	17 (70.8%)	9 (75.0%)	26 (72.2%)	28 (77.8%)	54 (75.0%)	0.7953
Female	7 (29.2%)	3 (25.0%)	10 (27.8%)	8 (22.2%)	18 (25.0%)	
Race						
American Indian or Alaska Native	0	0	0	0	0	0.7525
Asian	2 (8.3%)	1 (9.1%)	3 (8.6%)	12 (33.3%)	15 (21.1%)	
Black	10 (41.7%)	6 (54.5%)	16 (45.7%)	11 (30.6%)	27 (38.0%)	
Native Hawaiian or Pacific Islander	0	0	0	0	0	
White	12 (50.0%)	4 (36.4%)	16 (45.7%)	13 (36.1%)	29 (40.8%)	
Other	0	0	0	0	0	
Not Permitted	0	1	1	0	1	
Ethnicity						
Hispanic or Latino	6 (25.0%)	4 (36.4%)	10 (28.6%)	5 (13.9%)	15 (21.1%)	0.4959
Not Hispanic or Latino	18 (75.0%)	7 (63.6%)	25 (71.4%)	31 (86.1%)	56 (78.9%)	
Not Permitted	0	1	1	0	1	
Body mass index (kg/m^2)						
N	24	12	36	36	72	0.5913
Mean (SD)	26.0 (5.38)	24.8 (4.58)	25.6 (5.09)	26.5 (5.76)	26.1 (5.42)	
Median	24.7	24.3	24.7	25.6	25.0	
Q1, Q3	21.4, 30.2	21.8, 27.8	21.7, 29.5	22.7, 29.4	22.1, 29.4	
Min, max	18.4, 37.1	18.7, 33.5	18.4, 37.1	14.9, 42.6	14.9, 42.6	

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile
Denominator for percentages was the Safety Analysis Set.
Age (in years) was calculated from the date of first study drug dosing (Day 1) if dosed or enrollment if not dosed.
Not Permitted = local regulators did not allow collection of race or ethnicity information.
Body mass index (kg/m^2) = [Weight (kg)/Height (cm)^2]*10,000.
P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.
Participants who reported "Not Permitted" were excluded from the percentage and *P* value calculation.

Table 31 GS-US-200-4625: Other Baseline Disease Characteristics: HIV and Antiretroviral Medication History (Safety Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
HIV-1 RNA (log_{10} copies/mL)						
N	24	12	36	36	72	0.0041
Mean (SD)	3.97 (0.922)	4.87 (0.393)	4.27 (0.890)	4.06 (1.164)	4.17 (1.034)	
Median	4.19	4.93	4.50	4.49	4.49	
Q1, Q3	3.20, 4.57	4.46, 5.26	4.08, 4.89	3.28, 4.90	3.51, 4.90	
Min, max	2.33, 5.40	4.33, 5.33	2.33, 5.40	1.28, 5.70	1.28, 5.70	
HIV-1 RNA categories (copies/mL)						
≤ 100,000	23 (95.8%)	6 (50.0%)	29 (80.6%)	29 (80.6%)	58 (80.6%)	0.0012
> 100,000	1 (4.2%)	6 (50.0%)	7 (19.4%)	7 (19.4%)	14 (19.4%)	
CD4 cell count (cells/µL)						
N	24	12	36	36	72	0.0062
Mean (SD)	199 (166.1)	85 (62.9)	161 (149.5)	258 (273.4)	210 (224.2)	
Median	172	85	127	195	150	
Q1, Q3	99, 248	39, 109	79, 201	56, 392	76, 286	
Min, max	16, 827	6, 237	6, 827	3, 1296	3, 1296	
CD4 cell count categories (cells/µL)						
< 50	3 (12.5%)	4 (33.3%)	7 (19.4%)	9 (25.0%)	16 (22.2%)	0.4276
≥ 50 to < 200	13 (54.2%)	7 (58.3%)	20 (55.6%)	10 (27.8%)	30 (41.7%)	
≥ 200 to < 350	6 (25.0%)	1 (8.3%)	7 (19.4%)	8 (22.2%)	15 (20.8%)	
≥ 350 to < 500	1 (4.2%)	0	1 (2.8%)	4 (11.1%)	5 (6.9%)	
≥ 500	1 (4.2%)	0	1 (2.8%)	5 (13.9%)	6 (8.3%)	
CD4 percentage (%)						
N	24	12	36	36	72	0.0317
Mean (SD)	10.8 (7.77)	5.9 (4.12)	9.2 (7.11)	11.5 (8.62)	10.3 (7.93)	
Median	10.5	4.5	6.9	10.4	8.9	
Q1, Q3	5.6, 14.8	3.6, 7.7	4.5, 12.6	3.5, 17.5	4.2, 15.1	
Min, max	1.0, 32.0	1.2, 16.4	1.0, 32.0	0.4, 29.5	0.4, 32.0	
Number of prior ARV medications						
N	24	12	36	36	72	0.7876
Mean (SD)	11 (6.2)	10 (6.0)	11 (6.1)	13 (5.6)	12 (5.9)	
Median	9	9	9	13	11	
Q1, Q3	8, 16	5, 13	7, 14	10, 17	8, 16	
Min, max	2, 24	3, 22	2, 24	3, 25	2, 25	

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)			
Known resistance to ≥ 2 drugs in class						
NRTI	23 (95.8%)	12 (100.0%)	35 (97.2%)	36 (100.0%)	71 (98.6%)	—
NNRTI	22 (91.7%)	12 (100.0%)	34 (94.4%)	36 (100.0%)	70 (97.2%)	
PI	20 (83.3%)	8 (66.7%)	28 (77.8%)	30 (83.3%)	58 (80.6%)	
INSTI	20 (83.3%)	7 (58.3%)	27 (75.0%)	23 (63.9%)	50 (69.4%)	

ARV = antiretroviral; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Q1 = first quartile; Q3 = third quartile
Prior ARV = nonstudy drug ARV with the start date prior to the first dose date of study drug.
When counting number of ARVs and summarizing by drug class, cobicistat and ritonavir used as a boosting agent were excluded.
P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.

Table 32 HIV subtypes

HIV-1 Subtype	Number (%) of Participants			
	Cohort 1		Cohort 2	All (N = 72)
	A: LEN + FR (n = 24)	B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	
Participants With Data	24	12	36	72
B Subtype	22 (91.7%)	11 (91.7%)	23 (63.9%)	56 (77.8%)
Non-B Subtype	2 (8.3%)	1 (8.3%)	13 (36.1%)	16 (22.2%)
AE	2 (8.3%)	1 (8.3%)	8 (22.2%)	11 (15.3%)
AG	0	0	2 (5.6%)	2 (2.8%)
C	0	0	2 (5.6%)	2 (2.8%)
BF	0	0	1 (2.8%)	1 (1.4%)

In cohort 1 the most common prior ARV medications were as follows: INSTI (97.2%), NRTI (94.4%), NNRTI (88.9%), and PI (83.3%). Known resistance to ≥ 2 drugs in class was as follows: NRTI (97.2%), NNRTI (94.4%), PI (77.8%), and INSTI (75.0%).

Differences were seen between the LEN and placebo groups in HIV-1 RNA (log10 copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage.

A higher number of participants in Cohort 2 had a non-B HIV-1 subtype compared to Cohort 1 (13 of 36 compared to 3 of 36, respectively) reflecting the higher geographical diversity of participants in Cohort 2 compared to Cohort 1 according to the applicant.

Failing Regimens and Optimised Background Regimens

Cohort 1

For Cohort 1 in Study GS-US-200-4625, the median number of ARVs in the failing regimen was 3 (range: 1 to 7). The compositions of participants' failing regimens were characteristic of those of PWH with multidrug resistance, for example, PI (boosted darunavir twice daily), INSTI (dolutegravir twice daily), chemokine receptor 5 entry inhibitor (maraviroc), CD4-directed post-attachment inhibitor (ibalizumab), attachment inhibitor (fostemsavir, which was investigational at the time of enrolment), and fusion inhibitor (enfuvirtide).

The median number of ARVs in the OBR was 4 (range: 2 to 7). The compositions of participants' failing regimens and OBRs were similar, suggesting that they had few remaining treatment options prior to enrolling. Specifically, 16.7% of participants (6 of 36 participants) continued their failing regimen as their OBR, suggesting that there were no viable agents that could have further optimd the regimen.

The percentages of participants by number of fully active ARV agents in the OBR were as follows: 16.7%, 6 participants (no fully active ARV agents); 38.9%, 14 participants (1 fully active ARV agent); 25.0%, 9 participants (2 fully active ARV agents); and 19.4%, 7 participants (≥ 3 fully active ARV agents).

Cohort 2

The failing regimens and OBRs for Cohort 2 in Study GS-US-200-4625 were similar to those of Cohort 1 and were consistent with the profile of the HTE population.

Table 33 GS-US-200-4625: Other Baseline Characteristics: Failing Regimens and Optimized Background Regimens (Safety Analysis Set)

	Cohort 1			Cohort 2	Total	Cohort 1 LEN vs Placebo
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)	(N = 36)	(N = 72)	
Baseline OBR drug class exposure						
NRTI	23 (95.8%)	9 (75.0%)	32 (88.9%)	29 (80.6%)	61 (84.7%)	—
NNRTI	6 (25.0%)	4 (33.3%)	10 (27.8%)	14 (38.9%)	24 (33.3%)	
PI	12 (50.0%)	9 (75.0%)	21 (58.3%)	24 (66.7%)	45 (62.5%)	
INSTI	16 (66.7%)	9 (75.0%)	25 (69.4%)	22 (61.1%)	47 (65.3%)	
Fusion inhibitor	1 (4.2%)	2 (16.7%)	3 (8.3%)	2 (5.6%)	5 (6.9%)	
CCR5 entry inhibitor	2 (8.3%)	4 (33.3%)	6 (16.7%)	4 (11.1%)	10 (13.9%)	
CD4-directed post-attachment inhibitor	9 (37.5%)	3 (25.0%)	12 (33.3%)	5 (13.9%)	17 (23.6%)	
Attachment inhibitor	3 (12.5%)	0	3 (8.3%)	5 (13.9%)	8 (11.1%)	
Number of fully active ARV agents from baseline OBR						
0	4 (16.7%)	2 (16.7%)	6 (16.7%)	6 (16.7%)	12 (16.7%)	—
1	7 (29.2%)	7 (58.3%)	14 (38.9%)	13 (36.1%)	27 (37.5%)	
2	9 (37.5%)	0	9 (25.0%)	10 (27.8%)	19 (26.4%)	
3 or more	4 (16.7%)	3 (25.0%)	7 (19.4%)	7 (19.4%)	14 (19.4%)	
OSS based on baseline OBR						
N	24	12	36	36	72	0.4750
Mean (SD)	1.8 (1.04)	1.5 (1.01)	1.7 (1.02)	1.8 (0.93)	1.8 (0.97)	
Median	2.0	1.3	1.8	2.0	2.0	
Q1, Q3	1.0, 2.5	1.0, 2.5	1.0, 2.5	1.0, 2.3	1.0, 2.5	
Min, max	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	
OSS category based on baseline OBR						
0	2 (8.3%)	1 (8.3%)	3 (8.3%)	2 (5.6%)	5 (6.9%)	0.6960
0.5	2 (8.3%)	1 (8.3%)	3 (8.3%)	3 (8.3%)	6 (8.3%)	
1	4 (16.7%)	4 (33.3%)	8 (22.2%)	5 (13.9%)	13 (18.1%)	
1.5	2 (8.3%)	2 (16.7%)	4 (11.1%)	6 (16.7%)	10 (13.9%)	
2	7 (29.2%)	1 (8.3%)	8 (22.2%)	11 (30.6%)	19 (26.4%)	
> 2	7 (29.2%)	3 (25.0%)	10 (27.8%)	9 (25.0%)	19 (26.4%)	

ARV = antiretroviral; BID = twice daily; CCR5 = chemokine receptor 5; DRV = darunavir; DTG = dolutegravir; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; OSS = overall susceptibility score; PI = protease inhibitor; Q1 = first quartile; Q3 = third quartile

Failing regimen = nonstudy drug ARV taken on the day before the first dose date of study drug (Day −1); fully active agent = OSS for that agent is 1.

When counting number of ARVs and summarizing by drug class, cobicistat and ritonavir used as a boosting agent were excluded.

OBR at baseline was defined as any nonstudy drug ARV medications that were started on or prior to Study Day 28 from the first dose date of open-label LEN and were used for a minimum duration of 28 days, regardless of temporary interruption, on or after the first dose of open-label LEN.

The OSS for the failing regimen was calculated by summing up the sensitivity/susceptibility scores from all drugs in the failing regimen.

The OSS for the baseline OBR was calculated by summing up the sensitivity/susceptibility scores from all drugs in the baseline OBR.

P value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) for categorical data and the 2-sided Wilcoxon rank sum test for continuous data.

P value was not provided for drug class exposure summary as a participant could have more than 1 drug class exposure.

Overall, DTG was part of the failing regimen in 29.2% and 41.7% in the LEN and placebo groups respectively. DRV was part of the failing regimen in 20.8% and 25% in the LEN and placebo groups respectively. Of these some were dosed BID with DTG or DRV as increased posology is advised for these drugs in presence of class-specific resistance mutations. More patients in the LEN group were treated with DRV+DTG BID compared to placebo (16.7% vs 8.3%).

A larger proportion of patients in the LEN group were treated with ibalizumab (37.5% in the LEN group vs. 8.3% in placebo group) and fostemsavir was used in 8.3% in the LEN group compared to 0% in the placebo group. Taken together it seems that in the failing regimen the overall DRV and DTG use was

slightly higher in the placebo group, while in the LEN group BID treatment with DTG + DRV, ibalizumab or fostemsavir was somewhat more common.

According to the protocol atazanavir (ATV), efavirenz (EFV), nevirapine (NVP) and etravirine (ETV) were prohibited medications during the study due to potential drug-drug interaction with lenacapavir. ATV, EFV, NVP and ETV are mentioned in the SmPC as "not recommended". ETV has CYP3A inductive effects which may lead to lowering of LEN plasma concentrations and the P-gp inhibition could lead to opposite effects. One single patient was on ETV while on LEN and had plasma concentrations within expected range.

The OBR at baseline is only taken into account if used for a minimum duration of 28 days on or after the first dose date of open-label LEN. This definition of OBR was included in the SAP for the "DMC Analysis" which was finalized on 30 September 2020 before the unblinding of study data on 11 November 2020. This definition was therefore not informed by knowledge of the data. Changes in OBR were allowed during the whole study duration.

Numbers analysed

Analysis Populations

Table 34 GS-US-200-4625: Analysis Sets (All Enrolled Analysis Set)

Analysis Set	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo (N = 12)	Total (N = 36)		
All Enrolled Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Full Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
Per-Protocol Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	11 (91.7%)	35 (97.2%)	0	35 (48.6%)
Added a new ARV during the Functional Monotherapy Period[a]	0	1 (8.3%)	1 (2.8%)	0	1 (1.4%)
Full Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Safety Analysis Set for the Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
Safety Analysis Set for the All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
PK Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)

ARV = antiretroviral; LEN = lenacapavir; PK = pharmacokinetic(s)
a Initiated optimized background regimen on Day 1 in error.
Denominator for percentages was the All Enrolled Analysis Set.

All subjects randomised in Cohort 1 were included in the primary efficacy analysis set (FAS). For Cohort 1 one participant in the placebo group received a new ARV during the Functional Monotherapy Period and was excluded from the Per-Protocol (PP) Analysis Set. Study sample size is small, however, challenges to recruit this HTE population with failing regimen is recognized. All subjects enrolled in Cohort 1 completed week 26 and 35 completed week 52.

Overall, in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: LEN, 24 participants; placebo, 12 participants; Cohort 2: LEN + optimized background regimen [OBR], 36 participants). All 72 participants completed the Functional Monotherapy and all received Day 1 SC LEN.

Outcomes and estimation

Primary Efficacy End Point: *Reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL From Baseline*

Table 35 GS-US-200-4625: Number and Proportion of Participants Achieving a Reduction in HIV-1 RNA of ⩾ 0.5 log10 copies/mL From Baseline – Functional Monotherapy Period Analysis (Full Analysis Set)

	Cohort 1		LEN vs Placebo	
	LEN (N = 24)	Placebo (N = 12)	*P* Value	Proportional Difference (95% CI)
Number and proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline	21 (87.5%)	2 (16.7%)	< 0.0001	70.8% (34.9% to 90.0%)

LEN = lenacapavir
The 95% CI of the difference in percentages of response between treatment groups and the corresponding *P* value were calculated based on an unconditional exact method using 2 invert 1-sided tests (Chan and Zhang method).

One participant in the placebo group who initiated an OBR on Day 1 rather than Day 15 had a reduction in HIV-1 RNA of 1.929 log10 copies/mL from baseline at Day 15; this participant was excluded from the PP Analysis Set. The results based on the PP Analysis Set were consistent with those for the FAS and confirmed the primary efficacy end point (reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline: LEN 87.5%, 21 of 24 participants; placebo 9.1%, 1 of 11 participants; P < 0.0001).

Two participants in Cohort 1 had a value imputed using the last observation carried forward method: 1 participant in the LEN group and 1 in the placebo group. A worst-case sensitivity analysis, with the participant in the LEN group being considered a non-responder and the participant in the placebo group being a responder, showed that the between group difference remained high (58.3% [95% CI 15.1% to 81.8%]) and statistically significant.

To address the imbalance in baseline HIV-1 RNA between the LEN and placebo groups, a post hoc analysis of the primary efficacy end point with adjustment for baseline HIV-1 RNA using rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant: 87.5% versus 16.7%; P = 0.0003.

To address the imbalance in baseline CD4 cell counts between the LEN and placebo groups, post hoc analyses of the primary efficacy end point were conducted in participants with comparable or clinically

relevant CD4 cell counts. In a subset of participants in the LEN group with the lowest baseline CD4 counts (ie, lower than the overall median) (12 participants; median: 98.5 cells/μL) versus the placebo group (12 participants; median: 84.5 cells/μL), the difference between the 2 groups remained statistically significant (proportional difference: 66.7%; 95% CI: 25.2% to 90.5%; P = 0.0008).

Results were similar in the subgroup of participants with CD4 count < 200 cells/μL in both treatment groups. For LEN 87.5% (14/16) had HIV-1 RNA ≥0.5 log10 copies/mL from Baseline and for placebo 9.1% (1/11) (proportional difference: 78.4%; 95% CI: 39.0% to 95.0%; P < 0.0001). The response rate was also similar in participants receiving LEN with CD4 cell counts ≥200 cell/μL: 87.5% (7/8) had HIV-1 RNA ≥0.5 log10 copies/mL. There was only 1 participant in the placebo group with a baseline CD4 ≥200/μL. This participant achieved a reduction in HIV 1 RNA ≥0.5 log10 copies/mL from baseline. It is noted that this participant initiated the OBR on Day 1 during the Functional Monotherapy Period in violation of the protocol.

The median OSS based on the failing regimen is different between the groups (1 vs 0.5 in LEN and placebo respectively). For participants with OSS 0 to 0.5 or 1 to 1.5 there were similar proportion of participants in both treatment groups, however, more participants in the LEN groups achieved ≥0.5 log10 reduction. This data is limited by the small sample size.

Table 36 GS-US-200-4625: Number and Proportion of Participants Achieving ⩾ 0.5 log10 Reduction from Baseline in HIV-1 RNA by OSS of the Failing Regimen (Baseline) in Functional Monotherapy Period

OSS	LEN (n = 24)	Placebo (n = 12)	*P* value	Difference in Proportion (95% CI)
0 to 0.5	10/11 (90.9%)	2/7 (28.6%)	0.0061	62.3% (12.2% to 90.9%)
1 to 1.5	7/8 (87.5%)	0/4	0.0027	87.5% (25.9% to 99.7%)
≥ 2	4/5 (80.0%)	0/1	0.1596	80.0% (−36.7% to 99.5%)

LEN = lenacapavir (GS-6207); OSS = overall susceptibility score

Of the participants in the LEN group about 12.5% had fully active PI, 46% had less active and 42% had no active PI. Between these groups similar proportions of participants achieved ≥ 0.5 Log10 reduction (82-100%).

In the LEN group 21% had a fully active INSTI, 50% had less active and 29% no active INSTI. No major difference in percent of patient achieving ≥ 0.5 Log10 reduction was seen between those groups.

Between LEN and placebo the proportions of active, less than active or no active PI or INSTI were similar. With regard to outcomes, in the LEN groups significantly more participants achieved ≥ 0.5 Log10 reduction compared to placebo, and this do not seem to be dependent on active PI or INSTI in the failing regimen although when comparing these subgroups numbers are small.

Table 37 GS-US-200-4625: Number and Proportion of Participants Achieving a Reduction in HIV-1 RNA of ⩾ 0.5 log10 copies/mL From Baseline by Either Fully Active PI or INSTI in the Failing Regimen (Baseline) in Functional Monotherapy Period

Failing Regimen	LEN (n = 24)	Placebo (n = 12)	*P* value	Difference in Proportion (95% CI)
PI				
With fully active PI	3/3 (100.0%)	0/2	0.0346	100.0% (−6.3% to 100.0%)
With less than fully active PI	9/11 (81.8%)	0/4	0.0040	81.8% (17.8% to 97.7%)
With no PI	9/10 (90.0%)	2/6 (33.3%)	0.0186	56.7% (2.8% to 89.4%)
INSTI[a]				
With fully active INSTI	4/5 (80.0%)	0/2	0.0539	80.0% (−13.8% to 99.5%)
With less than fully active INSTI	12/12 (100.0%)	2/5 (40.0%)	0.0042	60.0% (13.2% to 94.7%)
With no INSTI	5/7 (71.4%)	0/4	0.0162	71.4% (5.8% to 96.3%)
PI or INSTI				
With fully active PI or INSTI	6/7 (85.7%)	0/3	0.0102	85.7% (12.2% to 99.6%)
With less than fully active PI or INSTI	13/14 (92.9%)	2/7 (28.6%)	0.0026	64.3% (16.2% to 91.4%)
With no PI or INSTI	2/3 (66.7%)	0/2	0.1287	66.7% (−36.0% to 99.2%)

INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir (GS-6207); PI = protease inhibitor
a. In the placebo group, INSTI-resistance data were available for 11 of 12 participants (PC-200-2043).

The distribution of the number of fully active ARV agents in the failing regimen was comparable between the LEN and placebo group. In the LEN group, the number of fully active ARV in the failing regimen appeared not to have major influence on the primary endpoint of achieving a reduction of ≥0.5 log10 copies/mL HIV-1 RNA from baseline, as the results were comparable between the different strata.

Table 38 GS-US-200-4625: Number and Proportion of Participants Achieving a Reduction in HIV-1 RNA of ⩾ 0.5 log10 copies/mL From Baseline by Fully Active ARV Agents in the Failing Regimen – Functional Monotherapy Period Analysis (Full Analysis Set)

Number of Fully Active ARV Agents in the Failing Regimen	LEN (N = 24)	Placebo (N = 12)	*P* Value	Difference in Proportion (95% CI)
0	10/12 (83.3%)	2/7 (28.6%)	0.0128	54.8% (5.4% to 85.8%)
1	7/7 (100.0%)	0/4	0.0007	100.0% (37.7% to 100.0%)
2	3/4 (75.0%)	0/1	0.1975	75.0% (−46.1% to 99.4%)
3 or more	1/1 (100.0%)	0/1	NA	NA

Secondary Efficacy End Points

HIV-1 RNA < 50 and < 200 copies/mL at Week 26 and week 52 in Cohort 1 (US FDA-Defined Snapshot Algorithm)

Table 39 GS-US-200-4625: Virologic Outcome at Week 26 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cut-off at 50 and 200 copies/mL – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	8 (66.7%)	29 (80.6%)	29 (80.6%)	58 (80.6%)
95% CI	67.6% to 97.3%	34.9% to 90.1%	64.0% to 91.8%	64.0% to 91.8%	69.5% to 88.9%
HIV-1 RNA ≥ 50 copies/mL	3 (12.5%)	4 (33.3%)	7 (19.4%)	6 (16.7%)	13 (18.1%)
HIV-1 RNA ≥ 50 copies/mL in Week 26 Window	3 (12.5%)	4 (33.3%)	7 (19.4%)	5 (13.9%)	12 (16.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0	0	1 (2.8%)	1 (1.4%)

No Virologic Data in Week 26 Window	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to AE/Death	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	0	0	0	0	0
Missing Data During Window but on Study Drug	0	0	0	0	0
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	23 (95.8%)	9 (75.0%)	32 (88.9%)	31 (86.1%)	63 (87.5%)
95% CI	78.9% to 99.9%	42.8% to 94.5%	73.9% to 96.9%	70.5% to 95.3%	77.6% to 94.1%
HIV-1 RNA ≥ 200 copies/mL	1 (4.2%)	3 (25.0%)	4 (11.1%)	4 (11.1%)	8 (11.1%)
HIV-1 RNA ≥ 200 copies/mL in Week 26 Window	1 (4.2%)	3 (25.0%)	4 (11.1%)	3 (8.3%)	7 (9.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 200 copies/mL	0	0	0	1 (2.8%)	1 (1.4%)
No Virologic Data in Week 26 Window	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to AE/Death	0	0	0	1 (2.8%)	1 (1.4%)
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 200 copies/mL	0	0	0	0	0
Missing Data During Window but on Study Drug	0	0	0	0	0

AE = adverse event; LEN = lenacapavir

a Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The Week 26 window is between Days 184 and 232 (inclusive).

Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last SC LEN, was used in this analysis.

The 95% CIs of the proportions of subjects with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 were calculated based on the Exact method.

Table 40 GS-US-200-4625: The Proportion of Participants With HIV-1 RNA < 50 and < 200 copies/mL at Week 52 Using the US FDA-Defined Snapshot Algorithm – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 9)	Total (N = 45)
Using HIV-1 RNA Cutoff at 50 copies/mL					
HIV-1 RNA < 50 copies/mL	21 (87.5%)	9 (75.0%)	30 (83.3%)	5 (55.6%)	35 (77.8%)
95% CI	67.6% to 97.3%	42.8% to 94.5%	67.2% to 93.6%	21.2% to 86.3%	62.9% to 88.8%
HIV-1 RNA ≥ 50 copies/mL	2 (8.3%)	3 (25.0%)	5 (13.9%)	3 (33.3%)	8 (17.8%)
HIV-1 RNA ≥ 50 copies/mL in Week 52 Window	2 (8.3%)	3 (25.0%)	5 (13.9%)	2 (22.2%)	7 (15.6%)
Discontinued Study Drug Due To Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL	0	0	0	1 (11.1%)	1 (2.2%)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 9)	Total (N = 45)
No Virologic Data in Week 52 Window	1 (4.2%)	0	1 (2.8%)	1 (11.1%)	2 (4.4%)
Discontinued Study Drug Due To AE/Death	0	0	0	1 (11.1%)	1 (2.2%)
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	1 (4.2%)	0	1 (2.8%)	0	1 (2.2%)
Missing Data During Window But on Study Drug	0	0	0	0	0
Using HIV-1 RNA Cutoff at 200 copies/mL					
HIV-1 RNA < 200 copies/mL	22 (91.7%)	9 (75.0%)	31 (86.1%)	6 (66.7%)	37 (82.2%)
95% CI	73.0% to 99.0%	42.8% to 94.5%	70.5% to 95.3%	29.9% to 92.5%	67.9% to 92.0%
HIV-1 RNA ≥ 200 copies/mL	1 (4.2%)	3 (25.0%)	4 (11.1%)	2 (22.2%)	6 (13.3%)
HIV-1 RNA ≥ 200 copies/mL in Week 52 Window	1 (4.2%)	3 (25.0%)	4 (11.1%)	1 (11.1%)	5 (11.1%)
Discontinued Study Drug Due To Lack of Efficacy	0	0	0	0	0
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA ≥ 200 copies/mL	0	0	0	1 (11.1%)	1 (2.2%)
No Virologic Data in Week 52 Window	1 (4.2%)	0	1 (2.8%)	1 (11.1%)	2 (4.4%)
Discontinued Study Drug Due To AE/Death	0	0	0	1 (11.1%)	1 (2.2%)
Discontinued Study Drug Due To Other Reasons[a] and Last Available HIV-1 RNA < 200 copies/mL	1 (4.2%)	0	1 (2.8%)	0	1 (2.2%)
Missing Data During Window But on Study Drug	0	0	0	0	0

AE = adverse event; LEN = lenacapavir

a Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Cohort 2 ongoing participants who have missing HIV-1 RNA at Week 52 and have not reached the upper limit of the analysis window for Week 52 are excluded.

The Week 52 window is between Days 324 and 414 (inclusive).

Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last subcutaneous LEN, was used in this analysis.

The 95% CIs of the percentages of participants with HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Week 52 were calculated based on the Exact method.

Other Analyses Related to Efficacy

HIV-1 RNA < 50 and < 200 copies/mL in Cohort 2

At Week 26, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 80.6% (58 of 72 participants) and 87.5% (63 of 72 participants), respectively. At Week 52, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants), respectively.

Twenty-eight participants enrolled into Cohort 2 met the randomization criteria and would have been eligible for Cohort 1 (if not fully enrolled). All achieved HIV-1 RNA reduction ≥ 0.5 log10 copies/mL from baseline at Day 1 SC (28 of 28, 100%), although it should be noted that they all started an OBR at baseline (ie, Day 1) per the protocol, which likely contributed to the reduction in HIV-1 RNA. Of the same 28 participants, 22 (78.6%) achieved HIV-1 RNA < 50 copies/mL at Week 26.

Of the 8 participants in Cohort 2 who did not meet the randomization criteria for Cohort 1, 3 had HIV-1 RNA reduction ≥ 0.5 log10 copies/mL from baseline at Day 1 SC visit; 2 had HIV-1 RNA ≥ 400 copies/mL at Screening, but < 50 copies/mL at Day 1, and 3 had low viral load at Day 1 (range 91 to 1230 copies/mL); 7 achieved HIV-1 RNA < 50 copies/mL at Week 26.

Table 41 Virologic Outcome for Participants in Cohort 2 (N = 36) Who Met and Did Not Meet the Randomizationisation Criteria for Cohort 1 (Full Analysis Set) – GS-US-200-4625

Outcome	Participants in Cohort 2 Meeting the Randomisation Criteria (n = 28)	Participants in Cohort 2 not Meeting the Randomisation Criteria (n = 8)
Achieving HIV-1 RNA reduction ≥ 0.5 $\log_{10}$ copies/mL from Baseline at Day 1 SC visit	28 (100.0%)	3 (37.5%)
HIV-1 RNA < 50 copies/mL at Week 26	22 (78.6%)	7 (87.5%)

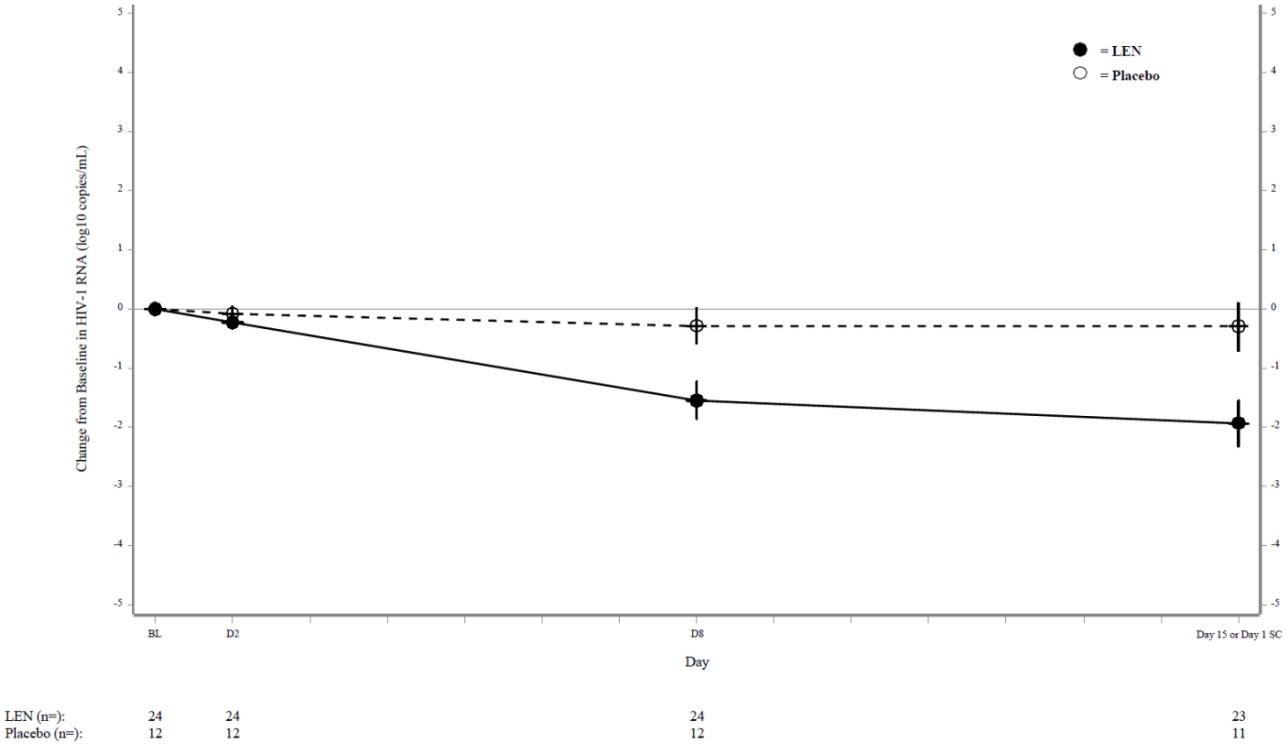
SC = subcutaneous

Change From Baseline in HIV-1 RNA

Functional Monotherapy Period

The mean (SD) baseline HIV-1 RNA value was lower for participants who received LEN than those who received placebo, as follows: LEN 3.97 (0.922) log10 copies/mL; placebo 4.87 (0.393) log10 copies/mL (difference in LSM: −0.90 [95% CI: −1.47 to −0.33]; P = 0.0028). The mean (SD) change from baseline in HIV-1 RNA at the end of the Functional Monotherapy Period was greater for participants who received LEN than those who received placebo, as follows: LEN −1.93 (0.893) log10 copies/mL; placebo −0.29 (0.614) log10 copies/mL (adjusted difference in LSM by baseline log10 HIV-1 RNA: −2.17 [95% CI: −2.74 to −1.59]; P < 0.0001).

Figure 15 GS-US-200-4625: Mean (95% CI) Change From Baseline in HIV-1 RNA (log10 copies/mL) by Visit – Functional Monotherapy Period Analysis (Full Analysis Set)



BL = baseline; Dx = Day x; LEN = lenacapavir; SC = subcutaneous

Baseline value was the last available value collected on or prior to the first dose date/time of blinded study drug.

Two participants had missing Day 15 HIV-1 RNA due to one not attending Day 15/Day 1 SC visit and for the other the Day 15 plasma sample was damaged.

Table 42 GS-US-200-4625: Change from Baseline in HIV-1 RNA on Days 2, 8, and Day 1 SC (Day 15) — Functional Monotherapy Period Analysis (Full Analysis Set)

	Cohort 1		LEN vs Placebo	
	LEN (N = 24)	Placebo (N = 12)	*P* value	Diff in LSM (95% CI)
Baseline				
N	24	12		
Mean (SD)	3.97 (0.922)	4.87 (0.393)	0.0028	−0.90 (−1.47, −0.33)
95% CI	(3.58, 4.36)	(4.62, 5.12)		
Median	4.19	4.93		
Q1, Q3	3.20, 4.57	4.46, 5.26		
Min, Max	2.33, 5.40	4.33, 5.33		
Change at Day 2				
N	24	12		
Mean (SD)	−0.22 (0.224)	−0.08 (0.214)	0.0380	−0.19 (−0.37 to −0.01)
95% CI	(−0.32, −0.13)	(−0.22, 0.06)		
Median	−0.17	−0.05		
Q1, Q3	−0.40, −0.07	−0.15, 0.06		
Min, Max	−0.81, 0.13	−0.60, 0.19		
Change at Day 8				
N	24	12		
Mean (SD)	−1.54 (0.745)	−0.28 (0.488)	< 0.0001	−1.67 (−2.15 to −1.20)
95% CI	(−1.86, −1.23)	(−0.59, 0.03)		
Median	−1.61	−0.07		
Q1, Q3	−1.96, −1.19	−0.40, −0.02		
Min, Max	−2.88, −0.01	−1.36, 0.36		
Change at Day 15 or Day 1 SC				
N	23	11		
Mean (SD)	−1.93 (0.893)	−0.29 (0.614)	< 0.0001	−2.17 (−2.74 to −1.59)
95% CI	(−2.31, −1.54)	(−0.70, 0.12)		
Median	−2.00	−0.08		
Q1, Q3	−2.83, −1.16	−0.42, 0.04		
Min, Max	−3.29, −0.29	−1.93, 0.31		

ANCOVA = analysis of covariance; ANOVA = analysis of variance; Diff = difference; LEN = lenacapavir (GS-6207); LSM = least squares mean; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of blinded study drug (LEN or placebo).
P value, difference in least squares means (Diff in LSM), and its 95% CI for baseline HIV-1 RNA were from ANOVA model with treatment group as a fixed effect in the model.
P value, difference in least squares means (Diff in LSM), and its 95% CI for postbaseline HIV-1 RNA and change from baseline at postbaseline visits were from ANCOVA model with treatment group as a fixed effect in the model and baseline HIV-1 RNA as a covariate.
One participant from Cohort 1 LEN group missed the Day 1 SC visit and 1 participant from Cohort 1 placebo group had Day 15 HIV-1 value missing.

All LEN Analysis

Table 43 GS-US-200-4625: Change From Baseline in HIV-1 RNA on Days 2, 8, and Day 1 SC — All LEN Analysis (Full Analysis Set)

	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Baseline					
N	24	12	36	36	72
Mean (SD)	3.97 (0.922)	4.56 (0.712)	4.17 (0.893)	4.06 (1.164)	4.11 (1.031)
95% CI	(3.58, 4.36)	(4.11, 5.02)	(3.86, 4.47)	(3.67, 4.46)	(3.87, 4.36)
Median	4.19	4.60	4.46	4.49	4.47
Q1, Q3	3.20, 4.57	4.39, 5.04	3.68, 4.77	3.28, 4.90	3.35, 4.87
Min, Max	2.33, 5.40	2.61, 5.33	2.33, 5.40	1.28, 5.70	1.28, 5.70
Change at Day 2					
N	24	11	35	34	69
Mean (SD)	−0.22 (0.224)	−0.11 (0.205)	−0.19 (0.222)	−0.12 (0.193)	−0.15 (0.209)
95% CI	(−0.32, −0.13)	(−0.25, 0.03)	(−0.26, −0.11)	(−0.19, −0.05)	(−0.21, −0.10)
Median	−0.17	−0.16	−0.16	−0.10	−0.14
Q1, Q3	−0.40, -0.07	−0.27, 0.01	−0.30, −0.02	−0.25, 0.01	−0.27, −0.01
Min, Max	−0.81, 0.13	−0.37, 0.31	−0.81, 0.31	−0.56, 0.28	−0.81, 0.31
Change at Day 8					
N	24	12	36	35	71
Mean (SD)	−1.54 (0.745)	−1.31 (0.559)	−1.47 (0.689)	−1.36 (0.628)	−1.41 (0.657)
95% CI	(−1.86, −1.23)	(−1.67, -0.96)	(−1.70, −1.23)	(−1.58, −1.14)	(−1.57, −1.26)
Median	−1.61	−1.36	−1.42	−1.51	−1.49
Q1, Q3	−1.96, −1.19	−1.58, −1.02	−1.95, −1.19	−1.74, −0.83	−1.80, −1.16
Min, Max	−2.88, −0.01	−2.21, −0.40	−2.88, −0.01	−2.61, 0.00	−2.88, 0.00
Change at Day 1 SC					
N	24	12	36	36	72
Mean (SD)	−1.97 (0.897)	−1.92 (0.712)	−1.95 (0.830)	−1.90 (0.939)	−1.93 (0.880)
95% CI	(−2.35, −1.59)	(−2.37, −1.47)	(−2.23, −1.67)	(−2.22, −1.59)	(−2.13, −1.72)
Median	−2.07	−2.09	−2.09	−2.05	−2.07
Q1, Q3	−2.83, −1.26	−2.44, −1.58	−2.64, −1.36	−2.47, −1.64	−2.54, −1.49
Min, Max	−3.29, −0.29	−2.74, −0.43	−3.29, −0.29	−4.09, 0.17	−4.09, 0.17

CSR = clinical study report; LEN = lenacapavir (GS-6207); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous
Baseline value was the last available value collected on or prior to the first dose date/time of oral LEN.
Change at Day 1 SC = Day 15 from the first dose of LEN (ie, corresponding to Day 15 in the study for LEN and Day 29 in the study for placebo).

Table 44 GS-US-200-4625: Change From Baseline in HIV-1 RNA by Visit (Log10 copies/mL) – All LEN Analysis (Full Analysis Set)

Analysis Set	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Baseline					
N	24	12	36	36	72
Mean (SD)	3.97 (0.922)	4.56 (0.712)	4.17 (0.893)	4.07 (1.158)	4.12 (1.028)
95% CI	(3.58 to 4.36)	(4.11 to 5.02)	(3.86 to 4.47)	(3.67 to 4.46)	(3.87 to 4.36)
Median	4.19	4.60	4.46	4.49	4.47
Q1, Q3	3.20, 4.57	4.39, 5.04	3.68, 4.77	3.28, 4.90	3.35, 4.87
Min, Max	2.33, 5.40	2.61, 5.33	2.33, 5.40	1.28, 5.70	1.28, 5.70
Change at Week 26					
N	24	12	36	34	70
Mean (SD)	−2.52 (1.057)	−2.69 (1.042)	−2.58 (1.040)	−2.47 (1.333)	−2.53 (1.184)
95% CI	(−2.97 to −2.07)	(−3.35 to −2.03)	(−2.93 to −2.23)	(−2.94 to −2.01)	(−2.81 to −2.24)
Median	−2.89	−3.08	−2.96	−2.76	−2.91
Q1, Q3	−3.27, −1.92	−3.24, −1.95	−3.27, −1.92	−3.56, −1.48	−3.32, −1.84
Min, Max	−4.06, −0.36	−4.00, −0.70	−4.06, −0.36	−4.43, 0.28	−4.43, 0.28
Change at Week 52					
N	23	12	35	7	42
Mean (SD)	−2.53 (0.972)	−2.63 (1.118)	−2.57 (1.009)	−2.14 (1.734)	−2.50 (1.145)
95% CI	(−2.96 to −2.11)	(−3.34 to −1.92)	(−2.91 to −2.22)	(−3.75 to −0.54)	(−2.85 to −2.14)
Median	−2.87	−3.11	−2.88	−3.13	−2.89
Q1, Q3	−3.28, −1.84	−3.49, −1.30	−3.30, −1.67	−3.50, −0.04	−3.30, −1.53
Min, Max	−3.88, −0.68	−4.00, −1.00	−4.00, −0.68	−3.95, 0.33	−4.00, 0.33

LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Baseline value was the last available value collected on or prior to the first dose date/time of LEN.

Change From Baseline in CD4 Cell Count

Mean (SD) baseline CD4 cell count value of participants in Cohorts 1 and 2 at baseline was 212 (226.2) cells/μL. At Week 26, mean (SD) change from baseline was 89 (106.7) cells/μL. At Week 52, mean (SD) change from baseline was 94 (121.5) cells/μL.

Table 45 GS-US-200-4625: CD4 Cell Counts (/uL) in 5 Categories by Visit – All LEN Analysis (Full Analysis Set)

Analysis Set	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Baseline					
N	24	12	36	36	72
< 50	3 (12.5%)	5 (41.7%)	8 (22.2%)	9 (25.0%)	17 (23.6%)
≥ 50 to < 200	13 (54.2%)	6 (50.0%)	19 (52.8%)	10 (27.8%)	29 (40.3%)
≥ 200 to < 350	6 (25.0%)	0	6 (16.7%)	8 (22.2%)	14 (19.4%)
≥ 350 to < 500	1 (4.2%)	1 (8.3%)	2 (5.6%)	4 (11.1%)	6 (8.3%)
≥ 500	1 (4.2%)	0	1 (2.8%)	5 (13.9%)	6 (8.3%)
Week 26					
N	22	12	34	33	67
< 50	0	0	0	0	0
≥ 50 to < 200	8 (36.4%)	9 (75.0%)	17 (50.0%)	9 (27.3%)	26 (38.8%)
≥ 200 to < 350	7 (31.8%)	1 (8.3%)	8 (23.5%)	11 (33.3%)	19 (28.4%)
≥ 350 to < 500	6 (27.3%)	1 (8.3%)	7 (20.6%)	5 (15.2%)	12 (17.9%)
≥ 500	1 (4.5%)	1 (8.3%)	2 (5.9%)	8 (24.2%)	10 (14.9%)
Week 52					
N	23	12	35	6	41
< 50	0	1 (8.3%)	1 (2.9%)	0	1 (2.4%)
≥ 50 to < 200	8 (34.8%)	5 (41.7%)	13 (37.1%)	0	13 (31.7%)
≥ 200 to < 350	10 (43.5%)	5 (41.7%)	15 (42.9%)	4 (66.7%)	19 (46.3%)
≥ 350 to < 500	2 (8.7%)	1 (8.3%)	3 (8.6%)	0	3 (7.3%)
≥ 500	3 (13.0%)	0	3 (8.6%)	2 (33.3%)	5 (12.2%)

Ancillary analyses

HIV-1 RNA < 50 copies/mL Using Imputation Methods (Missing = Failure and Missing = Excluded)

At Week 26 for the M = F analysis, the percentage of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 copies/mL was 80.6% (58 of 72 participants). At Week 52, the percentage of participants with HIV-1 RNA < 50 copies/mL was 77.8% (35 of 45 participants). As 3 participants discontinued study drug by Week 52, similar results were seen for the M = E approach at both Weeks 26 and 52.

Table 46 GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 26 and 52 Using Imputation Methods (Missing = Failure and Missing = Excluded) – All LEN Analysis (Full Analysis Set)

Participants With HIV-1 RNA < 50 copies/mL	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)		
Missing = Failure					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	29/36 (80.6%)	58/72 (80.6%)
Week 52	21/24 (87.5%)	9/12 (75.0%)	30/36 (83.3%)	5/9 (55.6%)	35/45 (77.8%)
Missing = Excluded					
Week 26	21/24 (87.5%)	8/12 (66.7%)	29/36 (80.6%)	29/34 (85.3%)	58/70 (82.9%)
Week 52	21/23 (91.3%)	9/12 (75.0%)	30/35 (85.7%)	5/7 (71.4%)	35/42 (83.3%)

LEN = lenacapavir
For the missing = failure analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis, excluding ongoing participants who had missing HIV-1 RNA at a visit and had not reached the upper limit of the analysis window for the corresponding visit.
For the missing = excluded analysis, the denominator for percentages was based on the number of participants in the Full Analysis Set for the All LEN Analysis with nonmissing HIV-1 RNA value at each visit. HIV-1 RNA data up to the final data extraction date were included.

Sensitivity analysis: OBR Switch Within 28 Days of Treatment Failure

Sensitivity analysis for the number and proportion of participants with HIV-1 RNA < 50 copies/mL at Week 26 and Week 52 who switched their OBR within 28 days and were counted as failures is shown in Table below.

Table 47 Number and Proportion of Participants with HIV 1 RNA < 50 copies/mL (Cohorts 1 and 2) at Weeks 26 and 52 (Modified FDA Snapshot Algorithm: OBR Switch Within 28 Days

of Treatment Failure [Sensitivity Analysis]) — All LEN Analysis (Full Analysis Set) – GS-US-200-4625

	Cohort 1				
	LEN (N = 24)	**Placebo → LEN (N = 12)**	**All LEN (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
Week 26[a]	21 (87.5%)	8 (66.7%)	29 (80.6%)	28 (77.8%)	57 (79.2%)
Week 52[b, c]	21 (87.5%)	8 (66.7%)	29 (80.6%)	5/9 (55.6%)	34/45 (75.6%)

FDA = Food and Drug Administration; LEN = lenacapavir (GS-6207); OBR = optimised background regimen; SC = subcutaneous

The Week 26 window was between Days 184 and 232 (inclusive). The Week 52 window was between Days 324 and 414 (inclusive).

a. Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the first SC LEN, was used in this analysis.

b. Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from Week 26 SC LEN, was used in this analysis.

c. For Week 52, ongoing Cohort 2 participants who had missing HIV-1 RNA at Week 52 and had not reached the upper limit of the analysis window for Week 52 were excluded.

Comparison of Results in Subpopulations

The proportion of participants with HIV 1 RNA < 50 copies/mL at Week 26 using the US FDA-defined snapshot algorithm based on the FAS was numerically higher in participants aged < 50 years, in female participants, participants with baseline CD4 cell count ≥ 200 cells/µL, and participants with baseline viral load ≤ 100,000 copies/mL.

Table 48 GS-US-200-4625: Number and Proportion of Participants With HIV-1 RNA < 50 copies/mL at Week 26 Using the US FDA-Defined Snapshot Algorithm by Subgroup – All LEN Analysis (Full Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	All LEN (N = 36)	Cohort 2 (N = 6)	Total (N = 42)
Baseline CD4 cell count categories (cells/μL)					
< 200	14/16 (87.5%)	7/11 (63.6%)	21/27 (77.8%)	1/2 (50.0%)	22/29 (75.9%)
≥ 200	7/8 (87.5%)	1/1 (100.0%)	8/9 (88.9%)	3/4 (75.0%)	11/13 (84.6%)
Baseline HIV-1 RNA categories (copies/mL)					
≤ 100,000	20/23 (87.0%)	5/6 (83.3%)	25/29 (86.2%)	4/5 (80.0%)	29/34 (85.3%)
> 100,000	1/1 (100.0%)	3/6 (50.0%)	4/7 (57.1%)	0/1	4/8 (50.0%)
Overall susceptibility score based on baseline OBR					
0 to < 1	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1 to < 2	6/6 (100.0%)	5/6 (83.3%)	11/12 (91.7%)	2/3 (66.7%)	13/15 (86.7%)
≥ 2	12/14 (85.7%)	2/4 (50.0%)	14/18 (77.8%)	0/1	14/19 (73.7%)
Number of fully active ARV agents in the baseline OBR					
0	3/4 (75.0%)	1/2 (50.0%)	4/6 (66.7%)	2/2 (100.0%)	6/8 (75.0%)
1	6/7 (85.7%)	6/7 (85.7%)	12/14 (85.7%)	2/3 (66.7%)	14/17 (82.4%)
≥ 2	12/13 (92.3%)	1/3 (33.3%)	13/16 (81.3%)	0/1	13/17 (76.5%)
Resistance categories based on baseline INSTI resistance profile					
With INSTI resistance	19/20 (95.0%)	4/7 (57.1%)	23/27 (85.2%)	3/5 (60.0%)	26/32 (81.3%)
Without INSTI resistance	2/4 (50.0%)	3/4 (75.0%)	5/8 (62.5%)	1/1 (100.0%)	6/9 (66.7%)
Use of DTG and/or DRV					
With DTG and DRV	6/6 (100.0%)	4/6 (66.7%)	10/12 (83.3%)	0/1	10/13 (76.9%)
With DTG, without DRV	4/4 (100.0%)	1/2 (50.0%)	5/6 (83.3%)	2/3 (66.7%)	7/9 (77.8%)
Without DTG, with DRV	5/6 (83.3%)	2/3 (66.7%)	7/9 (77.8%)	1/1 (100.0%)	8/10 (80.0%)
Without DTG or DRV	6/8 (75.0%)	1/1 (100.0%)	7/9 (77.8%)	1/1 (100.0%)	8/10 (80.0%)
Use of IMAB					
With IMAB	8/9 (88.9%)	1/3 (33.3%)	9/12 (75.0%)	0/1	9/13 (69.2%)
Without IMAB	13/15 (86.7%)	7/9 (77.8%)	20/24 (83.3%)	4/5 (80.0%)	24/29 (82.8%)

ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; FDA = Food and Drug Administration; IMAB = ibalizumab; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; OBR = optimized background regimen; US = United States
The Week 26 window is between Days 184 and 232 (inclusive).
Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the first subcutaneous LEN, was used in this analysis.

The proportion of participants in Cohorts 1 and 2 with HIV 1 RNA < 50 copies/mL at Week 52 using the US FDA-defined snapshot algorithm based on the FAS was numerically higher in female participants, in nonblack participants, participants in ex-US region, participants with baseline CD4 cell count ≥ 200 cells/μL, and participants with baseline viral load ≤ 100,000 copies/mL.

At Week 26, although limited by small sample size, the data indicate consistent efficacy of LEN regardless of the region (United States [US] vs ex-US) for both Cohorts 1 and 2.

Since the Week 52 data cut occurred when all participants from Cohort 1 had completed the Week 52 visit, HIV 1 RNA data was available for only 9 of 36 participants in Cohort 2, however, data was consistent with Week 26.

Table 49 Virologic Outcomes (HIV-1 RNA < 50 copies/mL) by Region at Weeks 26 (FDA Snapshot Algorithm) — All LEN Analysis – GS-US-200-4625

	Cohort 1				
	LEN (N = 24)	**Placebo > LEN (N = 12)**	**All LEN (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**
Week 26					
US	18/20 (90.0%)	6/9 (66.7%)	24/29 (82.8%)	9/13 (69.2%)	33/42 (78.6%)
95% CI	68.3% to 98.8%	29.9% to 92.5%	64.2% to 94.2%	38.6% to 90.9%	63.2% to 89.7%
Ex-US	3/4 (75.0%)	2/3 (66.7%)	5/7 (71.4%)	20/23 (87.0%)	25/30 (83.3%)
95% CI	19.4% to 99.4%	9.4% to 99.2%	29.0% to 96.3%	66.4% to 97.2%	65.3% to 94.4%

FDA = Food and Drug Administration; LEN = lenacapavir (GS-6207); SC = subcutaneous; US = United States
The Week 26 window was between Days 184 and 232 (inclusive).
Only HIV-1 RNA collected on-treatment, defined as HIV-1 RNA collected up to 28 weeks from the last SC LEN, was used in this analysis.
The 95% CIs of the proportions of participants with HIV-1 RNA < 50 copies/mL were calculated based on the exact method.

Discontinuations

In Study GS-US-200-4625, no participants in either Cohort 1 or 2 prematurely discontinued study drug due to lack of efficacy through Week 52, and all participants who changed OBR continued on the study. Eight participants changed OBR between the Week 26 and Week 52 analyses; 4 participants had HIV-1 RNA < 50 copies/mL at Week 52 and the other 4 participants are still on study drug but have not yet reached Week 52.

Study GS-US-200-4334

Methods

Study Title: A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination With Other Antiretroviral Agents in People Living With HIV

This is an ongoing Phase 2, randomised, open-label, active-controlled, multicentre study evaluating the safety and efficacy of LEN in combination with other ARV agents in treatment-naive PWH. Participants who met all eligibility criteria were randomised in a 2:2:2:1 ratio to 1 of the 4 treatment groups below. Randomisation was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

The interim analysis at Week 28 and Week 54, was conducted after all participants had completed the Week 28 or 54 visit or prematurely discontinued the study drug.

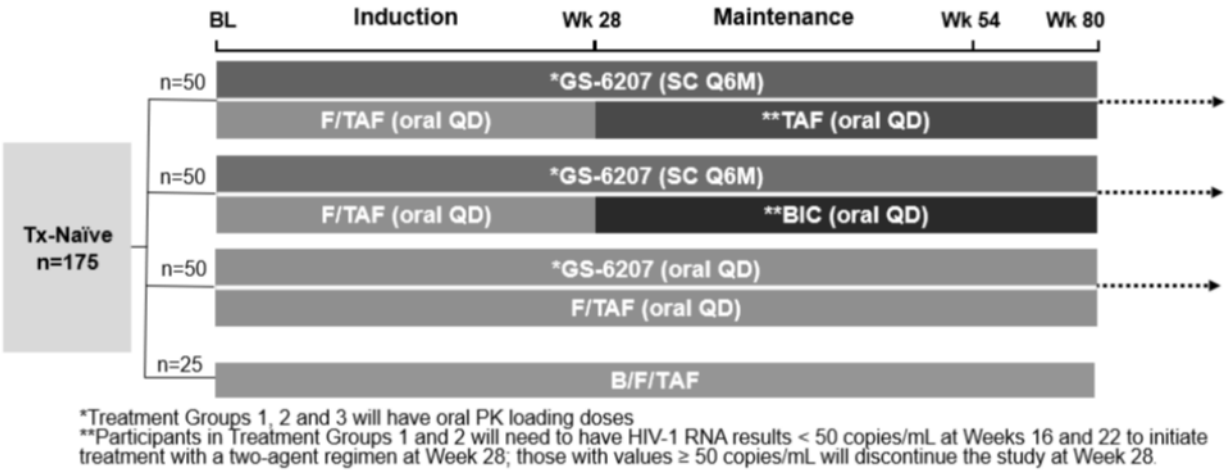


Figure 16 Study design

Study Participants

Main inclusion criteria

People with HIV who met the following criteria were included: aged ≥ 18 years, antiretroviral (ARV) naive (no use of any ARV within 1 month of screening); furthermore, at screening, participants had plasma HIV-1 RNA ≥ 200 copies/mL and CD4 cell count ≥ 200 cells/µL.

Main exclusion criteria

These include chronic HBV or HCV. Furthermore, the following laboratory measures were not allowed:

- Estimated glomerular filtration rate (eGFR) ≤ 50 mL/min according to the
- Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}
- Alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN)
- Direct bilirubin > 1.5 x ULN
- Platelets < 50,000/mm3
- Haemoglobin < 8.0 g/dL

Treatments

Treatment Group 1 (SC LEN + [DVY → TAF]) (N = 52):

- Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks + SC LEN injection 927 mg on Day 15
- Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily TAF 25 mgc

Treatment Group 2 (SC LEN + [DVY → BIC]) (N = 53):

- Induction Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + oral daily DVY (F/TAF 200/25 mg) from Day 1 onwards for a total of 28 weeks + SC LEN injection 927 mg on Day 15
- Maintenance Period: SC LEN injection 927 mg at Week 28 and every 6 months (26 weeks) thereafter + oral daily BIC 75 mgc

Treatment Group 3 (Oral LEN + DVY) (N = 52):

- oral LEN 600 mg on Days 1 and 2 and oral daily LEN 50 mg from Day 3 onwards + oral daily DVY (F/TAF 200/25 mg)

Treatment Group 4 (BVY) (N = 25): oral daily BVY (B/F/TAF 50/200/25 mg)

Outcomes/endpoints

The primary endpoint

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm

The secondary endpoints

- The proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 as determined by the US FDA-defined snapshot algorithm
- The change from baseline in log10 HIV-1 RNA and in CD4 cell count at Weeks 28, 38, 54, and 80
- Incidences of treatment-emergent adverse events (AEs) and graded laboratory abnormalities
- PK parameters for TAF, tenofovir (TFV), and tenofovir diphosphate (TFV-DP

Randomisation, blinding (masking) and sample size

Eligible subjects were randomised to treatment group 1, 2, 3 or 4 using an allocation ratio of 2:2:2:1. Randomisation was stratified by screening HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL). Blinding (masking) of treatment was not applicable since this is an open-label study.

A sample size of 50 subjects in the treatment groups 1 to 3, respectively, was chosen to estimate the primary endpoint response rate of HIV-1 RNA < 50 copies/mL at Week 54. A total sample size of 75 subjects for each pair of comparisons, i.e., between each of the LEN-containing regimen groups 1 to 3 (n = 50) and the B/F/TAF treatment group 4, (n = 25) were to provide 39% power to evaluate non-inferiority assuming a response rate of 90.9% for each treatment group and a non-inferiority margin of 0.12.

Statistical methods

The SAP (version 1.0) dated 13 April 2021 described the analysis plan for the initially submitted Week 28 interim analysis for which database finalisation was stated to have occurred 14 April 2021. The SAP referred to the CSP version amendment 3 (01 September 2020) and according to the CSR there were no changes made to planned analyses.

Currently, also the week 54 interim analysis have been performed. Database Finalisation was 27 October 2021. The week 54 interim analysis SAP (Version 1.0) was dated 26 October 2021. This SAP is an update concerning a few analysis features. A per protocol analysis set was added and a secondary analysis based on this PP analysis set for assessment of robustness. In addition, wording was updated to mirror the week 54 analysis time-point.

The Week 28 interim analysis was conducted after all subjects had completed the Week 28 visit or had prematurely discontinued the study drug. Three additional interim analyses had been planned: week 38, week 54 (primary analysis), and week 80 analyses. Hence, the analysis of the primary efficacy endpoint had not been performed at the time-point for the initially submitted analysis given that the majority of subjects had not reached Week 54. With the D120 LoQ answers, the CSR had been

updated (addendum 1: 24 January 2022) including data for the primary efficacy endpoint at week 54, additional efficacy endpoints at weeks 38 and 54, and a cumulative safety analysis for treatment groups 1 to 4 through Week 54. The week 54 interim analysis was the planned primary analysis and was conducted after all subjects have completed Week 54 visit or have prematurely discontinued the study drug. Adjustments for multiplicity were not planned justified by this being a phase 2, non-confirmatory trial.

The proportion of subjects with HIV-1 RNA < 50 copies/mL (US FDA-defined snapshot algorithm) at week 28 was based on the Full Analysis Set (FAS) including all subjects who were randomised and had received at least 1 dose of study drug. The analysis window was defined as from study day 176 to study day 231, inclusive. All HIV-1 RNA data collected on-treatment (i.e., data collected up to 1 day after the last dose date) was used in the US FDA-defined snapshot algorithm.

Point estimates and 95% CI for the difference in the response rates between each of the LEN-containing regimen groups (groups 1 to 3) and the BVY group (group 4) were constructed using the stratum-adjusted Mantel-Haenszel (MH) proportion (Koch, 1989), stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL). The number and percentage of participants with HIV-1 RNA < 50 copies/mL at Week 28 have been summarised. The associated p-values were estimated based on the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

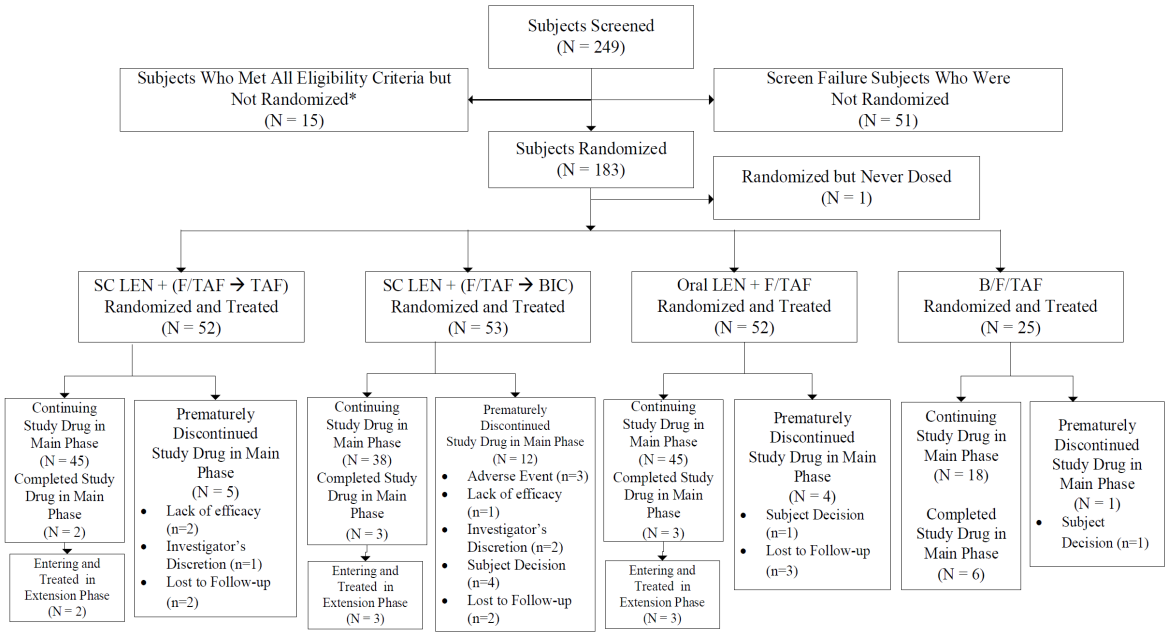
The primary endpoint was the proportion of participants with HIV-1 RNA < 50 copies/mL at Week 54 (US FDA-defined snapshot algorithm). The analysis window at Week 54 was defined as from Study Day 323 to Study Day 413, inclusive. The analysis was planned and have been performed analogous the week 28 endpoint.

A secondary analysis based on the Week 54 PP Analysis Set instead of the FAS was also performed to evaluate the robustness of the primary analysis of the primary end point. Participants excluded from the Week 54 PP Analysis Set were determined before database lock.

Results

Participant flow

Figure 17 GS-US-200-4334: Disposition of Participants (All Screened Participants)



BIC, B = bictegravir; B/F/TAF = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy, BVY); F/TAF = emtricitabine/tenofovir alafenamide (coformulated; Descovy, DVY); LEN = lenacapavir; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide
Included case report form data collected up to 30 September 2021.
*Among 15 participants who met all eligibility criteria but not randomized, the reasons (n) were: investigator's discretion (1); withdrew consent (9); lost to follow-up (3); and outside of visit window (1). One participant is not screen failure (missed two criteria but met all other criteria) and not enrolled due to lost to follow-up.
Screen failure participants are the participants who did not meet all eligibility criteria.

Recruitment

Study centres: One site in Dominican Republic and 40 sites in the United States (US) (not including 1 site that accepted a participant transfer)

Table 50 GS-US-200-4334: Key Dates

Event	Date
First Participant Screened	22 November 2019
First Participant Randomized	18 December 2019
Last Participant Last Visit for the Primary Efficacy End Point[a]	05 October 2021
Last Participant Last Visit for the Week 54 Analysis[b]	30 September 2021
Database Finalization	27 October 2021

a Last participant last visit for the primary efficacy end point was based on the latest collection of HIV-1 RNA data that included a retest for one participant.
b Last participant last visit for the Week 54 analysis was based on the last Week 54 planned visit without considering a retest

Conduct of the study

The original protocol (02 October 2019) was amended 3 times (05 November 2019,24 January 2020, and 01 September 2020). Key changes to the study protocol are described below.

Protocol Amendment 1 (05 November 2019)

- No major amendment.

Protocol Amendment 2 (24 January 2020)

- Updated eligibility criteria enabling a broader range of people living with HIV, who may safely do so, to safely participate in the study and making it more in line with the treatment guideline by the US Department of Health and Human Services (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV) and current standard of care in clinical practice.

Protocol Amendment 3 (01 September 2020)

- Corrected SC dose from 300 mg to 309 mg and due to the corrected SC dose concentration updated from 900 mg to 927 mg.
- Updated statistical method to assess demographic and baseline characteristics comparability across the four treatment groups. For continuous demographic and baseline characteristics, the 2-sided Kruskal-Wallis instead of Wilcoxon rank sum test will be used to compare across treatment groups.

No changes from the protocol-specified efficacy, PK, or safety analyses were planned.

Baseline data

Table 51 GS-US-200-4334: Demographic and Baseline Characteristics (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
Age (years)								
N	52	53	52	25	105	157	182	0.3837
Mean (SD)	33 (9.5)	30 (8.8)	32 (12.3)	33 (11.1)	32 (9.3)	32 (10.3)	32 (10.4)	
Median	31	28	28	29	30	29	29	
Q1, Q3	26, 40	24, 33	24, 36	26, 33	25, 36	24, 36	24, 36	
Min, max	19, 61	19, 56	19, 72	21, 61	19, 61	19, 72	19, 72	
Sex at birth								
Male	47 (90.4%)	52 (98.1%)	46 (88.5%)	25 (100.0%)	99 (94.3%)	145 (92.4%)	170 (93.4%)	0.0908
Female	5 (9.6%)	1 (1.9%)	6 (11.5%)	0	6 (5.7%)	12 (7.6%)	12 (6.6%)	
Race								
American Indian or Alaska Native	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)	1 (0.5%)	0.6726
Asian	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)	2 (1.1%)	
Black	24 (46.2%)	24 (45.3%)	31 (59.6%)	16 (64.0%)	48 (45.7%)	79 (50.3%)	95 (52.2%)	
Native Hawaiian or Pacific Islander	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)	2 (1.1%)	
White	23 (44.2%)	28 (52.8%)	19 (36.5%)	8 (32.0%)	51 (48.6%)	70 (44.6%)	78 (42.9%)	
Other	2 (3.8%)	0	1 (1.9%)	1 (4.0%)	2 (1.9%)	3 (1.9%)	4 (2.2%)	
Race group								
Black	24 (46.2%)	24 (45.3%)	31 (59.6%)	16 (64.0%)	48 (45.7%)	79 (50.3%)	95 (52.2%)	0.2313
Non-Black	28 (53.8%)	29 (54.7%)	21 (40.4%)	9 (36.0%)	57 (54.3%)	78 (49.7%)	87 (47.8%)	
Ethnicity								
Hispanic or Latino	25 (48.1%)	21 (39.6%)	24 (46.2%)	12 (48.0%)	46 (43.8%)	70 (44.6%)	82 (45.1%)	0.8178
Not Hispanic or Latino	27 (51.9%)	32 (60.4%)	28 (53.8%)	13 (52.0%)	59 (56.2%)	87 (55.4%)	100 (54.9%)	

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
Body mass index (kg/m^2)								
N	52	53	52	25	105	157	182	0.7920
Mean (SD)	27.3 (7.82)	26.2 (5.90)	26.6 (5.67)	27.1 (6.05)	26.8 (6.91)	26.7 (6.51)	26.8 (6.43)	
Median	26.4	24.9	26.0	26.9	25.2	25.8	25.8	
Q1, Q3	21.1, 30.0	21.9, 28.7	22.4, 30.4	23.3, 31.0	21.6, 29.3	21.9, 29.5	22.2, 29.8	
Min, max	17.5, 51.1	18.7, 48.9	17.3, 44.3	17.0, 44.1	17.5, 51.1	17.3, 51.1	17.0, 51.1	

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
Denominator for percentages was the Safety Analysis Set.
Age (in years) was collected on the first dose date of study drug (Day 1) if dosed, randomization if not dosed, or informed consent if not enrolled.
Body mass index (kg/m^2) = [Weight (kg)/Height (cm)^2]*10,000
For categorical data, *P* value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) to compare across treatment groups.
For continuous data, *P* value was from the 2-sided Kruskal-Wallis test to compare across treatment groups.

Table 52 cont.– GS-US-200-4334: Baseline Disease Characteristics (Safety Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 182)	*P* Value
HIV-1 RNA (log_{10} copies/mL)								
N	52	53	52	25	105	157	182	0.5266
Mean (SD)	4.18 (0.672)	4.35 (0.670)	4.33 (0.722)	4.35 (0.780)	4.27 (0.673)	4.29 (0.688)	4.30 (0.700)	
Median	4.27	4.32	4.53	4.37	4.32	4.36	4.37	
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.88, 4.70	3.85, 4.73	3.86, 4.74	
Min, max	2.27, 5.63	2.46, 5.75	2.35, 5.54	2.10, 5.92	2.27, 5.75	2.27, 5.75	2.10, 5.92	
HIV-1 RNA categories (copies/mL)								
≤ 100,000	47 (90.4%)	44 (83.0%)	43 (82.7%)	21 (84.0%)	91 (86.7%)	134 (85.4%)	155 (85.2%)	0.6630
> 100,000	5 (9.6%)	9 (17.0%)	9 (17.3%)	4 (16.0%)	14 (13.3%)	23 (14.6%)	27 (14.8%)	
CD4 cell count (cells/µL)								
N	52	53	52	25	105	157	182	0.6194
Mean (SD)	506 (297.0)	490 (209.9)	470 (221.7)	534 (260.0)	498 (255.7)	489 (244.6)	495 (246.5)	
Median	404	450	409	482	434	417	437	
Q1, Q3	320, 599	332, 599	301, 600	393, 527	321, 599	320, 599	332, 599	
Min, max	213, 1846	187, 991	175, 1091	232, 1443	187, 1846	175, 1846	175, 1846	
CD4 cell count categories (cells/µL)								
< 50	0	0	0	0	0	0	0	0.4852
≥ 50 to < 200	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)	4 (2.2%)	
≥ 200 to < 350	17 (32.7%)	15 (28.3%)	16 (30.8%)	4 (16.0%)	32 (30.5%)	48 (30.6%)	52 (28.6%)	
≥ 350 to < 500	17 (32.7%)	15 (28.3%)	15 (28.8%)	11 (44.0%)	32 (30.5%)	47 (29.9%)	58 (31.9%)	
≥ 500	18 (34.6%)	22 (41.5%)	18 (34.6%)	10 (40.0%)	40 (38.1%)	58 (36.9%)	68 (37.4%)	
CD4 percentage (%)								
N	52	53	52	25	105	157	182	0.2088
Mean (SD)	24.2 (9.92)	24.1 (8.04)	22.7 (8.28)	26.2 (8.18)	24.2 (8.98)	23.7 (8.75)	24.0 (8.70)	
Median	22.4	24.6	20.9	26.1	23.3	22.5	23.1	
Q1, Q3	18.9, 27.3	17.7, 29.1	17.4, 25.5	20.5, 30.0	18.4, 28.5	18.1, 27.9	18.5, 28.2	
Min, max	8.0, 63.0	8.0, 40.4	8.9, 45.8	12.0, 43.5	8.0, 63.0	8.0, 63.0	8.0, 63.0	

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
For categorical data, *P* value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data) to compare across treatment groups.
For continuous data, *P* value was from the 2-sided Kruskal-Wallis test to compare across treatment groups.

Numbers analysed

Table 53 GS-US-200-4334: Analysis Sets

Analysis set	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 26)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 183)
All Randomized Analysis Set	52	53	52	26	105	157	183
Full Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
Safety Analysis Set	52 (100.0%)	53 (100.0%)	52 (100.0%)	25 (96.2%)	105 (100.0%)	157 (100.0%)	182 (99.5%)
PK Analysis Set	49 (94.2%)	49 (92.5%)	52 (100.0%)	25 (96.2%)	98 (93.3%)	150 (95.5%)	175 (95.6%)
PK Substudy Analysis Set	11 (21.2%)	14 (26.4%)	9 (17.3%)	0	25 (23.8%)	34 (21.7%)	34 (18.6%)
PBMC PK Substudy Analysis Set	7 (13.5%)	12 (22.6%)	0	0	19 (18.1%)	19 (12.1%)	19 (10.4%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); LEN = lenacapavir; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; SC = subcutaneous; TAF = tenofovir alafenamide; TFV = tenofovir
The denominator for percentage is the number of participants in the All Randomized Analysis Set.

A total of 162 participants were included in the Per-Protocol Analysis Set at Week 54.

Analysis set	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 26)	SC LEN Total (N = 105)	LEN Total (N = 157)	Total (N = 183)
Participants in Week 54 Per-Protocol (PP) Analysis Set	47 (90.4%)	46 (86.8%)	47 (90.4%)	22 (84.6%)	93 (88.6%)	140 (89.2%)	162 (88.5%)

Outcomes and estimation

Primary endpoint

HIV-1 RNA < 50 copies/mL at Week 54 (US FDA-Defined Snapshot Algorithm)

The proportion of participants were similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group, as follows:

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

The proportion of participants in the Week 54 PP Analysis Set with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were consistent with those for the FAS.

For participants with HIV-1 RNA < 50 copies/mL at Week 28, the proportion with HIV-1 RNA < 50 copies/mL at Week 54 were also similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group, as follows:

- LEN total: 135 of 147 participants (91.8%)
- SC LEN + (DVY → TAF): 46 of 49 participants (93.9%)
- SC LEN + (DVY → BIC): 45 of 49 participants (91.8%)
- Oral LEN + DVY: 44 of 49 participants (89.8%)
- BVY: 23 of 25 participants (92.0%)

Five participants who had the virologic outcome of HIV-1 RNA <50 copies/mL at Week 28 had that of HIV-1 RNA ≥ 50 copies/mL at Week 54 using the US FDA-defined snapshot algorithm (SC LEN + [DVY → TAF]: 2 participants [4.1%]; Oral LEN + DVY:3 participants [6.1%]).

Otherwise, the remaining participants who did not have HIV-1 RNA < 50 copies/mL at Week 54 discontinued study drug (SC LEN + [DVY → TAF]: 1 participant [2.0%], SC LEN + [DVY → BIC]: 4 participants [8.2%], Oral LEN + DVY:1 participant [2.0%], and BVY. 1 participant [4.0%]) or had missing data (Oral LEN + DVY:1 participant [2.0%], and BVY. 1 participant [4.0%]).

Secondary endpoint

HIV-1 RNA < 50 copies/mL at Week 28 and 38 (US FDA-Defined Snapshot Algorithm)

The percentages of participants with HIV-1 RNA < 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group, as follows:

- LEN total: 93.6%, 147 of 157 participants
- SC LEN + (DVY → TAF): 94.2%, 49 of 52 participants
- SC LEN + (DVY → BIC): 92.5%, 49 of 53 participants
- Oral LEN + DVY: 94.2%, 49 of 52 participants

- BVY: 100.0%, 25 of 25 participants

A total of 2 participants had HIV-1 RNA ≥ 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm. Both participants were in the SC LEN + (DVY → BIC) group and had prematurely discontinued study drug before the Week 28 window, as follows:

- One participant did not meet the protocol-defined criterion of HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate the maintenance regimen at Week 28; the participant started dolutegravir, lamivudine/zidovudine, and tenofovir disoproxil fumarate and had HIV-1 RNA < 50 copies/mL at Week 28.
- One participant prematurely discontinued study drug due to participant decision on Day 2.

Table 54 GS-US-200-4334: Virologic Outcome at Week 28 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cut-off at 50 copies/mL (Full Analysis Set)

	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
HIV-1 RNA < 50 copies/mL	49 (94.2%)	49 (92.5%)	49 (94.2%)	25 (100.0%)	98 (93.3%)	147 (93.6%)
HIV-1 RNA ≥ 50 copies/mL	0	2 (3.8%)	0	0	2 (1.9%)	2 (1.3%)
HIV-1 RNA ≥ 50 copies/mL in Week 28 window	0	0	0	0	0	0
Discontinued study drug due to lack of efficacy	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA ≥ 50 copies/mL	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
No virologic data in Week 28 window	3 (5.8%)	2 (3.8%)	3 (5.8%)	0	5 (4.8%)	8 (5.1%)
Discontinued study drug due to adverse event/death	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Discontinued study drug due to other reasons* and last available HIV-1 RNA < 50 copies/mL	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Missing data during window but on study drug	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
LEN vs BVY						
P value	0.2398	0.1639	0.2307	—	0.1794	0.1916
Difference in percentage (95% CI)	−5.5% (−15.9% to 4.8%)	−7.4% (−18.3% to 3.4%)	−5.7% (−16.3% to 4.9%)	—	−6.9% (−16.1% to 2.4%)	−6.5% (−15.1% to 2.2%)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); FDA = Food and Drug Administration; LEN = lenacapavir; SC = subcutaneous; TAF = tenofovir alafenamide; US = United States

* Other reasons include participants who discontinued study drug due to investigator's discretion, participant decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

The Week 28 window is between Days 176 and 231 (inclusive).

The difference in percentage of participants with HIV-1 RNA < 50 copies/mL between each of the LEN-containing treatment groups and the BVY group and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

P value was from the Cochran-Mantel-Haenszel tests stratified by baseline HIV-1 RNA stratum (≤ 100,000 vs > 100,000 copies/mL).

The proportion of participants in the FAS with HIV-1 RNA < 50 copies/mL at Week 38 using the US FDA-defined snapshot algorithm were similar in each treatment group, with no significant difference between each of the LEN-containing groups and the BVY group, as follows:

- LEN total: 140 of 157 participants (89.2%)
- SC LEN + (DVY → TAF): 47 of 52 participants (90.4%)
- SC LEN + (DVY → BIC): 47 of 53 participants (88.7%)
- Oral LEN + DVY: 46 of 52 participants (88.5%)
- BVY: 24 of 25 participants (96.0%)

Change From Baseline in HIV-1 RNA

Mean baseline HIV-1 RNA values and mean changes from baseline in HIV-1 RNA at Week 28, 38 and 54 were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group.

Table 55 GS-US-200-4334: Change From Baseline in HIV-1 RNA (log10 copies/mL) by Visit (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Baseline						
N	52	53	52	25	105	157
Mean (SD)	4.18 (0.672)	4.35 (0.670)	4.33 (0.722)	4.35 (0.780)	4.27 (0.673)	4.29 (0.688)
95% CI	(3.99, 4.37)	(4.17, 4.54)	(4.13, 4.53)	(4.03, 4.67)	(4.14, 4.40)	(4.18, 4.40)
Median	4.27	4.32	4.53	4.37	4.32	4.36
Q1, Q3	3.77, 4.63	3.96, 4.74	3.82, 4.83	4.09, 4.77	3.88, 4.70	3.85, 4.73
Min, Max	2.27, 5.63	2.46, 5.75	2.35, 5.54	2.10, 5.92	2.27, 5.75	2.27, 5.75
LEN vs. BVY						
P-value	0.5267	0.9455	0.8150		0.6826	0.7062
Diff in LSM (95% CI)	−0.09 (−0.38, 0.20)	−0.01 (−0.28, 0.26)	−0.03 (−0.32, 0.26)		−0.05 (−0.30, 0.20)	−0.05 (−0.28, 0.19)
Change at Week 28						
N	49	51	50	25	100	150
Mean (SD)	−2.92 (0.649)	−3.04 (0.638)	−3.01 (0.716)	−3.07 (0.774)	−2.98 (0.643)	−2.99 (0.666)
95% CI	(−3.11, −2.73)	(−3.22, −2.86)	(−3.22, −2.81)	(−3.39, −2.75)	(−3.11, −2.85)	(−3.10, −2.88)
Median	-3.05	-3.03	-3.17	-3.10	-3.04	-3.05
Q1, Q3	−3.36, −2.57	−3.46, −2.68	−3.51, −2.53	−3.49, −2.81	−3.41, −2.65	−3.45, −2.57
Min, Max	−4.35, −0.99	−4.26, −1.18	−4.26, −1.08	−4.56, −0.82	−4.35, −0.99	−4.35, −0.99
LEN vs. BVY						
P-value	0.5755	0.8697	0.7052		0.6732	0.6595
Diff in LSM (95% CI)	0.08 (−0.20, 0.37)	0.02 (−0.25, 0.29)	0.06 (−0.23, 0.35)		0.05 (−0.19, 0.29)	0.05 (−0.18, 0.29)

	SC LEN + (DVY -> TAF) (N = 52)	SC LEN + (DVY -> BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Change at Week 38						
N	49	51	47	25	100	147
Mean (SD)	−2.96 (0.639)	−3.06 (0.641)	−3.02 (0.771)	−3.04 (0.760)	−3.01 (0.639)	−3.01 (0.681)
95% CI	(−3.14, −2.77)	(−3.24, −2.88)	(−3.24, −2.79)	(−3.36, −2.73)	(−3.13, −2.88)	(−3.12, −2.90)
Median	−3.06	−3.04	−3.26	−3.04	−3.05	−3.11
Q1, Q3	−3.36, −2.59	−3.46, −2.68	−3.59, −2.53	−3.49, −2.81	−3.43, −2.66	−3.46, −2.58
Min, Max	−4.35, −0.99	−4.26, −1.18	−4.26, −1.08	−4.46, −0.82	−4.35, −0.99	−4.35, −0.99
LEN vs. B/F/TAF						
P-value	0.8942	0.9058	0.8129		0.9845	0.9149
Diff in LSM (95% CI)	0.02 (−0.26, 0.30)	−0.02 (−0.28, 0.25)	0.04 (−0.27, 0.35)		0.00 (−0.24, 0.24)	0.01 (−0.23, 0.26)
Change at Week 54						
N	49	47	47	23	96	143
Mean (SD)	−2.95 (0.636)	−3.12 (0.589)	−2.85 (0.840)	−3.08 (0.787)	−3.04 (0.616)	−2.98 (0.700)
95% CI	(−3.14, −2.77)	(−3.30, −2.95)	(−3.10, −2.61)	(−3.42, −2.74)	(−3.16, −2.91)	(−3.09, −2.86)
Median	−3.06	−3.13	−3.03	−3.10	−3.06	−3.06
Q1, Q3	−3.36, −2.59	−3.48, −2.77	−3.51, −2.36	−3.56, −2.81	−3.45, −2.67	−3.45, −2.57
Min, Max	−4.27, −0.99	−4.26, −1.76	−4.08, −0.74	−4.64, −0.82	−4.27, −0.99	−4.27, −0.74
LEN vs. B/F/TAF						
P-value	0.7864	0.7013	0.2753		0.9851	0.5943
Diff in LSM (95% CI)	0.04 (−0.25, 0.33)	−0.05 (−0.31, 0.21)	0.22 (−0.18, 0.62)		0.00 (−0.24, 0.24)	0.08 (−0.21, 0.36)

ANOVA = analysis of variance; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; LSM = least squares mean; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 copies/mL HIV-1 RNA Detected" were replaced as 19 copies/mL for analysis purpose.
P-value, difference in least squares means (Diff in LSM), and its 95% CI were from ANOVA model adjusting for the baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

Change From Baseline in CD4 Cell Count

Mean baseline CD4 cell counts and mean changes from baseline in CD4 cell count at Week 28, 38 and 54 were similar across treatment groups in Study GS-US-200-4334, with no significant differences between each of the LEN-containing groups and the BVY group.

Table 56 GS-US-200-4334: Change From Baseline in CD4 Cell Count (/µL) by Visit (Full Analysis Set)

	SC LEN + (DVY -> TAF) (N=52)	SC LEN + (DVY -> BIC) (N=53)	Oral LEN + DVY (N=52)	BVY (N=25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Baseline						
N	52	53	52	25	105	157
Mean (SD)	506 (297.0)	490 (209.9)	470 (221.7)	534 (260.0)	498 (255.7)	489 (244.6)
95% CI	(423, 589)	(433, 548)	(408, 532)	(427, 641)	(449, 548)	(450, 527)
Median	404	450	409	482	434	417
Q1, Q3	320, 599	332, 599	301, 600	393, 527	321, 599	320, 599
Min, Max	213, 1846	187, 991	175, 1091	232, 1443	187, 1846	175, 1846
LEN vs. B/F/TAF						
P-value	0.5528	0.4360	0.2744		0.4678	0.3701
Diff in LSM (95% CI)	−41 (−177, 96)	−42 (−149, 65)	−63 (−176, 51)		−40 (−151, 70)	−47 (−150, 56)
Change at Week 28						
N	49	50	50	25	99	149
Mean (SD)	172 (178.2)	158 (164.1)	206 (154.6)	163 (157.7)	165 (170.5)	179 (166.0)
95% CI	(121, 224)	(112, 205)	(162, 250)	(98, 228)	(131, 199)	(152, 206)
Median	143	193	194	155	179	183
Q1, Q3	78, 301	91, 264	99, 306	59, 257	78, 278	89, 283
Min, Max	−230, 556	−331, 457	−129, 573	−88, 488	−331, 556	−331, 573
LEN vs. B/F/TAF						
P-value	0.7751	0.9549	0.2603		0.8778	0.6238
Diff in LSM (95% CI)	12 (−73, 97)	−2 (−79, 75)	44 (−33, 120)		6 (−68, 80)	17 (−53, 88)
Change at Week 38						
N	49	51	46	25	100	146
Mean (SD)	195 (164.6)	219 (187.4)	210 (167.1)	232 (209.3)	207 (176.1)	208 (172.7)
95% CI	(148, 242)	(166, 271)	(161, 260)	(146, 318)	(172, 242)	(180, 236)
Median	175	216	184	220	204	194
Q1, Q3	112, 317	91, 363	89, 304	62, 331	107, 327	97, 320
Min, Max	−175, 701	−203, 638	−66, 597	−77, 624	−203, 701	−203, 701
LEN vs. B/F/TAF						
P-value	0.4827	0.7844	0.6082		0.5835	0.5565
Diff in LSM (95% CI)	−31 (−119, 57)	−13 (−106, 81)	−23 (−112, 66)		−22 (−103, 58)	−23 (−98, 53)
Change at Week 54						
N	49	47	47	23	96	143
Mean (SD)	206 (187.0)	212 (187.1)	220 (175.5)	193 (191.1)	209 (186.1)	213 (182.1)
95% CI	(152, 259)	(158, 267)	(169, 272)	(110, 276)	(171, 247)	(183, 243)
Median	180	242	238	177	208	219
Q1, Q3	110, 311	94, 343	102, 293	30, 290	103, 330	102, 318
Min, Max	−291, 673	−301, 631	−74, 603	−59, 749	−301, 673	−301, 673
LEN vs. B/F/TAF						
P-value	0.6614	0.6791	0.5563		0.6393	0.6091
Diff in LSM (95% CI)	21 (−73, 115)	20 (−75, 115)	27 (−65, 120)		20 (−65, 105)	21 (−60, 102)

ANOVA = analysis of variance; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); Diff = difference; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; LSM = least squares mean; N = number of participants; Q1 = first quartile; Q3 = third quartile; SC = subcutaneous; TAF = tenofovir alafenamide
P-value, difference in least squares means (Diff in LSM), and its 95% CI were from ANOVA model adjusting for the baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL).

The proportion of participants with HIV-1 RNA < 50 copies/mL and the change from baseline in log10 HIV-1 RNA and in CD4 cell count at Week 28, 38 and 54 support the efficacy of LEN in combination with emtricitabine and tenofovir alafenamide in antiretroviral naïve participants with HIV-1.

Clinical Virology

For the purpose of screening, genotyping and phenotyping of CA were performed for all participants enrolled in Studies GS-US-200-4072, GS-US-200-4334, and GS-US-200-4625. Genotypic assays for HIV-1 protease (PR), reverse transcriptase (RT), and integrase (IN) were performed.

Table 57 Resistance Substitutions by Antiretroviral Class

Resistance Associated Mutations[a]	
Drug Class	**Drugs and Codon Mutations**
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (N(t)RTIs)	*Abacavir, Emtricitabine, Lamivudine, Tenofovir, Zidovudine, Didanosine, Stavudine*
Primary NRTI-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219E/Q
Multi-NRTI (Thymidine Analogue Mutations [TAMs])	M41L, D67N, K70R, L210W, T215Y/F[b], K219Q/E/N/R
Multi-NRTI: T69 Insertion Complex[b]	T69 Insertion/Deletion: T69S-SS, -SA, -SG, or others
Multi-NRTI: 151 Complex	A62V, V75I, F77L, F116Y, Q151M
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	*Delavirdine, Doravirine, Efavirenz, Etravirine, Nevirapine, Rilpivirine*
Primary NNRTI-R substitutions	L100I, K101E/H/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106I/T, V179D/F/T, G190E, F227L/R, L234I
Protease Inhibitors (PIs)	*Atazanavir, Darunavir, Lopinavir, Tipranavir, Fosamprenavir, 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
Secondary PI-R substitutions	L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33F/I/V, E34Q, E35G, M36I/L/V, K43T, F53L/Y, I54A/S/T, D60E, I62V, L63P, I64L/M/V, H69K/R, A71V/T/I/L, G73A/C/S/T, V77I, V82I, I85V, N88D, L89M/I/V, I93L/M
Entry Inhibitors	*Enfuvirtide, Maraviroc, Fostemsavir*
Resistance-associated substitutions (*env*)	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, S153F/Y, E157K/Q
Capsid Inhibitors (CAIs)	*Lenacapavir*
Primary CAI-R substitutions[c]	L56I, M66I, Q67H, K70N, N74D/S, T107N

CAI = capsid inhibitor; FTC = emtricitabine; INSTI = integrase strand-transfer inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; -R = resistant; RT = reverse transcriptase; TAF = tenofovir alafenamide; TAM = thymidine analogue mutation

a Adapted from the current International Antiviral Society-USA (IAS-USA) Guidelines lists, with some modifications {Wensing 2019}

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 FTC or TAF

c Mutations observed during in vitro resistance selection experiments (PC-200-2025); all mutations observed at these positions will be reported, regardless of substitution

Virology Resistance Analyses at Baseline and in the Resistance Analysis Population From Phase 2/3, Phase 2, and Phase 1b Studies

Study GS-US-200-4072

Study GS-US-200-4072 was the phase 1 monotherapy study.

Baseline Virology Data

Consistent with enrollment criteria, all enrolled participants demonstrated genotypic sensitivity to LEN, BIC, FTC, and TFV at baseline. Pre-existing resistance mutations to antiviral agents were present at low levels (0 to 23.1% across ARV classes) in the study population.

Virology Analyses in Participants at Day 10

All 39 enrolled and treated participants in Part A were evaluated for the development of resistance at Day 10. Two participants who received LEN during the monotherapy period developed the Q67H CA mutation at Day 10. Following dosing with LEN 20 mg, one participant developed the Q67Q/H mixture with WT; phenotypic resistance was low (phenotypic fold change from WT virus = 1.55). One participant (LEN 50 mg group) developed genotypic resistance to LEN (Q67H); phenotypic assessment of this sample was not successful. Neither participant experienced viral rebound during the monotherapy period.

In vitro data has shown low level LEN resistance for the Q67H variant (EC_{50} fold change of 5.7 in MT-2 cells) with replication capacity ranging 58-100%.

Virology Analyses in Participants Experiencing Virologic Failure After Monotherapy (Day 10 Through Day 225)

Two participants (5.1%) met the criteria for inclusion in the post-monotherapy RAP, one participant who received LEN 150 mg and one participant who received placebo. The placebo participant had no resistance emerging in RT and IN assay failure and resuppression to < 50 copies/mL upon further treatment with BVY. The LEN treated participant was viraemic at the final visit on Day 225 and had no genotypic or phenotypic resistance to LEN, FTC, TFV, or BIC.

Study GS-US-200-4334

Baseline Virology Data

Baseline genotypic data for HIV-1 PR/RT, IN, and CA were obtained at screening to assess for pre-existing resistance for all participants in Study GS-US-200-4334. All enrolled participants demonstrated full genotypic sensitivity to LEN, BIC, FTC, and TFV at baseline, except for one participant with M41L + T215Y in RT. Pre-existing resistance mutations to antiviral agents were present at low levels (0 to 15.9% across ARV classes) in the study population.

Consistent with the CA genotyping results, participants were sensitive to LEN based on phenotypic assessments (data available for 175/182 participants; mean phenotypic FC from WT virus = 1.01 [Range: 0.50–2.53]).

Table 58 GS-US-200-4334: Summary of Pre-treatment HIV-1 Subtype and CA, PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Participants, n (%)				
	SC LEN + (DVY → TAF) (n = 52)	SC LEN + (DVY → BIC) (n = 53)	Oral LEN + DVY (n = 52)	Oral BVY (n = 25)	All (n = 182)
Subtype B	47 (90.4)	49 (92.5)	50 (96.2)	23 (92.0)	169 (92.9)
Non-B Subtype	5 (9.6)	4 (7.5)	2 (3.8)	2 (8.0)	13 (7.1)
CAI-Associated	0	0	0	0	0
NRTI-Associated	0 (0.0)	3 (5.7)	0 (0.0)	0 (0.0)	3 (1.6)
INSTI-Associated (Primary)	0	0	0	0	0
NNRTI-Associated	5 (9.6)	8 (15.1)	11 (21.2)	5 (20.0)	29 (15.9)
PI-Associated (Primary)	1 (1.9)	1 (1.9)	1 (1.9)	0 (0.0)	3 (1.6)

BIC = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy®); CA = capsid; CAI = capsid inhibitor; DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy®); IN = integrase; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PR = protease; -R = resistant; RT = reverse transcriptase; SC = subcutaneous; TAF = tenofovir alafenamide

Virology Analyses in Participants in the Resistance Analysis Population

Of the 182 participants enrolled and treated in Study GS-US-200-4334, 3 (1.6%) met the virologic failure (VF) criteria, or demonstrated irregular viral response consistent with VF, through Week 28 and were included in the RAP. The RAP consisted of 3 participants who received LEN and were evaluated for the development of resistance through Week 28.

Through Week 54 a total of 6 (3.3%) met the VF criteria, or demonstrated irregular viral response consistent with VF, and were included in the RAP. The RAP comprised 5 participants who received LEN (SC LEN + [DVY → TAF]: 1 of 52, 1.9%; SC LEN + [DVY → BIC]: 1 of 53, 1.9%; Oral LEN + DVY: 3 of 52, 5.8%) and 1 participant (1 of 25, 4.0%) who received BVY. Three participants receiving LEN achieved RNA resuppression to < 50 copies/mL with further treatment, did not have emergent resistance, and were therefore not included in the final RAP.

The final RAP comprised 1 participant in the SC LEN + (DVY → BIC) treatment group (1 of 53, 1.9%,) and 1 participant in the Oral LEN + DVY group.

- The participant from the SC LEN + (DVY → BIC) treatment group did not meet the protocol-defined criterion of HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate the maintenance regimen at Week 28; started dolutegravir + zidovudine/3TC + tenofovir disoproxil fumarate and had HIV-1 RNA < 50 copies/mL at Week 28. The participant had developed genotypic and phenotypic resistance to both LEN (Q67H + K70R; LEN fold change = 20) and FTC (M184M/I; FTC fold change > 58); resistance to TFV was not observed (TFV fold change = 0.46).
- The participant in the Oral LEN + DVY group developed genotypic and phenotypic resistance to LEN (Q67H; LEN FC = 7.28) with no RT resistance emerging.

Study GS-US-200-4625

Baseline Virology Data

Resistance reports (screening genotypic/phenotypic assays or historical reports) were obtained prior to enrolment as part of the enrolment criteria for all 72 participants who entered study GS-US-200-4625. Overall Susceptibility Scores were obtained from the resistance reports for all ARVs from the 4 main drug classes (26 drugs).

A genotypic susceptibility score (GSS), phenotypic susceptibility score (PSS), and overall susceptibility score (OSS) for drugs from the 4 main drug classes and entry inhibitors were determined based on the baseline resistance results. Possible scores for these categories are 1, 0.5, or 0, corresponding to sensitive, partially sensitive/resistant, or resistant, respectively. Susceptibility scores were used to assess the strength of incoming failing treatment regimens as well as the potential strength of OBRs.

Consistent with study entry criteria, all 71 participants had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV drugs (NRTI, NNRTI, PI, INSTI). One participant showed required resistance to the INSTI and NNRTI classes but only partial resistance to 1 NRTI (didanosine), as resistance to emtricitabine (FTC) and lamivudine (3TC) in the presence of M184V/I did not count towards the total number of resistant NRTIs.

Across HTE participants, the median number of ARV agents with resistance per class approached the total number of ARV agents per class (median of 4 out of a total of 4, median of 5 out of a total of 6, median of 5 out of a total of 7, and median of 7 out of a total of 9, for INSTIs, NNRTIs, NRTIs, and PIs, respectively. Almost half of the participants had HIV-1 with 4-class resistance (45.8%).

No participant harboured LEN-associated resistance mutations at study entry (L56I, M66I, Q67H, K70N, N74D/S and T107N in CA).

Resistance testing was performed for any participant meeting the criteria of the Resistance Analysis Population (RAP):

- The RAP included any participants who received at least 1 dose of study drug, maintained their study regimen, and had confirmed virologic failure through the end of study or at key study end points, or was viraemic at the last study visit (completion or early discontinuation).
- The final RAP did not include participants who remained on study medication and later suppressed HIV-1 RNA to < 50 copies/mL in the absence of emerging resistance mutations.

Resistance analyses consisted of genotypic and phenotypic assessment of the HIV-1 CA, PR, RT, and IN proteins.

Table 59 GS-US-200-4625: Overall Combinations of Class Resistance (≥ 2 Drug Resistance per Drug Class) at Baseline

Drug Classes	Number of Participants, n (%)			
	Cohort 1[a]		Cohort 2	
	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
All Four Classes	14 (58.3)	3 (25)	16 (44.4)	33 (45.8)
NNRTI-NRTI-PI	4 (16.7)	5 (41.7)	13 (36.1)	22 (30.6)
INSTI-NRTI-PI	2 (8.3)	0	0	2 (2.8)
INSTI-NNRTI-PI	0	0	1 (2.8)	1 (1.4)
INSTI-NNRTI-NRTI	4 (16.7)	4 (33.3)	5 (13.9)	13 (18.1)
Totals	24	12	35[b]	71[b]

FR = failing regimen; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor

a → Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.

b → Participant who was enrolled with resistance to only 2 drug classes instead of ≥ 3 (protocol requirement) is not included.

Table 60 GS-US-200-4625: Summary of Baseline HIV-1 Subtype and CA, PR, RT, and IN Resistance Mutations Detected

HIV-1 Subtype and Mutation Class[a]	Number of Participants, n (%)			
	Cohort 1[b]		Cohort 2	
	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
Subtype B	22 (91.7)	11 (91.7)	23 (63.9)	56 (77.8)
Non-B Subtype	2 (8.3)	1 (8.3)	13 (36.1)	16 (22.2)
CAI-Associated	0	0	0	0
NRTI-Associated	23 (95.8)	12 (100)	35 (100)	70 (98.6)
INSTI-Associated (Primary)	18 (75)	6 (60)	22 (62.9)	46 (66.7)
INSTI-R (Secondary)	19 (79.2)	7 (70)	22 (62.9)	48 (69.6)
NNRTI-Associated	21 (87.5)	12 (100)	34 (97.1)	67 (94.4)
PI-Associated (Primary)	20 (83.3)	7 (63.6)	31 (86.1)	59 (83.1)
PI-Associated (Secondary)	24 (100)	11 (100)	34 (94.4)	69 (97.2)

CA = capsid; CAI = capsid inhibitor; FR = failing regimen; IN = integrase; INSTI = integrase strand-transfer inhibitor; LEN = lenacapavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; OBR = optimized background regimen; PI = protease inhibitor; PR = protease; -R = resistant; RT = reverse transcriptase

a Drug resistance mutations are defined in Table 20

b Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15

To further characterise participants' resistance profiles, baseline susceptibility analysis of HIV-1 entry inhibitors was conducted after enrolment; these data were not used to determine eligibility.

Table 61 GS-US-200-4625: Summary of Baseline Resistance to HIV-1 Entry Inhibitors

	Number of Participants With OSS = 0[a]/Number of Participants With Data (%)			
	Cohort 1[b]		Cohort 2	
Drug Name	Cohort 1A: LEN + FR (n = 24)	Cohort 1B: Placebo + FR (n = 12)	LEN + OBR (n = 36)	All (n = 72)
Enfuvirtide	2/23 (8.7)	3/10 (30)	0/25 (0)	5/58 (8.6)
Fostemsavir	5/23 (21.7)	5/10 (50)	7/21 (33.3)	17/54 (31.5)
Ibalizumab	8/23 (34.8)	3/10 (30)	6/25 (24)	17/58 (29.3)
Maraviroc	19/24 (79.2)	8/11 (72.7)	14/26 (53.8)	41/61 (67.2)

FR = failing regimen; LEN = lenacapavir; OBR = optimized background regimen; OSS = overall susceptibility score
a Possible scores for OSS are 1, 0.5, or 0, corresponding to sensitive, partially sensitive/resistant, or resistant, respectively.
b Participants continued their FR during the randomized functional monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN on Day 15.

As part of the baseline analysis, 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.

The Week 26 interim efficacy analysis comprises 42 participants with virologic data through Week 26, including all 36 participants from Cohort 1 and 6 of 36 participants from Cohort 2. An analysis of the treatment response at Week 26 (US FDA-defined snapshot algorithm) according to the OSS of OBR was conducted for the 36 participants from the randomised cohort (Cohort 1).

A direct correlation between OSS of OBR and treatment response was not observed in this interim dataset, the mean OSS of OBR for participants with treatment success and treatment failure was 1.7 and 1.8, respectively and a wide range of OSS was observed for both response categories (OBR OSS ranging from 0 to 4 and 0.5 to 3 for participants with treatment success and participants with treatment failure, respectively).

The Week 52 efficacy analysis comprised 43 participants with virologic data through Week 52, including 35 participants from Cohort 1 and 8 participants from Cohort 2. One participant in Cohort 1 and 1 participant in Cohort 2 had no virologic data at Week 52. An analysis of the treatment response at Week 52 (US-FDA Snapshot Algorithm) per OSS of OBR was conducted for all 43 participants with virologic data through week 52.

A direct correlation between OSS of OBR and treatment response was not observed in the interim Week 52 dataset, as the mean OSS of OBR for participants with treatment success and treatment failure were similar (mean OSS of 1.6 and 2.1, respectively) and a wide range of OSS ranging from 0 to 4 and 0.5 to 4 for participants with success and failure, respectively, was observed.

Virology Analyses in Participants Experiencing Virologic Failure in Study GS-US-200-4625

The Week 26 analysis includes all 72 participants enrolled in the study, 42 of them with data through Week 26, including all 36 participants from Cohort 1 and 6 of 36 participants from Cohort 2.

The Week 52 analysis also includes all 72 participants enrolled in the study, 45 of them with data through Week 52, including all 36 participants from Cohort 1 and 9 participants from Cohort 2.

The final RAP comprised 13 participants, including 7 participants from Cohort 1 and 6 participants from Cohort 2.

The LEN-associated CA mutation M66I was observed in 6 participants, alone or with other LEN-associated substitutions (at CA residues 67, 70, 74, and 107), and was associated with a median LEN phenotypic FC of 234 in comparison to the WT control. The Q67H + K70R resistance pattern was observed in 1 participant, with a LEN phenotypic FC of 14.8. One participant had emergence of a K70H mutation, which has not been previously observed in vitro, along with T107T/N, with a LEN FC of 265. Substitutions at position A105 (A105T or A105A/S/T) were observed in 4 participants along with M66I (n=3) or K70H (n=1), suggesting that substitutions at residue A105 may play a role in resistance.

R229R/K mutation was observed in 2 participants who also developed M66I or M66M/I. The potential role of that substitution is unknown, but that residue is located outside of the LEN binding site, near the C-terminus of the CA protein. An S41A mutation (evolving from S41T at baseline) was observed in 2 participants who also developed M66I or M66M/I. Its role in resistance to LEN is unknown, the S41A substitution alone showed no effect on LEN resistance in vitro.

Two RAP participants had emerging resistance mutation(s) outside of the capsid protein: One developed the K103N/S and M184M/I/V RT mutations while receiving an OBR composed of the NNRTI doravirine along with the INSTI/NRTI fixed dose combination of BIC, FTC and TAF. This participant met the criteria for resistance analysis due to suboptimal virologic response at week 4but was resuppressed to <50 copies/mL by Week 52 and was not included in the final RAP. Another participant developed the V82V/A mutation in PR at Week 26 while receiving an OBR including the PI darunavir along with the NNRTI doravirine, NRTIs emtricitabine and tenofovir alafenamide, and INSTI dolutegravir. The participant was resuppressed to <50 copies/mL at subsequent visits and was not included in the final RAP.

Table 62 GS-US-200-4625: Summary of HIV-1 Capsid Genotypic Resistance Observed Through Week 26

Resistance Categories	Cohort 1		Cohort 2	All
	A: LEN + FR[a] (N = 24)	B: Placebo + FR[a] (N = 12)	LEN + OBR (N = 36)	(N = 72)
RAP	6 (25%)	5 (41.7%)	6 (16.7%)	17 (23.6%)
With Data	6 (25%)	5 (41.7%)	6 (16.7%)	17 (23.6%)
Resuppressed < 50	2 (8.3%)	0	1 (2.8%)	3 (4.2%)
Final RAP[b]	4 (16.7%)	5 (41.7%)	5 (13.9%)	14 (19.4%)
With data	4 (16.7%)	5 (41.7%)	5 (13.9%)	14 (19.4%)
With CA-R emerging	1 (4.2%)	3 (25%)	4 (11.1%)	8 (11.1%)
M66I	1 (4.2%)	3 (25%)	2 (5.6%)	6 (8.3%)
Q67H/K/N	0	1 (8.3%)	2 (5.6%)	3 (4.2%)
K70H/N/R/S	1 (4.2%)	0	3 (8.3%)	4 (5.6%)
N74D	0	1 (8.3%)	0	1 (1.4%)
A105S/T	0	2 (16.7%)	1 (2.8%)	3 (4.2%)
T107A/C/N	0	0	3 (8.3%)	3 (4.2%)
No CA-R emergence	3 (12.5%)	2 (16.7%)	1 (2.8%)	6 (8.3%)

CA = capsid; FR = failing regimen; OBR = optimized background regimen; RAP = resistance analysis population; -R = resistance

a Participants continued their failing regimen during the randomized virtual monotherapy period and switched to OBR on Day 15. Participants in the placebo group started to receive LEN + OBR on Day 15.

b Participants who resuppressed HIV-1 RNA < 50 copies/mL in the absence of CA resistance emergence were excluded from the final RAP.

Table 63 Resistance Analyses Population and Emergence of Capsid Resistance Mutations by Week 52

Resistance Categories	Cohort 1 (n = 36)	Cohort 2 (n = 36)	All (N = 72)
RAP	11 (31%)	10 (28%)	21 (29%)
With Data	11 (31%)	9 (25%)	20 (28%)
Resuppressed <50	4 (11%)	4 (11%)	8 (11%)
Final RAP[a,b]	7 (19%)	6 (17%)	13 (18%)
With data	7 (19%)	5 (14%)	12 (17%)
▪ With CA-R Emerging	4 (11%)	4 (11%)	8 (11%)
▪ →M66I	4 (11%)	2 (6%)	6 (8%)
▪ →Q67H/K/N	1 (3%)	2 (6%)	3 (4%)
▪ →K70H/N/R/S	1 (3%)	3 (8%)	4 (6%)
▪ →N74D/H/S	3 (8%)	0	3 (4%)
→A105S/T	3 (8%)	1 (3%)	4 (6%)
→T107A/C/N[b]	1 (3%)	3 (8%)	4 (6%)
No CA-R Emergence	3 (8%)	1 (3%)	4 (6%)

CA = capsid; FR = failing regimen; OBR: optimized background regimen; RAP = resistance analyses population; -R: resistance

a → Participants who resuppressed HIV-1 RNA <50 copies/mL in the absence of CA resistance emergence were excluded from the final RAP.

b → Participant had a T107A emergent CA mutation with no loss in LEN susceptibility before achieving HIV-1 RNA suppression. This participant was not included in the final RAP, but the mutation is included above.

The CA mutation M66I which confers high level resistance to LEN was observed in 6 patients with or without additional mutations in CA (median FC 234).

Q67H + K70R was observed in one patient similar to the virus isolate from the one patient with CA mutation in the phase 2 study. The Q67H+K70R seem to confer moderate LEN resistance with fold change 14.8-20 in these two patients.

One patient developed T107T/N + K70H mutations with a LEN fold change of 265. In vitro T107N results in a LEN fold change of 4. Thus, the K70H mutation which has not been isolated in vitro previously, seem to substantially increase LEN resistance. In 5 out of the 8 patients the CA mutations were observed at week 4. Lenacapavir appears to have a rather low barrier to selection of virus with substitutions associated with reduced susceptibility which is of concern. Wording in 4.2 has been proposed to highlight the importance of adherence. Based on precedent decisions for long acting injectable antiretrovirals a warning is included in Section 4.4 regarding the risk of resistance following discontinuation of LEN treatment.

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 64 Summary of efficacy for trial GS-US-200-4625 ('CAPELLA') – Interim data Week 26

Title: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance

Study identifier	GS-US-200-4625 ('CAPELLA')	
Design	Study GS-US-200-4625 is an ongoing Phase 2/3, global, randomised, placebo-controlled, multicentre study of LEN in combination with an optimised background regimen (OBR) in heavily treatment experienced (HTE) people with HIV (PWH) with multidrug resistance (MDR).	
	Duration of main phase:	Participants are treated for at least 54 weeks.
Hypothesis	Superiority (primary endpoint)	
Treatments groups	Cohort 1	N = 36: Cohort 1A (N = 24): •Functional Monotherapy Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + failing regimen •Maintenance Period: SC LEN injection 927 mg + OBR on Day 1 SC and every 6 months (26 weeks) thereafter Cohort 1B (N = 12): •Functional Monotherapy Period: placebo on Days 1, 2, and 8 + failing regimen •Maintenance Period: oral LEN 600 mg on Days 15 and 16 and 300 mg on Day 22 + SC LEN injection 927 mg on Day 1 SC + OBR and every 6 months (26 weeks) thereafter
	Cohort 2	Cohort 2 (N = 36): •Oral Lead-in Period: oral LEN 600 mg on Days 1 and 2 and 300 mg on Day 8 + OBR •Maintenance Period: SC LEN injection 927 mg + OBR on Day 1 SC and every 6 months (26 weeks) thereafter
Endpoints and definitions	Primary endpoint	Proportion of Participants Achieving ≥ 0.5 log10 copies/mL Reduction From Baseline in HIV-1 RNA at the end of the functional monotherapy.
	Secondary endpoint	The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 treatment based on the US FDA-defined snapshot algorithm.
Database lock	Week 26: 20 April 2021	
Results and Analysis		
Analysis description	**Primary Analysis**	

Analysis population and time point description	Full Analysis Set (FAS) for the Functional Monotherapy Period analysis Day 15		
Descriptive statistics	Treatment group	Cohort 1A – LEN	Cohort 1B - Placebo
	Number of subjects	24	12
	Proportion of Participants Achieving ≥ 0.5 log10 copies/mL Reduction From Baseline in HIV-1 RNA	21 (87.5%)	2 (16.7%)
Effect estimate per	Primary endpoint	Comparison groups	Cohort 1A (LEN) vs Cohort 1B (placebo)
		Proportional difference	70.8%
		95% CI	34.9% to 90.0%
		P-value	<0.0001
Analysis description	**Secondary analysis**		
Analysis population and time point description	FAS Week 26		
Descriptive statistics and estimate variability	Treatment group	Cohort 1 (All LEN)	
	Number of subjects	36	
	HIV-1 RNA < 50 copies/mL (number and proportion)	29 (80.6%)	
	95% CI	64.0% to 91.8%	
	HIV-1 RNA < 200 copies/mL (number and proportion)	32 (88.9%)	
	95% CI	73.9% to 96.9%	
Analysis population and time point description	FAS Week 52		
Descriptive	Treatment group	Cohort 1 (All LEN)	Cohort 2 (All LEN)

statistics and estimate variability	Number of subjects	36	9
	HIV-1 RNA < 50 copies/mL (number and proportion)	30 (83.3%)	5 (55.6%)
	95% CI	67.2% to 93.6%	21.2% to 86.3%
	HIV-1 RNA < 200 copies/mL (number and proportion)	31 (86.1%)	6 (66.7%)
	95% CI	70.5% to 95.3%	29.9% to 92.5%

2.6.5.3. Clinical studies in special populations

Table 65 Number of Participants 65 Years and Older Included in Clinical Studies GS-US-200-4625 and GS-US-200-4334

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Study GS-US-200-4625[b]	5/72	1/72	0/72
Study GS-US-200-4334[c]	1/183	0/183	0/183

a Participants above 65 years of age were only enrolled in Studies GS-US-200-4625 and GS-US-200-4334.

b Study GS-US-200-4625 includes all enrolled participants.

c Study GS-US-200-4334 includes all enrolled participants

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6. Supportive studies

N/A

2.6.6. Discussion on clinical efficacy

GS-US-200-4625 – Phase 2/3 Study

This study is an ongoing Phase 2/3, randomised, placebo-controlled, multicentre study of LEN in combination with an optimd background regimen (OBR) in HIV+ patients with multidrug resistance. Eligible participants were HTE PWH aged ⩾ 18 years (all sites) or aged ⩾ 12 years and weighing ⩾ 35 kg (sites in North America and Dominican Republic) who were receiving a stable failing regimen for > 8 weeks before screening. Participants were to have plasma HIV-1 RNA ⩾ 400 copies/mL at screening; resistance to ⩾ 2 ARV medications from each of ⩾ 3 of the 4 main classes of ARV medications, ⩽ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined. Interim data from week 26 has been submitted with this application.

Participants were enrolled in either Cohort 1 (<0.5 log10 HIV-1 RNA decline between 14 and 30 days after the screening visit) or Cohort 2 (>0.5 log10 HIV-1 RNA decline from screening). In Cohort 1 participants were randomised to receive LEN + failing regimen (n=24) or placebo + failing regimen (n=12) for 14 days i.e., the functional monotherapy period. Starting Day 15 (maintenance period) and onwards all participants were treated with LEN + optimized background regimen (OBR).

In this population with a diverse underlying resistance profile, there is no standardized background regimen that can be used for all individuals. By addition of the test drug to the failing regimen during a short-term functional monotherapy period and with placebo control the assessment of viral decline can provide information on the benefit of the test drug. This approach is considered ethical and is consistent with the EMA guidelines (EMEA/CPMP/EWP/633/02 Rev. 3).

Enrolment into Cohort 2 occurred when Cohort 1 was fully enrolled or if a subject did not meet the criteria for randomisation in Cohort 1 (i.e., they had ⩾ 0.5 log10 HIV-1 RNA decline compared to the Screening visit or HIV-1 RNA < 400 copies/mL at the cohort selection visit). In Cohort 2 (nonrandomised and unblinded) all participants received LEN+ OBT from Day 1. Upon request, the Applicant clarified that of the 36 participants enrolled in Cohort 2, 28 participants could have enrolled in Cohort 1. Subgroup analyses showed that the results for those 28 in Cohort 2 were in line with the results achieved for Cohort 1 although the contribution of OBR cannot be disentangled from the effect of Lenacapavir. Among the 8 participants who did not meet randomisation criteria, 3 (37.5%) achieved HIV-1 RNA reduction of ≥0.5 log10 copies/mL from baseline to Day 1 SC, probably due to the low viral load measured in these patients at Day 1, making it difficult to achieve this reduction. At week 26, the proportion of participants achieving HIV-1 RNA <50 copies/mL was 87.5% (7 out of 8 participants), which is comparable to Cohort 1.

Randomisation was only applicable for subjects eligible to be enrolled in cohort 1. There was no stratification. This may have been due to the limited sample size but could eventually have been considered at least for the most important prognostic variable. In the end, there were baseline imbalances between the treatment arms with regard to HIV-1 RNA, CD4 cell count as well as residual activity of the failing regimen.

The imbalances in baseline HIV-1 RNA and CD4 cell count respectively are of such magnitude that the probability of this imbalance occurring by chance is quite low. If the imbalance did not occur by chance, it is implied that the randomisation procedure may have failed in some sense. However, considering the magnitude of the difference in effect based on the primary responder endpoint, in a subgroup analysis of subjects with HIV-1 RNA ⩽100,000 log10 copies/mL at baseline, the outcome would still be in favour of lenacapavir. Hence, this imbalance is not considered to alter study conclusions. Still, the Applicant was asked to discuss possible causes whereby the randomisation procedure was clarified, and it was confirmed that a fixed block size of 3 was used. The fixed block size may have implied that the allocation was potentially predictable and could possibly have contributed to

the imbalance in baseline characteristics due to selection. This cannot be completely resolved and therefore, is not further pursued. However, as 31 sites were included, without stratified randomisation for each site, it is unlikely that this would have had major impact.

Subject treatment allocation was unblinded at completion of the functional monotherapy period (cohort 1) in order to decide maintenance treatment regimen.

The OBR at baseline is only taken into account if used for a minimum duration of 28 days on or after the first dose date of open-label LEN. This definition of OBR was not pre-specified in the protocol, but has been added in the SAP, which was finalized close to final data analysis after all participants were unblinded. This choice may have been informed by knowledge of the data. Changes in OBR were allowed during the whole study duration. However, the number of participants who switched agents in the OBR within 28 days of initiating the OBR was small (n=2) and the reasons for switches were all due to safety/toxicity reasons and not due to efficacy reasons. In addition, a sensitivity analysis in which patients who switched their OBR within 28 days were counted as failures, showed that this did not impact the overall results substantially.

The SAP was finalized very late in the study, when all participants were unblinded and all relevant information had been collected. Based on a concern regarding data driven specifications in the SAP that had not been specified in the protocol, the applicant was asked to explain. The Applicant clarified that the SAP submitted was for the "Primary Analysis" conducted after all participants in Cohort 1 had completed the Week 26 visit or had prematurely discontinued from the study. Prior to this analysis, an analysis was performed after all participants in Cohort 1 had completed the double-blind period. A separate SAP for this Data Monitoring Committee analysis was finalized on 30 September 2020 before the unblinding of study data on 11 November 2020. No significant changes between the now provided SAP for "DMC Analysis" and the SAP submitted previously have been observed. It is therefore acknowledged that study integrity was maintained.

The exact method for the test of treatment differences and the construct of 95% confidence intervals is accepted. It was not pre-planned to take any baseline factors into account. This is in alignment with that no stratification was used at randomisation. To address the imbalance in baseline HIV-1 RNA a rank analysis of covariance with adjustment for baseline HIV-1 RNA has been presented. To also address the imbalance in baseline CD4 cell count, subgroup analyses have been performed. These analyses supported primary conclusion.

The planned primary approach for handling missing HIV-1 RNA data by the use of last-observation-carried-forward (LOCF) is not supported. Missing equals failure is the standard approach in HIV trials. However, in the end, all 24 (lenacapavir) and 12 (placebo) subjects randomised within cohort 1 completed the functional monotherapy period (on study drug) and at the time-point for the current analysis, had either completed the main phase/up to week 52 or were still ongoing. From the dataset provided it seemed as if LOCF had been used for 2 subjects, one in each arm. This was confirmed by the Applicant. A sensitivity analysis showed that even in the worst-case scenario for missing HIV-1 RNA values, with the participant in the LEN group being considered a non-responder and the participant in the placebo group being a responder, the conclusion maintains, as the between-group difference remained high (58.3% [95% CI 15.1% to 81.8%]) and statistically significant.

For the assessment of robustness, a PP analysis was performed but is considered less useful since based on randomised subject data exclusion. However, only one subject (placebo) was excluded based on having received a new ARV during the functional monotherapy period.

The original protocol (dated 25 September 2019) was amended twice, 18 December 2019 and 01 September 2020.

Study GS-US-200-4334 - Phase 2

This study is a randomized, open-label, active-controlled, multicentre Phase 2 study and with this application the interim data through week 54 has been submitted.

The study recruited people aged ⩾ 18 years, with HIV who were antiretroviral (ARV) naive (no use of any ARV within 1 month of screening) and at screening had plasma HIV-1 RNA ⩾ 200 copies/mL and CD4 cell count ⩾ 200 cells/μL. Study sites were located in the Dominican Republic (one site) and the United States (40 sites). Participant were treated with bictegravir/emitricitabin/tenofovir alafenamide or with lenacapavir (SC or oral) in combination with emitricitabin and tenofovir alafenamide. The efficacy outcomes included proportion of participants with HIV-1 RNA < 50 copies/mL and change from baseline in log10 HIV-1 RNA and in CD4 cell count.

Randomisation was in a 2:2:2:1 ratio to three LEN-containing regimens and the B/F/TAF treatment control group and was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening. The sample size, 50 per LEN-arm and 25 in the control arm, was not chosen to provide sufficient power (estimated at 39% based on an NI-margin of -0.12) but is stated to have been chosen for the estimation of week 54 primary endpoint response rates. Given that this study is not intended to support a broad indication for the treatment of HIV, but is rather a phase II study, the design and analyses are acceptable.

Efficacy data and additional analyses

GS-US-200-4625

Differences in baseline characteristics were seen between the LEN and placebo groups in HIV-1 RNA (log10 copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage. A higher number of participants in Cohort 2 had a non-B HIV-1 subtype compared to Cohort 1 (13 of 36 compared to 3 of 36, respectively) reflecting the higher geographical diversity of participants in Cohort 2 compared to Cohort 1 according to the Applicant. The majority of the participants had subtype B.

DTG was part of the failing regimen in 29.2% and 41.7% in the LEN and placebo groups respectively. DRV was part of the failing regimen in 20.8% and 25% in the LEN and placebo groups respectively. Of these a smaller proportion were dosed BID with DTG or DRV as increased posology is advised for these drugs in presence of class-specific resistance mutations. More patients in the LEN group were treated with DRV+DTG BID compared to placebo (16.7% vs 8.3%). A larger proportion of patients in the LEN group were treated with ibalizumab (37.5% in the LEN group vs.8.3% in placebo group) and fostemsavir was used in 8.3% in the LEN group compared to 0% in the placebo group. Taken together it seems that in the failing regimen the overall DRV and DTG use was slightly higher in the placebo group, while in the LEN group BID treatment with DTG + DRV, ibalizumab or fostemsavir was somewhat more common.

A higher median OSS is noted for the LEN group in the failing regimen and more patients in the LEN group had one or more fully active ARVs. In a study setting participant are likely to better adhere to their background regimen which may have consequences for the overall outcome. For patients with fully active ARVs the increased adherence may have had some impact on the efficacy outcome. According to the protocol atazanavir (ATV), efavirenz (EFV), nevirapine (NVP) and etravirine (ETV) were prohibited medications during the study due to potential drug-drug interaction with lenacapavir and are mentioned in the SmPC as "not recommended". Etravirine has CYP3A inductive effects which may lead to lowering of LEN plasma concentrations and the P-gp inhibition could lead to opposite effects. Based on the impact of etravirine on sildenafil and digoxin (CYP3A and Pgp model victims), significant loss of efficacy cannot be excluded on coadministration, based on decreased LEN exposure.

The number of participants in Cohort 2 (n=36) was lower than originally planned (n=64). The explanation by the Applicant is acknowledged; the substantiation of the number of subjects enrolled in cohort 2 is acceptable and Cohort 2 may have improved the validity of the results in Cohort 1. As clear

from the D120 LoQ response, the main reason for enrolling Cohort 2 was that participants who would not meet the criteria for randomisation in Cohort 1 may create an unintended incentive for participants to remain nonadherent to their "failing" regimen during screening in the hope of having stable viremia and being randomised. All subjects enrolled in Cohort 1 completed week 26. A significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ⩾ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period than those receiving placebo (87.5% versus 16.7%; P < 0.0001). Observed differences in baseline characteristics such as viral load and CD4 cell counts have been taken into consideration in a post hoc analysis in which significance remained. As noted above median OSS based on the failing regimen is different between the groups (1 vs 0.5 in LEN and placebo respectively). For participants with OSS 0 to 0.5 or 1 to 1.5 there were similar proportion of participants in both treatment groups, however, more participant in the LEN groups achieved ⩾0.5 log10 reduction. In addition, in the placebo group, only participants without any fully active ARVs in the failing ARV achieved the primary endpoint. Although this data is limited by the small sample size it adds support to the efficacy of LEN in this setting.

The secondary endpoint was the proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment based on the US Food and Drug Administration (FDA)–defined snapshot algorithm. Virologic suppression was sustained through Week 26 for 80.6% (29 of 36 participants) with HIV-1 RNA < 50 copies/mL using the US FDA–defined snapshot algorithm. In Cohort 1 seven participants (19.4%) had HIV-1 RNA ⩾ 50 copies/mL at Week 26. At Week 52, the percentages of participants in Cohorts 1 and 2 with HIV-1 RNA < 50 and < 200 copies/mL were 77.8% and 82.2%, respectively. The study design does not allow for isolation of drug effects in this phase, which is considered descriptive, as well as useful for understanding drug resistance. According to the judgment of the assessor, at least half of the patients in the study may, based on their PI and/or INSTI use, and in the light of the reported resistance, be able to reach long term virological suppression with the OBR alone. This is not unanticipated given previous experience of similar studies in this setting. This does not impact conclusions on efficacy but illustrates that the week 26 does not isolate the effects of LEN in the absence of a comparator.

With regard to the OBR, the number of participants who switched agents in the OBR within 28 days of initiating the OBR was small (n=2) and the reasons for switches were all due to safety/toxicity reasons and not due to efficacy reasons. In total 16 patients changed OBR during the study up until the Week 52 data cut, of which 12 patients had changes that included adding a new ARV (n=9 in Cohort 1 and n=3 in Cohort 2). The majority of patients had ARV added either around week 24 or after week 52, therefore the impact on the efficacy outcomes is considered minimal.

The mean (SD) baseline HIV-1 RNA value was lower for participants who received LEN than those who received placebo, as follows: LEN 3.97 (0.922) log10 copies/mL; placebo 4.87 (0.393) log10 copies/mL (difference in LSM: −0.90 [95% CI: −1.47 to −0.33]; P = 0.0028). This imbalance is not believed to have any major impact on the outcome.

The proportion of participants with HIV 1 RNA < 50 copies/mL at Week 26 using the US FDA-defined snapshot algorithm based on the FAS was numerically higher in participants aged < 50 years, in female participants, participants with baseline CD4 cell count ⩾ 200 cells/μL, and participants with baseline viral load ⩽ 100,000 copies/mL.

Study GS-US-200-4334

Baseline characteristics were well balanced between the groups and reflected a treatment-naïve population. Over 90% of the participants treated with LEN in combination with emtricitabine and tenofovir alafenamide had < 50 copies/mL at Week 28. This outcome would not have been expected with only two NRTIs such as emtricitabine and tenofovir alafenamide and thus support of the efficacy of LEN. Of those participants that transitioned to a two-agent regimen, including SC LEN with either

tenofovir alafenamide or bictegravir at week 28, over 84% had < 50 copies/mL at week 54.

Clinical Virology

Study GS-US-200-4072

Two participants who received LEN during the monotherapy period developed the Q67H CA mutation at Day 10. Following dosing with LEN 20 mg, one participant developed the Q67Q/H mixture with WT; phenotypic resistance was low (phenotypic fold change from WT virus = 1.55). One participant (LEN 50 mg group) developed genotypic resistance to LEN (Q67H); phenotypic assessment of this sample was not successful. Neither participant experienced viral rebound during the monotherapy period. In vitro data has shown low level LEN resistance for the Q67H variant (EC50 fold change of 5.7 in MT-2 cells) with replication capacity ranging 58-100%.

Study GS-US-200-4334

One participant from the SC LEN + (DVY → BIC) group did not meet the protocol-defined criterion of HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate the maintenance regimen at Week 28; started dolutegravir + zidovudine/3TC + tenofovir disoproxil fumarate and had HIV-1 RNA < 50 copies/mL at Week 28. The participant had developed genotypic and phenotypic resistance to both LEN (Q67H + K70R; LEN fold change = 20) and FTC (M184M/I; FTC fold change > 58); resistance to TFV was not observed (TFV fold change = 0.46). Another participant in the Oral LEN + DVY group developed genotypic and phenotypic resistance to LEN (Q67H; LEN FC = 7.28) with no RT resistance emerging.

Study GS-US-200-4625

The CA mutation M66I which confers high level resistance to LEN was observed in 6 patients with or without additional mutations in CA (median FC 234). Q67H + K70R was observed in one patient similar to the virus isolate from the one patient with CA mutation in the phase 2 study. The Q67H+K70R seem to confer moderate LEN resistance with fold change 14.8-20 in these two patients. One patient developed T107T/N + K70H mutations with a LEN fold change of 265. In vitro T107N results in a LEN fold change of 4. Thus, the K70H mutation which has not been isolated in vitro previously, seem to substantially increase LEN resistance. In 5 out of the 8 patients the CA mutations were observed at week 4. Lenacapavir appears to have a rather low barrier to selection of virus with substitutions associated with reduced susceptibility which is of concern. Wording in 4.2 has been proposed to highlight the importance of adherence. Based on precedent decisions for long acting injectable antiretrovirals a warning is included in Section 4.4 regarding the risk of resistance following discontinuation of LEN treatment.

Summary evaluation

Lenacapavir is a first in class inhibitor of HIV-1 capsid function. Virological data do not indicate any cross resistance with available classes. Dose-ranging monotherapy data in treatment naïve subjects show a drug with antiviral potency in a similar range as the integrase inhibitors.

Study GS-US-200-4334, a traditionally designed phase II study in treatment naïve subjects show that lenacapavir can yield sustained virological suppression as backbone for two nukes. Non-clinical data, however, indicate that the barrier to resistance is relatively low, with high level treatment emergent resistance emerging in case of treatment failure. Adherence to the oral components will be crucial to avoid lenacapavir monotherapy and loss of this treatment option due to resistance.

Efficacy in the target population with MDR HIV may be inferred in two different ways. First, through the fact that cross-resistance with available agents is unlikely, and that the results of GS-US-200-4334 indicate that lenacapavir contributes to the activity and durability of response of a conventionally

designed treatment regimen; as well as through the activity shown in the first phase of the GS-US-200-4625 in MDR HIV patients. In the second phase of this study, all patients received an optimised background regimen and lenacapavir. Therefore, data are descriptive and do not conclusively isolate drug effects.

The data presently does not suffice to support approvability except in patients for whom a durable suppressive regimen cannot be composed due to drug resistance. In addition, the level of evidence is currently not considered sufficient to remove the oral lead-in phase from the posology, and a conservative approach of including the oral lead-in is preferred. If more experience is gained with the simplified dosing regimen this position may be reconsidered.

2.6.7. Conclusions on the clinical efficacy

Lenacapavir is a potent antiretroviral agent of a new class, without cross resistance to available agents. It has been demonstrated that lenacapavir provides clinically relevant efficacy in patients with multi-drug-resistant HIV-1 with supportive data in treatment-naïve people with HIV-1. The resistance barrier is relatively low; hence, maintenance of adherence is of importance.

2.6.8. Clinical safety

Lenacapavir (LEN) is a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid function targeted for the treatment of HIV-1 infection. LEN is developed to meet the medical need in people with HIV (PWH) with multi-drug resistance (MDR) with limited treatment options. Two dosage forms of LEN are currently in development, a solution for SC injection, LEN SC injection 309 mg/mL and a film-coated tablet formulation, LEN 300 mg tablet, for initial loading. The recommended treatment regimen in adults consists of oral loading with lenacapavir tablets followed by once every 6 months maintenance dosing (subcutaneous injections). On treatment Day 1 and Day 2, the recommended dose of lenacapavir is 600 mg per day taken orally. On treatment Day 8, the recommended dose is 300 mg taken orally. Then, on treatment Day 15, the recommended dose is 927 mg administered by subcutaneous injection.

2.6.8.1. Patient exposure

Clinical safety and tolerability of LEN has been studied in eight Phase 1 studies (GS-US-200-4070, GS-US-200-4071, GS-US-200-4329, GS-US-200-4330, GS-US-200-4331, GS-US-200-4333, GS-US-200-4538, and GS-US-200-5709), one Phase 2 study (Study GS-US-200-4334) and one Phase 2/3 study (Study GS-US-200-4625).

The primary study that supports the safety and efficacy of LEN is the Phase 2/3 study in HTE PWH (Study GS-US-200-4625). Of the 72 participants in Cohorts 1 and 2 who received oral LEN, 72 participants received SC LEN on Day 1 SC, 70 participants (Cohort 1: 36 participants, Cohort 2: 34 participants) received a second dose of SC LEN at Week 26, and 36 participants (Cohort 1: 34 participants, Cohort 2: 2 participants) received a third dose of SC LEN at Week 52. The median (first quartile [Q1], third quartile [Q3]) duration on study was 484 (411, 559) and 317 (267, 352) days for Cohorts 1 and 2, respectively.

The primary study is supported by a Phase 2 study of LEN in treatment-naive PWH (Study GS-US-200-4334). By Week 54, 89.2% of participants in the LEN total group (140 of 157 participants) and 96.0% of those in the BVY group (24 of 25 participants) had been exposed to study drug for at least 54 weeks.

In an Integrated Summary of Safety (ISS), a pooled analysis is presented from the 8 Phase 1 studies, in healthy participants who were dosed with lenacapavir (LEN) (n = 365) or placebo (n = 49), regardless of the route, dose, or formulation.

Table 66 GS-US-200-4625 and GS-US-200-4334: Number of Participants Receiving Either 1, 2, 3, or 4 Doses of SC LEN

	GS-US-200-4625				**GS-US-200-4334**			
SC LEN Dose	**Study Day**	**Cohort 1 (N = 36)**	**Cohort 2 (N = 36)**	**Total (N = 72)**	**Study Day**	**SC LEN + (DVY →TAF) (N = 52)**	**SC LEN + (DVY →BIC) (N = 53)**	**Total SC LEN (N = 105)**
First dose	Day 1 SCa	36 (100%)	36 (100.0 %)	72 (100.0 %)	Day 15	51 (98.1%)	52 (98.1%)	103 (98.1%)
Second dose	Week 26	36 (100%)	34 (94.4%)	70 (97.2%)	Week 28	48 (92.3%)	47 (88.7%)	95 (90.5%)
Third dose	Week 52	34 (94.4%)	2 (5.6%)	36 (50.0%)	Week 54	47 (90.4%)	43 (81.1%)	90 (85.7%)
Fourth dose	Week 78	8 (22.2%)	1 (2.8%)	9 (12.5%)	Week 80	15 (28.8%)	11 (20.8%)	26 (24.8%)

BIC = bictegravir (GS-9883); DVY = emtricitabine/tenofovir alafenamide (coformulated; Descovy); LEN = lenacapavir (GS-6207); SC = subcutaneous; TAF = tenofovir alafenamide

a. For Study GS-US-200-4625, the first dose of SC LEN was Day 1 SC (15 Day after oral lead-in). For Study GS-US-200-4334, the first dose of SC LEN was on Day 15.

Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.1.3, GS-US-200-4334 Interim Week 54 CSR Addendum, Tables 15.11.5.1 and 15.8.4.1

2.6.8.2. Adverse events

Study GS-US-200-4625

Table 67 Treatment-Emergent Adverse Events: Overall Summary for Cohort 1 (Functional Monotherapy Period Analysis) (Safety Analysis Set)

Number (%) of Participants With Any	LEN (N = 24)	Placebo (N = 12)
TEAE	9 (37.5%)	3 (25.0%)
TEAE With Grade 3 or Higher	0	0
TEAE With Grade 2 or Higher	3 (12.5%)	0
TEAE Related to Study Drug	4 (16.7%)	1 (8.3%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0
TEAE Related to Study Drug With Grade 2 or Higher	2 (8.3%)	0
TE Serious AE	0	0
TE Serious AE Related to Study Drug	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0
TEAE Leading to Premature Discontinuation of Study	0	0
All Deaths	0	0

AE = adverse event; LEN = lenacapavir; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of blinded study drug and prior to the first dose date of the open-label study drug.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, July 2017).
Death includes any death that occurred during the Functional Monotherapy Period.
Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.1.1

During the functional monotherapy period for Cohort 1, the percentages of participants who experienced AEs were LEN 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants).

During the functional monotherapy period for Cohort 1, all AEs were Grade 1 or 2 in severity. No deaths, serious adverse events (SAEs), AEs leading to discontinuation of study drug, or Grade 3 or higher AEs were reported in either the LEN or placebo group.

Table 68 GS-US-200-4625: Treatment-Emergent Adverse Events by Preferred Term for Cohort 1 Reported in > 5% of Participants in Either Treatment Group (Functional Monotherapy Period Analysis) (Safety Analysis Set)

	LEN (N = 24)	**Placebo (N = 12)**
Number (%) of Participants With Any Treatment-Emergent Adverse Event	9 (37.5%)	3 (25.0%)
Nausea	3 (12.5%)	0
Diarrhoea	1 (4.2%)	1 (8.3%)
Abscess limb	0	1 (8.3%)
Neck pain	0	1 (8.3%)
Thrombocytopenia	0	1 (8.3%)
Vomiting	0	1 (8.3%)

Source: GS-US-200-4625 Interim Week 26 CSR, Table 15.11.2.1.3.1

Table 69 GS-US-200-4625: Treatment-Emergent Adverse Events: Overall Summary (All LEN Analysis) (Safety Analysis Set)

Number (%) of Participants With Any	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo LEN (N = 12)	Total (N = 36)		
TEAE	22 (91.7%)	12 (100.0%)	34 (94.4%)	33 (91.7%)	67 (93.1%)
TEAE With Grade 3 or Higher	3 (12.5%)	3 (25.0%)	6 (16.7%)	10 (27.8%)	16 (22.2%)
TEAE With Grade 2 or Higher	14 (58.3%)	7 (58.3%)	21 (58.3%)	25 (69.4%)	46 (63.9%)
TEAE Related to Study Drug	17 (70.8%)	6 (50.0%)	23 (63.9%)	25 (69.4%)	48 (66.7%)
TEAE Related to Study Drug With Grade 3 or Higher	0	0	0	4 (11.1%)	4 (5.6%)
TEAE Related to Study Drug With Grade 2 or Higher	7 (29.2%)	3 (25.0%)	10 (27.8%)	12 (33.3%)	22 (30.6%)
TE Serious AE	2 (8.3%)	3 (25.0%)	5 (13.9%)	3 (8.3%)	8 (11.1%)
TE Serious AE Related to Study Drug	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
TEAE Leading to Premature Discontinuation of Study	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)
All Deaths	0	0	0	1 (2.8%)	1 (1.4%)

AE = adverse event; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; TE = treatment emergent; TEAE = treatment-emergent adverse event
AEs were coded according to MedDRA Version 23.1.
TEAE was defined as an AE that began on or after the first dose date of LEN.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017).
Death includes any death that occurred on and after the first dose of LEN.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.2.1.1

The percentage of participants who received LEN in Cohorts 1 and 2 and experienced AEs was 93.1% (67 of 72 participants). Overall, 8 participants (11.1%) (5 in Cohort 1 and 3 in Cohort 2) experienced serious adverse events (SAEs). Since the Interim Week 26 analysis, 4 additional participants experienced SAEs.

Overall, 16 participants (22.2%) had Grade 3 or higher AEs (Cohort 1: 6 participants, 16.7%; Cohort 2: 10 participants, 27.8%). Since the Interim Week 26 analysis, 3 additional participants had Grade 3 or higher AEs and 16 new terms of Grade 3 or higher AEs were reported.

Table 70 GS-US-200-4625: Treatment-Emergent Adverse Events by Preferred Term for > 5% of Participants Overall (All LEN Analysis) (Safety Analysis Set)

	Cohort 1				
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	22 (91.7%)	12 (100.0%)	34 (94.4%)	33 (91.7%)	67 (93.1%)
Injection site pain	11 (45.8%)	3 (25.0%)	14 (38.9%)	13 (36.1%)	27 (37.5%)
Injection site swelling	9 (37.5%)	4 (33.3%)	13 (36.1%)	11 (30.6%)	24 (33.3%)
Injection site erythema	7 (29.2%)	2 (16.7%)	9 (25.0%)	11 (30.6%)	20 (27.8%)
Injection site nodule	9 (37.5%)	4 (33.3%)	13 (36.1%)	5 (13.9%)	18 (25.0%)
Injection site induration	2 (8.3%)	0	2 (5.6%)	9 (25.0%)	11 (15.3%)
Diarrhoea	4 (16.7%)	2 (16.7%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Nausea	6 (25.0%)	1 (8.3%)	7 (19.4%)	2 (5.6%)	9 (12.5%)
COVID-19	3 (12.5%)	1 (8.3%)	4 (11.1%)	4 (11.1%)	8 (11.1%)
Abdominal distension	5 (20.8%)	0	5 (13.9%)	2 (5.6%)	7 (9.7%)
Constipation	4 (16.7%)	2 (16.7%)	6 (16.7%)	1 (2.8%)	7 (9.7%)
Cough	3 (12.5%)	3 (25.0%)	6 (16.7%)	1 (2.8%)	7 (9.7%)
Arthralgia	4 (16.7%)	0	4 (11.1%)	2 (5.6%)	6 (8.3%)
Back pain	1 (4.2%)	1 (8.3%)	2 (5.6%)	4 (11.1%)	6 (8.3%)
Headache	2 (8.3%)	0	2 (5.6%)	4 (11.1%)	6 (8.3%)
Pyrexia	1 (4.2%)	2 (16.7%)	3 (8.3%)	3 (8.3%)	6 (8.3%)
Urinary tract infection	2 (8.3%)	0	2 (5.6%)	4 (11.1%)	6 (8.3%)
Rash	2 (8.3%)	0	2 (5.6%)	3 (8.3%)	5 (6.9%)
Dizziness	2 (8.3%)	0	2 (5.6%)	2 (5.6%)	4 (5.6%)
Fatigue	3 (12.5%)	1 (8.3%)	4 (11.1%)	0	4 (5.6%)
Oral candidiasis	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Vomiting	1 (4.2%)	0	1 (2.8%)	3 (8.3%)	4 (5.6%)

AE = adverse event; COVID-19 = coronavirus disease 2019; LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term
AEs were coded according to MedDRA Version 23.1.
Treatment-emergent AE was defined as an AE that began on or after the first dose date of LEN.
Multiple AEs were counted only once per participant for the highest severity grade for each PT.
PTs were presented by descending order of the total frequencies.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.2.1.3

Table 71 Study GS-US-200-4334: Treatment-Emergent Adverse Events: Overall Summary (Safety Analysis Set)

Number (%) of Participants With Any	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
TEAE	50 (96.2%)	45 (84.9%)	43 (82.7%)	21 (84.0%)	95 (90.5%)	138 (87.9%)
TEAE With Grade 3 or Higher	2 (3.8%)	5 (9.4%)	6 (11.5%)	2 (8.0%)	7 (6.7%)	13 (8.3%)
TEAE With Grade 2 or Higher	20 (38.5%)	17 (32.1%)	21 (40.4%)	13 (52.0%)	37 (35.2%)	58 (36.9%)
TEAE Related to Study Drug	34 (65.4%)	27 (50.9%)	8 (15.4%)	4 (16.0%)	61 (58.1%)	69 (43.9%)
TEAE Related to Study Drug With Grade 3 or Higher	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
TEAE Related to Study Drug With Grade 2 or Higher	9 (17.3%)	2 (3.8%)	0	0	11 (10.5%)	11 (7.0%)
TE Serious AE	3 (5.8%)	3 (5.7%)	4 (7.7%)	0	6 (5.7%)	10 (6.4%)
TE Serious AE Related to Study Drug	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)
TEAE Leading to Premature Discontinuation of Study	0	0	0	0	0	0
Death	0	0	0	0	0	0

AE = adverse event; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide; TE = treatment-emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.1.1

Similar percentages of participants in the LEN total (total of 157 participants) and BVY (total of 25 participants) groups had any AE by Week 54 (LEN total 87.9%, 138 participants; BVY 84.0%, 21 participants). The percentages of participants with Grade 3 or higher AEs were also similar between the LEN total and BVY groups (LEN total 8.3%, 13 participants; BVY 8.0%, 2 participants).

Serious AEs (SAEs) occurred only in the LEN total group (6.4%, 10 participants). None of the SAEs were considered related to the study drugs.

Adverse events related to the study drug occurred at a higher frequency in the SC LEN total group than in the Oral LEN + emtricitabine/tenofovir alafenamide (F/TAF; DVY) or BVY groups, mainly because of ISRs (SC LEN total 58.1% [61 of 105 participants], Oral LEN + DVY 15.4% [8 of 52 participants], and BVY 16.0% [4 of 25 participants]). Except for 1 participant (1.0%, 1 of 105) in the SC LEN total group with a Grade 3 AE related to study drug (injection site nodule), no other AEs related to study drug were Grade 3 or higher.

Since the Week 28 analysis, 2 additional AEs of Grade 3 or higher were reported in the LEN total group (SC LEN + [DVY → TAF] group: 1 participant; SC LEN + [DVY → BIC] group: 1 participant]) and 1 additional AE of Grade 3 or higher was reported in the BVY group (1 participant).

Table 72 GS-US-200-4334: Treatment-Emergent Adverse Events by Preferred Term Reported for ⩾ 5% of Participants in Any Treatment Group (Safety Analysis Set)

Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Adverse Events	50 (96.2%)	45 (84.9%)	43 (82.7%)	21 (84.0%)	95 (90.5%)	138 (87.9%)
Injection site erythema	21 (40.4%)	12 (22.6%)	0	0	33 (31.4%)	33 (21.0%)
Injection site swelling	16 (30.8%)	13 (24.5%)	0	0	29 (27.6%)	29 (18.5%)
Injection site pain	15 (28.8%)	10 (18.9%)	0	0	25 (23.8%)	25 (15.9%)
Headache	9 (17.3%)	5 (9.4%)	7 (13.5%)	3 (12.0%)	14 (13.3%)	21 (13.4%)
Nausea	10 (19.2%)	5 (9.4%)	6 (11.5%)	1 (4.0%)	15 (14.3%)	21 (13.4%)
COVID-19	5 (9.6%)	5 (9.4%)	5 (9.6%)	3 (12.0%)	10 (9.5%)	15 (9.6%)
Syphilis	5 (9.6%)	4 (7.5%)	5 (9.6%)	4 (16.0%)	9 (8.6%)	14 (8.9%)
Injection site nodule	9 (17.3%)	8 (15.1%)	0	0	17 (16.2%)	17 (10.8%)
Lymphadenopathy	4 (7.7%)	4 (7.5%)	6 (11.5%)	1 (4.0%)	8 (7.6%)	14 (8.9%)
Injection site inflammation	10 (19.2%)	4 (7.5%)	0	0	14 (13.3%)	14 (8.9%)
Diarrhoea	3 (5.8%)	4 (7.5%)	5 (9.6%)	1 (4.0%)	7 (6.7%)	12 (7.6%)
Injection site induration	8 (15.4%)	5 (9.4%)	0	0	13 (12.4%)	13 (8.3%)
Arthralgia	2 (3.8%)	4 (7.5%)	2 (3.8%)	4 (16.0%)	6 (5.7%)	8 (5.1%)
Back pain	1 (1.9%)	4 (7.5%)	4 (7.7%)	3 (12.0%)	5 (4.8%)	9 (5.7%)
Depression	1 (1.9%)	6 (11.3%)	3 (5.8%)	1 (4.0%)	7 (6.7%)	10 (6.4%)
Influenza	4 (7.7%)	2 (3.8%)	5 (9.6%)	0	6 (5.7%)	11 (7.0%)
Nasopharyngitis	4 (7.7%)	4 (7.5%)	3 (5.8%)	0	8 (7.6%)	11 (7.0%)
Anxiety	2 (3.8%)	2 (3.8%)	3 (5.8%)	2 (8.0%)	4 (3.8%)	7 (4.5%)
Fatigue	0	6 (11.3%)	2 (3.8%)	1 (4.0%)	6 (5.7%)	8 (5.1%)
Oropharyngeal pain	2 (3.8%)	4 (7.5%)	3 (5.8%)	0	6 (5.7%)	9 (5.7%)
Pyrexia	3 (5.8%)	2 (3.8%)	2 (3.8%)	2 (8.0%)	5 (4.8%)	7 (4.5%)
Dizziness	3 (5.8%)	2 (3.8%)	2 (3.8%)	1 (4.0%)	5 (4.8%)	7 (4.5%)
Gonorrhoea	2 (3.8%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)
Hypertension	3 (5.8%)	3 (5.7%)	1 (1.9%)	1 (4.0%)	6 (5.7%)	7 (4.5%)
Vitamin D deficiency	0	4 (7.5%)	3 (5.8%)	1 (4.0%)	4 (3.8%)	7 (4.5%)
Vomiting	3 (5.8%)	1 (1.9%)	4 (7.7%)	0	4 (3.8%)	8 (5.1%)
Weight increased	2 (3.8%)	1 (1.9%)	2 (3.8%)	3 (12.0%)	3 (2.9%)	5 (3.2%)
Abdominal pain	4 (7.7%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	5 (4.8%)	6 (3.8%)
Upper respiratory tract infection	2 (3.8%)	0	2 (3.8%)	3 (12.0%)	2 (1.9%)	4 (2.5%)
Urinary tract infection	1 (1.9%)	1 (1.9%)	4 (7.7%)	1 (4.0%)	2 (1.9%)	6 (3.8%)
Cough	3 (5.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	4 (3.8%)	5 (3.2%)
Insomnia	1 (1.9%)	0	2 (3.8%)	3 (12.0%)	1 (1.0%)	3 (1.9%)
Onychomycosis	3 (5.8%)	1 (1.9%)	2 (3.8%)	0	4 (3.8%)	6 (3.8%)
Oropharyngeal gonococcal infection	1 (1.9%)	1 (1.9%)	3 (5.8%)	1 (4.0%)	2 (1.9%)	5 (3.2%)
Rash	1 (1.9%)	0	3 (5.8%)	2 (8.0%)	1 (1.0%)	4 (2.5%)
Acarodermatitis	3 (5.8%)	0	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Anogenital warts	0	1 (1.9%)	3 (5.8%)	1 (4.0%)	1 (1.0%)	4 (2.5%)
Abdominal pain upper	2 (3.8%)	0	0	2 (8.0%)	2 (1.9%)	2 (1.3%)
Anal chlamydia infection	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Proctitis gonococcal	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Rhinitis allergic	0	1 (1.9%)	3 (5.8%)	0	1 (1.0%)	4 (2.5%)
Constipation	0	0	3 (5.8%)	0	0	3 (1.9%)
Hypertriglyceridaemia	0	3 (5.7%)	0	0	3 (2.9%)	3 (1.9%)
Otitis media	0	0	1 (1.9%)	2 (8.0%)	0	1 (0.6%)
Ligament sprain	0	0	0	2 (8.0%)	0	0

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); COVID-19 = coronavirus disease 2019; DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; SC = subcutaneous; TAF = tenofovir alafenamide

Adverse events were coded according to MedDRA Version 23.1.

Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.

Multiple adverse events were counted only once per participant for the highest severity grade for each preferred term.

Preferred terms were presented by descending order of the total frequencies.

Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.2.1.3

Table 73 ISS. (GS-US-200-4070, GS-US-200-4071, GS-US-200-4329, GS-US-200-4330, GS-US-200-4331, GS-US-200-4333, GS-US-200-4538, and GS-US-200-5709): Treatment-emergent Adverse Events: Overall Summary (Safety Analysis Set)

	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
TEAE	120 (84.5%)	14 (77.8%)	48 (21.7%)	14 (100.0%)	192 (52.6%)	27 (55.1%)
TEAE with Grade 3 or Higher	2 (1.4%)	1 (5.6%)	0	0	3 (0.8%)	2 (4.1%)
TEAE Related to Study Drug	107 (75.4%)	5 (27.8%)	14 (6.3%)	14 (100.0%)	139 (38.1%)	16 (32.7%)
TEAE Related to Study Drug with Grade 3 or Higher	0	1 (5.6%)	0	0	1 (0.3%)	0
TE Serious AE	2 (1.4%)	1 (5.6%)	0	0	3 (0.8%)	1 (2.0%)
TE Serious AE Related to Study Drug	0	1 (5.6%)	0	0	1 (0.3%)	0
TE Study-Drug-Related Injection Site Reaction (Excluding Injection Site Abscess) AEs	103 (72.5%)	0	0	14 (100.0%)	117 (32.1%)	16 (32.7%)
Death	0	0	0	0	0	0

AE = adverse event; IV = intravenous; LEN = lenacapavir (GS-6207); SC = subcutaneous; TE = treatment emergent; TEAE = treatment-emergent adverse event
Adverse events were coded according to MedDRA Version 24.1.
Treatment-emergent events began on or after the study drug start date, or led to premature study drug discontinuation.
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
Death includes any death that occurred during the study.
a. n = 32 from Study GS-US-200-4070, n = 80 from Study GS-US-200-4538, and n = 30 from Study GS-US-200-5709 (Cohort 1, SC period only)
b. n = 18 from Study GS-US-200-4329
c. n = 88 from Study GS-US-200-4071, n = 10 from Study GS-US-200-4330, n = 10 from Study GS-US-200-4331, n = 82 from Study GS-US-200-4333, and n = 31 from Study GS-US-200-5709 (Cohort 1, oral lead-in period only)
d. n = 14 from Study GS-US-200-5709 (Cohort 2 only)
Source: LEN Phase 1 ISS, Table 13338.4

Similar percentages of participants in the All LEN group (52.6%, 192 of 365 participants) and placebo group (55.1%, 27 of 49 participants) had an AE. Grade 3 or higher AEs were reported in 0.8% (3 of 365) participants of the All LEN group and 4.1% (2 of 49) participants of the placebo group.

Serious AEs were reported in 0.8% (3 of 365) participants of the All LEN group and 2.0% (1 of 49) participants of the placebo group.

Adverse events considered related to the study drug occurred in 38.1% (139 of 365) participants of the All LEN group and 32.7% (16 of 49) participants of the placebo group, including 1 SAE in the All LEN group.

The SC LEN-containing groups had greater percentages of participants (SC LEN, 75.4% [107 of 142] participants; SC + oral LEN, 100.0% [14 of 14] participants) with AEs considered related to the study

drug than the IV LEN group (27.8%, 5 of 18 participants) or oral LEN group (6.3%, 14 of 221 participants), primarily because of study drug-related ISRs (excluding injection site abscess) which were reported in 72.5% (103 of 142) participants of the SC LEN group and 100.0% (14 of 14) participants of the SC + oral LEN group.

One AE leading to premature discontinuation of study drug was a Grade 1, nonserious non-study drug-related AE of SARS-CoV-2 test positive in 1 participant who had received LEN.

Table 74 Treatment Adverse Events

	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Number (%) of Participants with Any Treatment-Emergent Adverse Event	120 (84.5%)	14 (77.8%)	48 (21.7%)	14 (100.0%)	192 (52.6%)	27 (55.1%)
Number (%) of Participants with Any Treatment-Emergent Adverse Event by Preferred Term						
Injection site induration	76 (53.5%)	0	0	14 (100.0%)	90 (24.7%)	6 (12.2%)
Injection site pain	65 (45.8%)	0	0	4 (28.6%)	69 (18.9%)	7 (14.3%)
Injection site erythema	62 (43.7%)	0	0	5 (35.7%)	67 (18.4%)	0
Headache	27 (19.0%)	1 (5.6%)	11 (5.0%)	2 (14.3%)	41 (11.2%)	6 (12.2%)
Injection site nodule	41 (28.9%)	0	0	0	41 (11.2%)	0
Injection site swelling	34 (23.9%)	0	0	0	34 (9.3%)	2 (4.1%)
Injection site bruising	15 (10.6%)	0	0	0	15 (4.1%)	9 (18.4%)
Back pain	6 (4.2%)	1 (5.6%)	4 (1.8%)	1 (7.1%)	12 (3.3%)	2 (4.1%)
Diarrhoea	1 (0.7%)	8 (44.4%)	2 (0.9%)	0	11 (3.0%)	1 (2.0%)
Oropharyngeal pain	7 (4.9%)	1 (5.6%)	2 (0.9%)	0	10 (2.7%)	2 (4.1%)

	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Upper respiratory tract infection	6 (4.2%)	1 (5.6%)	2 (0.9%)	0	9 (2.5%)	3 (6.1%)
SARS-CoV-2 test positive	9 (6.3%)	0	1 (0.5%)	0	10 (2.7%)	0
Viral upper respiratory tract infection	4 (2.8%)	0	0	1 (7.1%)	5 (1.4%)	2 (4.1%)
Injection site discolouration	4 (2.8%)	0	0	1 (7.1%)	5 (1.4%)	1 (2.0%)
Constipation	0	2 (11.1%)	2 (0.9%)	0	4 (1.1%)	1 (2.0%)
Nasal congestion	2 (1.4%)	1 (5.6%)	1 (0.5%)	0	4 (1.1%)	1 (2.0%)
Arthralgia	2 (1.4%)	2 (11.1%)	0	0	4 (1.1%)	0
Cough	2 (1.4%)	2 (11.1%)	0	0	4 (1.1%)	0
Injection site warmth	3 (2.1%)	0	0	1 (7.1%)	4 (1.1%)	0
Pain in extremity	1 (0.7%)	1 (5.6%)	0	1 (7.1%)	3 (0.8%)	1 (2.0%)
Asthenia	1 (0.7%)	1 (5.6%)	1 (0.5%)	0	3 (0.8%)	0
Dermatitis	0	1 (5.6%)	1 (0.5%)	0	2 (0.5%)	1 (2.0%)
Feeling hot	0	2 (11.1%)	0	0	2 (0.5%)	1 (2.0%)
Erythema	1 (0.7%)	1 (5.6%)	0	0	2 (0.5%)	0
Infusion site pain	0	2 (11.1%)	0	0	2 (0.5%)	0
Myalgia	1 (0.7%)	1 (5.6%)	0	0	2 (0.5%)	0
Pain	1 (0.7%)	1 (5.6%)	0	0	2 (0.5%)	0
Weight decreased	1 (0.7%)	1 (5.6%)	0	0	2 (0.5%)	0
Abnormal dreams	0	1 (5.6%)	0	0	1 (0.3%)	0
Body temperature increased	0	1 (5.6%)	0	0	1 (0.3%)	0
Bruxism	0	1 (5.6%)	0	0	1 (0.3%)	0
Burning sensation	0	1 (5.6%)	0	0	1 (0.3%)	0
Chills	0	1 (5.6%)	0	0	1 (0.3%)	0
Decreased appetite	0	1 (5.6%)	0	0	1 (0.3%)	0
Dermal cyst	0	1 (5.6%)	0	0	1 (0.3%)	0
Ear pain	0	0	0	1 (7.1%)	1 (0.3%)	0
Eye irritation	0	1 (5.6%)	0	0	1 (0.3%)	0

	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Gastrointestinal sounds abnormal	0	1 (5.6%)	0	0	1 (0.3%)	0
Haematochezia	0	1 (5.6%)	0	0	1 (0.3%)	0
Haematoma	0	1 (5.6%)	0	0	1 (0.3%)	0
Injection site discomfort	0	0	0	1 (7.1%)	1 (0.3%)	0
Muscle rigidity	0	1 (5.6%)	0	0	1 (0.3%)	0
Oliguria	0	1 (5.6%)	0	0	1 (0.3%)	0
Paraesthesia	0	1 (5.6%)	0	0	1 (0.3%)	0
Rhabdomyolysis	0	1 (5.6%)	0	0	1 (0.3%)	0
Scab	0	1 (5.6%)	0	0	1 (0.3%)	0
Skin laceration	0	1 (5.6%)	0	0	1 (0.3%)	0
Vessel puncture site pain	0	1 (5.6%)	0	0	1 (0.3%)	0

AE = adverse event; IV = intravenous; LEN = lenacapavir (GS-6207); PT = preferred term; SC = subcutaneous
Adverse events were coded according to MedDRA Version 24.1.
Treatment-emergent events began on or after the study drug start date, or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant for each PT.
Preferred terms were presented by descending order of total frequencies.
a. n = 32 from Study GS-US-200-4070, n = 80 from Study GS-US-200-4538, and n = 30 from Study GS-US-200-5709 (Cohort 1, SC period only)
b. n = 18 from Study GS-US-200-4329
c. n = 88 from Study GS-US-200-4071, n = 10 from Study GS-US-200-4330, n = 10 from Study GS-US-200-4331, n = 82 from Study GS-US-200-4333, and n = 31 from Study GS-US-200-5709 (Cohort 1, oral lead-in period only)
d. n = 14 from Study GS-US-200-5709 (Cohort 2 only)
Source: LEN Phase 1 ISS, Table 13338.5

Treatment-emergent symptoms of rhabdomyolysis

The applicant has assessed treatment-emergent symptoms of rhabdomyolysis identified using the Standardized MedDRA Query (SMQ) rhabdomyolysis (broad) and treatment-emergent Grade 3 or 4 laboratory abnormalities of creatine kinase (CK) increased from the Week 52 and Week 54 datasets from Studies GS-US-200-4625 and GS-US-200-4334, respectively.

A total of 13 participants experienced 15 adverse events (AEs) in the MedDRA SMQ rhabdomyolysis (broad) across both studies: 6 participants in Study GS-US-200-4625 experienced 8 AEs, and 7 participants in Study GS-US-200-4334 experienced 7 AEs. The AE of rhabdomyolysis was not reported for any participants in either study. In the majority of participants (11 of 13), the reported AEs were either Grade 1 or Grade 2 in severity, and only 2 participants had a study drug-related AE.

No participants discontinued study drug or the study due to an AE. At the time of the Week 52 and 54 data cuts, AEs had resolved in most of the participants (10 of 13).

Overall, the retrieved AEs were nonspecific muscular-skeletal (such as muscular weakness and musculoskeletal discomfort) or renal events (such as blood creatinine increased and renal impairment), and none were associated with CK elevations nor otherwise suggestive of rhabdomyolysis.

In the Week 52 dataset for Study GS-US-200-4625, no participant experienced a Grade 3 or 4 laboratory abnormality of CK increased. In the Week 54 dataset for Study GS-US-200-4334, 11 participants (7.0%) in the total LEN group and 1 participant (4.0%) in the bictegravir/emtricitabine/tenofovir alafenamide (coformulated; Biktarvy® [BVY]) group experienced a Grade 3 or 4 laboratory abnormality of CK increased.

The majority of Grade 3 or 4 CK elevations in participants receiving LEN were isolated occurrences with no consistent time to onset (range: 113 to 380 days), and all returned to normal (Grade 0) during continued exposure to LEN. There were no clinically relevant median changes from baseline in CK in Studies GS-US-200-4625 and GS-US-200-4334; overall median (Q1, Q3) change in the total LEN group was 14 (−17, 55) U/L at Week 52 in Study GS-US-200-4625 (n = 40) and 22 (−25, 90) U/L at Week 54 in Study GS-US-200-4334 (n = 144).

In summary, no participant experienced an AE of rhabdomyolysis in the Week 52 or 54 datasets from Studies GS-US-200-4625 and GS-US-200-4334.

The treatment-emergent adverse event of rhabdomyolysis reported in Study GS-US-200-4334 after the Week 54 data cut had a nondrug etiology according to the investigator and resolved during continued exposure to LEN.

Separate analysis of adverse events in the SOC of psychiatric disorders

In Study GS-US-200-4625, no participant experienced an AE within the psychiatric disorders system organ class (SOC) during the 14-day Functional Monotherapy Period. A total of 8 participants (11.1%) experienced AEs within the psychiatric disorders MedDRA SOC in the Week 52 dataset during the Maintenance Phase. One participant experienced an AE of depression not related to study drug.

Adverse events experienced in more than 1 participant were as follows: insomnia (3 participants [4.2%]), and anxiety and sleep disorder (2 participants each [2.8%]). Only 1 participant experienced an AE considered related to study drug (sleep disorder), and none of the AEs were reported as serious or resulted in discontinuation of study drug.

In Study GS-US-200-4334, AEs in the psychiatric disorders SOC in the Week 54 dataset were reported as follows: total LEN, 20 participants (12.7%); BVY, 5 participants (20.0%). The majority of AEs within the psychiatric disorders SOC occurred in only 1 participant. The most common AEs were as follows: total LEN group, depression (10 participants [6.4%]) and anxiety (7 participants [4.5%]); BVY group, insomnia (3 participants [12.0%]) and anxiety (2 participants [8.0%]). One participant in the total LEN group experienced AEs considered related to study drug (AEs of anxiety and self-esteem decreased in a participant with ongoing gender dysphoria and depression at baseline).

No participants discontinued LEN due to an AE in the psychiatric disorders SOC. Three participants in the total LEN group experienced 5 SAEs within the psychiatric disorders SOC: psychotic disorder (1 participant), bipolar disorder, mental disorder, and major depression (1 participant), and substance-induced psychotic disorder (1 participant). Upon individual assessment of the events, all had likely alternative etiologies including preexisting psychiatric conditions or concomitant substance abuse, and none were considered related to study drug.

In Studies GS-US-200-4625 and GS-US-200-4334, psychiatric disorders (PTs from the MedDRA SOC "Psychiatric Disorders") were commonly reported in participants' medical histories, as follows: Study GS-US-200-4625, 48.6% (35 of 72 participants); Study GS-US-200-4334, 34.6% (63 of 182 participants).

The incidence of participants experiencing an AE within the psychiatric disorders SOC at Weeks 52 and 54 of Studies GS-US-200-4625 and GS-US-200-4334, respectively, is consistent with the high rates of psychiatric comorbidities seen in PWH reported in the published literature, particularly in those with more advanced disease according to the applicant. In a recent systematic review and meta-analysis of

the global prevalence of depression in HIV/AIDS, the prevalence rate of major depression among PWH was 31% {Rezaei 2019}.

ISRs

In Study GS-US-200-4625, study drug-related injection site reactions (ISRs) occurred in 41 participants (56.9%) at Day 15, 29 participants (41.4%) at Week 26, and 15 participants (41.7%) at Week 52. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR (1 with swelling and erythema which resolved in 4 and 8 days after the first SC injection on Day 15, and 1 with pain which resolved in 1 day after the first injection). No participants experienced new Grade 3 or 4 ISRs beyond Week 26.

In Study GS-US-200-4334, study drug-related ISRs occurred in 39 participants (37.9%) at Day 15, 42 participants (44.2%) at Week 28, and 23 participants (25.6%) at Week 54. All were Grade 1 or 2, except 1 participant with Grade 3 injection site nodule following the second LEN injection (Day 194-ongoing). The participant discontinued study drug due to participant decision. No participants experienced new Grade 3 or 4 ISRs beyond Week 28.

In both studies, following the Day 1 SC dose of LEN, the most common ISRs included injection site swelling, injection site pain, injection site erythema, injection site nodule, and injection site induration. In Study GS-US-200-4625, a numerically lower percentage of participants had ISRs after the second and third LEN injection compared with the first injection. In Study GS-US-200-4334, a numerically lower percentage of participants had ISRs after the third LEN injection compared with the first and second injections.

The relation between time of lenacapavir injection and the onset, maximum and duration of the main side-effects such as nausea, depression and headache

The number of participants in both Studies GS-US-200-4625 and GS-US-200-4334, with AEs of nausea were (8.3% and 9.7%, respectively), headache (4.2% and 11.7%, respectively), and depression (1.4% and 5.8%, respectively). There was a numerically lower percentage of participants with nausea, headache, or depression after the second or third LEN injection compared with the first injection. No SAEs or Grade 3 or 4 AEs of nausea, headache, or depression were reported; none led to study drug discontinuation.

In Study GS-US-200-4625, nausea, headache, or depression occurred in total of 6 participants (8.3%), 3 participants (4.2%), and 1 participant (1.4%), respectively, during the SC phase (after oral LEN lead-in). The median duration (Q1, Q3) for nausea, headache, or depression was 95 (18, 329), 9 (2, 31) and 12 (12, 12) days. All AEs of nausea, headache, and depression were Grade 1 or 2 in severity.

In Study GS-US-200-4334, nausea, headache, or depression occurred in total of 10 participants (9.7%), 12 participants (11.7%), and 6 participants (5.8%), respectively. The median duration (Q1, Q3) for nausea, headache, or depression was 11 (2, 22), 15 (1, 46), and 218 (17, 315) days. All AEs of nausea, headache, and depression were Grade 1 or 2 in severity.

Table 75 Side-effects such as Nausea, Headache and Depression

		Nausea			**Headache**			**Depression**	
			Onseta (Median, Days	**Durationb (Median,**		**Onseta (Median, Days**	**Durationb (Median,**		**Ons (Me n, D**

		n/N (%)	[Q1, Q3])	Days [Q1, Q3])	n/N (%)	[Q1, Q3])	Days [Q1, Q3])	n/N (%)	[Q1, Q3])
Any SC dose		6/72 (8.3 %)	60 (22, 72)	95 (18, 329)	3/72 (4.2 %)	110 (46, 171)	9 (2, 31)	1/72 (1.4 %)	170 (170 170)
First dose (Day 15/Day 1 SC)		3/72 (4.2 %)	66 (22, 166)	48 (18, 531)	3/72 (4.2 %)	110 (46, 171)	9 (2, 31)	0/72 (0)	—
Second dose (Week 26)		2/70 (2.9 %)	63 (54, 72)	190 (95, 329)	0/70	—	—	1/70 (1.4 %)	170 (170 170)
Third dose (Week 52)		1/36 (2.8 %)	3 (3, 3)	1 (1, 1)	0/36	—	—	0/36 (0)	—
Fourth dose (Week 78)		0/9 (0)	—	—	0/9	—	—	0/9 (0)	—

LEN = lenacapavir (GS-6207); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous

a. Onset day was calculated relative to the latest SC injection received prior to the adverse event. If a participant had multiple events following the SC injection and before the next SC injection, the earliest onset date was used.

b. Duration was summarised for all events of interest. One participant could have multiple events. Participants may receive more than 1 SC injection.

Duration = stop date − onset date + 1.

Source: GS-US-200-4625 Week 52 Ad Hoc Analysis Table Req 13353.2, Table Req 13381.1 through Table Req 13381.6

	Nausea			Headache			Depression		
	n/N (%)	Onseta (Median, Days [Q1, Q3])	Durationb (Median, Days [Q1, Q3])	n/N (%)	Onseta (Median, Days [Q1, Q3])	Durationb (Median, Days [Q1, Q3])	n/N (%)	Onseta (Median, Days [Q1, Q3])	Durationb (Median, Days [Q1, Q3])

Any SC dosec	10/103 (9.7%)	64 (8, 102)	11 (2, 22)	12/103 (11.7%)	69 (24, 94)	15 (1, 46)	6/103 (5.8%)	57 (24, 137)	218 (17, 315)
First dose (Day 15)	6/103 (5.8%)	87 (13, 97)	4 (2, 17)	8/103 (7.8%)	42 (17, 95)	27 (1, 49)	3/103 (2.9%)	85 (29, 137)	178 (31, 310)
Second dose (Week 28)	6/95 (6.3%)	28 (7, 154)	22 (1, 100)	5/95 (5.3%)	70 (69, 70)	1 (1, 15)	3/95 (3.2%)	24 (4, 148)	218 (17, 365)
Third dose (Week 54)	0/90 (0)	—	—	0/90	—	—	0/90 (0)	—	—
Fourth dose (Week 80)	0/26 (0)	—	—	0/26	—	—	0/26 (0)	—	—

LEN = lenacapavir (GS-6207); Q1 = first quartile; Q3 = third quartile; SC = subcutaneous.

a. Onset day was calculated relative to the latest SC injection received prior to the adverse event. If a participant had multiple events following the SC injection and before the next SC injection, the earliest onset date was used.

b. Duration was summarised for all events of interest. One participant could have multiple events.

c. n is the total number of participants who experienced a given event. Participants may receive more than 1 SC injection.

Duration = stop date − onset date + 1.

Source: GS-US-200-4334 Week 54 Ad Hoc Analysis, Table Req 13354.2, Table Req 13380.1 through Table Req 13380.6

2.6.8.3. Serious adverse event/deaths/other significant events

Study GS-US-200-4625

Deaths

One participant in Cohort 2 died on Study Day 90; the cause of death was cancer. Due to deteriorating clinical status during hospitalisation, the subject was transferred to hospice, where he subsequently died. The subject had low CD4 (7 cell/ul) at baseline. Per the investigator, "the cause of death was updated to metastatic cancer. The subject did have a prior history of Non-Hodgkin's lymphoma and there was a suspected recurrence, but he expired prior to biopsy of the new lesions." No autopsy was performed, nor any further specific diagnosis on the type of cancer was provided by the investigator.

Serious Adverse Events

Interim week 26 analysis

Serious AEs were reported for 5.6% (4 of 72 participants) in the All LEN Analysis. The reported SAEs were proctalgia, pancreatic mass, abdominal pain, Clostridium difficile infection, dizziness, neoplasm malignant and femoral neck fracture. No SAEs were reported in > 1 participant. All SAEs considered not related to Study Drug.

Week 52 analysis

Serious AEs were reported for 11.1% (8 of 72 participants). Since the Interim Week 26 analysis, 4 additional participants experienced SAEs of COVID-19, (2 participants), septic shock, renal impairment, shock, pneumonia, and 2 participants who previously experienced SAEs experienced additional SAEs of anal squamous cell carcinoma, impaired healing, anal cancer and angina pectoris.

The only SAE that was reported for more than 1 participant was COVID-19 (2.8%, 2 participants). None of these SAEs led to discontinuation of study drug and none were considered related to study drug.

Study GS-US-200-4334

Deaths

There were no deaths by Week 54.

Serious Adverse Events

Week 28
SAEs were reported for 5.1% (8 of 157 participants) in the LEN total group and no participants in the BVY group. None of the SAEs were reported for > 1 participant in any treatment group, and none were considered related to the study drugs by the investigator. The reported SAEs were Pneumocystis jirovecii pneumonia, pneumothorax, psychotic disorder, poisoning, Escherichia infection, substance-induced psychotic disorder, perirectal abscess, bipolar disorder, major depression, staphylococcal infection, dyspnoea, lymphadenopathy mediastinal, pneumonia, vomiting, pleural effusion, non-small cell lung cancer, metastases to central nervous system. All SAEs were considered not related to Study Drug.

Multiple SAEs were reported in the MedDRA psychiatric disorders SOC. One participant with SAEs of bipolar disorder and major depression and a second participant with an SAE of psychotic disorder had relevant psychiatric medical histories that could have predisposed them to these SAEs, while a third participant experienced an SAE of substance-induced psychotic disorder.

Week 54
Serious AEs were reported for 6.4% (10 of 157 participants) in the LEN total group and none of the participants in the BVY group. None of the SAEs were reported for more than 1 participant in any treatment group, and all were considered not related to the study drugs. Since the Week 28 analysis, 1 additional SAE was reported in the SC LEN + (DVY → TAF) group (uterine leiomyoma) and 1 additional SAE was reported in the SC LEN + (DVY → BIC) total group (hepatitis A).

Rhabdomyolysis

Since the MAA submission, and after the Study GS-US-200-4334 Week 54 data cut, 1 AE of rhabdomyolysis was reported.

A male with less than 30 year of age in the daily oral LEN + emtricitabine/tenofovir alafenamide (coformulated; Descovy®) (DVY) group, experienced a serious adverse event (SAE) of rhabdomyolysis at Day 586, which resulted in hospitalisation.

Approximately 48 hours after beginning an exercise routine, the participant developed severe muscle pain and dark urine. He presented to the emergency room and was hospitalised the same day. At Day 587, the participant's CK was 82,625 IU/L, urine was positive for myoglobin, while his serum creatinine (0.74 mg/dL), estimated glomerular filtration rate (eGFR) (> 60 mL/min), and blood urea nitrogen (13 mg/dL) remained within the normal ranges. Ibuprofen and IV fluids were administered.

The participant was not receiving statins and had no history of drug or alcohol abuse. At Day 588, the participant's CK had decreased to 32,111 IU/L, then continued to decrease over the course of the next 7 days in the presence of ongoing exposure to LEN, and was 724 IU/L by Day 595. At Day 596, the AE of rhabdomyolysis resolved and the participant was discharged. The investigator considered that the event was due to exercise and not related to study drug. The participant continued with study drug.

Table 76 Treatment Emergent SAE

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Number (%) of Participants With Any Treatment-Emergent Serious Adverse Events	3 (5.8%)	3 (5.7%)	4 (7.7%)	0	6 (5.7%)	10 (6.4%)
Blood and lymphatic system disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Lymphadenopathy mediastinal	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Gastrointestinal disorders	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Vomiting	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Infections and infestations	2 (3.8%)	3 (5.7%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Escherichia infection	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hepatitis A	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Perirectal abscess	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Pneumocystis jirovecii pneumonia	0	0	1 (1.9%)	0	0	1 (0.6%)
Pneumonia	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Staphylococcal infection	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Injury, poisoning, and procedural complications	0	0	1 (1.9%)	0	0	1 (0.6%)
Poisoning	0	0	1 (1.9%)	0	0	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Metastases to central nervous system	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Non-small cell lung cancer	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Uterine leiomyoma	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)

System Organ Class Preferred Term	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Psychiatric disorders	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
Bipolar disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Major depression	0	0	1 (1.9%)	0	0	1 (0.6%)
Mental disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Psychotic disorder	0	0	1 (1.9%)	0	0	1 (0.6%)
Substance-induced psychotic disorder	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	0	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Dyspnoea	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pleural effusion	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Pneumothorax	0	0	1 (1.9%)	0	0	1 (0.6%)

BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); LEN = lenacapavir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; PT = preferred term; SC = subcutaneous; SOC = system organ class; TAF = tenofovir alafenamide
Adverse events were coded according to MedDRA Version 23.1.
Treatment-emergent events began on or after the first dose date of study drug up to last exposure date after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Multiple adverse events were counted only once per participant for the highest severity grade for each SOC and PT.
SOCs were presented alphabetically and PTs within SOC were presented by descending order of the total frequencies.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.3.1

Integrated summary of safety

Deaths

No deaths were reported in any of Phase 1 studies.

Serious adverse events

Serious adverse events were reported in 0.8% (3 of 365) participants of the All LEN group and 2.0% (1 of 49) participants of the placebo group.

1 participant who received a solution containing 20 mg LEN intravenously had a Grade 4 SAE of rhabdomyolysis on day 22. The grade 4 event was resolved on day 32.

Per hospital medical record, around Day 7, the participant had mild aches, muscle pain, and stiffness but no muscle weakness. On Day 23, the participant was hospitalised for rhabdomyolysis (CK: 10,221 U/L; LDH 585 U/L). Abnormalities regarding CK were not observed in preceding samples collected on day 1, 2, 4, 8 and 15. In the preceding days, he reported “considerable muscle stiffness”. The participant increased his walking but denied strenuous exercise or using any illicit substances. The participant did not have history of trauma or prior CK elevation and was not receiving any concomitant medications. Serum creatinine, electrolytes, and urinalysis were normal. Per hospital medical record, on Day 25, the CK peaked at 43,938 U/L. Urinalysis showed 2+ blood and occasional red blood cells (RBCs). Serum creatinine remained normal. Physical examination was unremarkable. The participant received IV fluids and was discharged on Day 27. On Day 35, the participant’s CK levels returned to normal.

The investigator's assessment in the SAE reporting, that the time of onset (Day 22) was unusual for drug-induced rhabdomyolysis. The concentration of LEN on Day 22 (1.43 ng/mL) was much lower than the maximum concentration (Cmax) achieved within 1 hour (210 ng/mL). CK continued to improve in the presence of ongoing GS-6207 exposure (i.e. continued decreasing concentrations of LEN following the single dose administered).

The other SAEs were abscess limb and tibia fracture in the SC LEN group and sepsis in the placebo group.

2.6.8.4. Laboratory findings

In general, the majority of participants in included studies had at least one laboratory abnormality. Most laboratory abnormalities were Grade 1 or 2. There were no clinically relevant changes from baseline in median values for haematology, clinical chemistry (including metabolic parameters) in Studies GS-US-200-4625 and GS-US-200-4334.

GS-US-200-4625

The majority of the participants had at least 1 graded laboratory abnormality (97.2%, 70 of 72 participants). The majority of abnormalities were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 16 participants (22.2%) and Grade 4 laboratory abnormalities were reported for 5 participants (6.9%).

Since the Interim Week 26 analysis, 1 additional participant had Grade 3 laboratory abnormalities and 1 additional participant had Grade 4 laboratory abnormalities. These laboratory abnormalities were either transient, returned to baseline, improved on subsequent visits despite continued exposure to the study drug, or occurred in participants with underlying conditions expected in the population (eg, diabetes, alcohol abuse, viral hepatitis).

Table 77 GS-US-200-4625: Grade 3 or 4 Laboratory Abnormalities Reported in ≥ 2 Participants – All LEN Analysis (Safety Analysis Set)

	Cohort 1				
Maximum Postbaseline Toxicity Grade	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)	Cohort 2 (N = 36)	Total (N = 72)
Participants With Postbaseline Value	24	12	36	36	72
Grade 3 or 4	9 (37.5%)	4 (33.3%)	13 (36.1%)	8 (22.2%)	21 (29.2%)
Grade 3	8 (33.3%)	3 (25.0%)	11 (30.6%)	5 (13.9%)	16 (22.2%)
Grade 4	1 (4.2%)	1 (8.3%)	2 (5.6%)	3 (8.3%)	5 (6.9%)
Chemistry					
ALT (SGPT), High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	2 (5.6%)	2 (2.8%)
Grade 4	0	0	0	0	0

Maximum Postbaseline Toxicity Grade	Cohort 1			Cohort 2 (N = 36)	Total (N = 72)
	LEN (N = 24)	Placebo → LEN (N = 12)	Total (N = 36)		
AST (SGOT), High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	2 (5.6%)	2 (2.8%)
Creatinine, High	24	12	36	36	72
Grade 3 or 4	5 (20.8%)	1 (8.3%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Grade 3	4 (16.7%)	1 (8.3%)	5 (13.9%)	2 (5.6%)	7 (9.7%)
Grade 4	1 (4.2%)	0	1 (2.8%)	1 (2.8%)	2 (2.8%)
Creatinine Clearance or eGFR, Low	24	12	36	36	72
Grade 3 or 4	5 (20.8%)	2 (16.7%)	7 (19.4%)	3 (8.3%)	10 (13.9%)
Grade 3	4 (16.7%)	2 (16.7%)	6 (16.7%)	3 (8.3%)	9 (12.5%)
Grade 4	1 (4.2%)	0	1 (2.8%)	0	1 (1.4%)
Direct Bilirubin, High	24	12	36	36	72
Grade 3 or 4	0	0	0	2 (5.6%)	2 (2.8%)
Grade 3	0	0	0	2 (5.6%)	2 (2.8%)
Grade 4	0	0	0	0	0
Hyperglycemia, Fasting	20	9	29	26	55
Grade 3 or 4	1 (5.0%)	2 (22.2%)	3 (10.3%)	0	3 (5.5%)
Grade 3	1 (5.0%)	1 (11.1%)	2 (6.9%)	0	2 (3.6%)
Grade 4	0	1 (11.1%)	1 (3.4%)	0	1 (1.8%)
Hyperglycemia, Nonfasting	18	9	27	27	54
Grade 3 or 4	2 (11.1%)	1 (11.1%)	3 (11.1%)	0	3 (5.6%)
Grade 3	2 (11.1%)	1 (11.1%)	3 (11.1%)	0	3 (5.6%)
Grade 4	0	0	0	0	0
Urinalysis					
Glycosuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 3	1 (4.2%)	2 (16.7%)	3 (8.3%)	1 (2.8%)	4 (5.6%)
Grade 4	0	0	0	0	0
Proteinuria (Dipstick)	24	12	36	36	72
Grade 3 or 4	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 3	1 (4.2%)	1 (8.3%)	2 (5.6%)	0	2 (2.8%)
Grade 4	0	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; LEN = lenacapavir; N = number of participants; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017).
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time after baseline.
For Urinalysis (ie, urine glucose, urine protein, and urine RBC), the highest grade is up to Grade 3.
Source: GS-US-200-4625 Interim Week 52 CSR Addendum, Table 15.11.6.4.2.2

GS-US-200-4334

The majority of the participants had at least 1 graded laboratory abnormality (LEN total 94.9% [149 of 157 participants]; BVY 100.0% [25 of 25 participants]). The majority of the laboratory abnormalities were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 16.6% of participants (26 of 157) in the LEN total group and 24.0% of participants (6 of 25) in the BVY group. Grade 4 laboratory abnormalities were reported for 8.3% of participants (13 of 157) in the LEN total group only.

Since the Week 28 analysis, Grade 3 laboratory abnormalities were reported for an additional 9 participants (LEN total group: 6 participants; BVY group: 3 participants) and Grade 4 laboratory abnormalities were reported for an additional 6 participants in the LEN total group only. None of these laboratory abnormalities were considered clinically relevant by the investigator, as they were transient or unconfirmed, participants had a medical history of underlying conditions (eg, diabetes), or there

was an alternative explanation (eg, creatine kinase or aspartate aminotransferase [AST] elevation after strenuous activity).

Table 78 GS-US-200-4334: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities for ≥ 3 Participants in Any Treatment Group (Safety Analysis Set)

Maximum Postbaseline Toxicity Grade	SC LEN + (DVY → TAF) (N = 52)	SC LEN + (DVY → BIC) (N = 53)	Oral LEN + DVY (N = 52)	BVY (N = 25)	SC LEN Total (N = 105)	LEN Total (N = 157)
Participants With Postbaseline Value	52	53	52	25	105	157
Grade 3 or 4	11 (21.2%)	15 (28.3%)	13 (25.0%)	6 (24.0%)	26 (24.8%)	39 (24.8%)
Grade 3	6 (11.5%)	11 (20.8%)	9 (17.3%)	6 (24.0%)	17 (16.2%)	26 (16.6%)
Grade 4	5 (9.6%)	4 (7.5%)	4 (7.7%)	0	9 (8.6%)	13 (8.3%)
Hematology						
Absolute Neutrophil Count (ANC), Low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Grade 3	2 (3.8%)	0	0	0	2 (1.9%)	2 (1.3%)
Chemistry						
ALT (SGPT), High	52	53	52	25	105	157
Grade 3 or 4	0	2 (3.8%)	3 (5.8%)	0	2 (1.9%)	5 (3.2%)
Grade 3	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Grade 4	0	1 (1.9%)	2 (3.8%)	0	1 (1.0%)	3 (1.9%)
AST (SGOT), High	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	2 (3.8%)	3 (5.8%)	0	4 (3.8%)	7 (4.5%)
Grade 3	2 (3.8%)	1 (1.9%)	3 (5.8%)	0	3 (2.9%)	6 (3.8%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Hyperbilirubinemia	52	53	52	25	105	157
Grade 3 or 4	0	1 (1.9%)	1 (1.9%)	1 (4.0%)	1 (1.0%)	2 (1.3%)
Grade 3	0	0	0	1 (4.0%)	0	0
Grade 4	0	1 (1.9%)	1 (1.9%)	0	1 (1.0%)	2 (1.3%)
Creatine Kinase, High	52	53	52	25	105	157
Grade 3 or 4	6 (11.5%)	2 (3.8%)	3 (5.8%)	1 (4.0%)	8 (7.6%)	11 (7.0%)
Grade 3	2 (3.8%)	1 (1.9%)	2 (3.8%)	1 (4.0%)	3 (2.9%)	5 (3.2%)
Grade 4	4 (7.7%)	1 (1.9%)	1 (1.9%)	0	5 (4.8%)	6 (3.8%)
Creatinine, High	52	53	52	25	105	157
Grade 3 or 4	1 (1.9%)	4 (7.5%)	1 (1.9%)	2 (8.0%)	5 (4.8%)	6 (3.8%)
Grade 3	1 (1.9%)	3 (5.7%)	1 (1.9%)	2 (8.0%)	4 (3.8%)	5 (3.2%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Creatinine Clearance or eGFR, Low	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	7 (13.2%)	3 (5.8%)	3 (12.0%)	9 (8.6%)	12 (7.6%)
Grade 3	2 (3.8%)	6 (11.3%)	3 (5.8%)	3 (12.0%)	8 (7.6%)	11 (7.0%)
Grade 4	0	1 (1.9%)	0	0	1 (1.0%)	1 (0.6%)
Triglycerides (Fasting)	48	51	49	23	99	148
Grade 3 or 4	0	4 (7.8%)	0	1 (4.3%)	4 (4.0%)	4 (2.7%)
Grade 3	0	3 (5.9%)	0	1 (4.3%)	3 (3.0%)	3 (2.0%)
Grade 4	0	1 (2.0%)	0	0	1 (1.0%)	1 (0.7%)
Lipase, High	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	0	0	3 (2.9%)	3 (1.9%)
Grade 3	1 (1.9%)	1 (1.9%)	0	0	2 (1.9%)	2 (1.3%)
Grade 4	1 (1.9%)	0	0	0	1 (1.0%)	1 (0.6%)
Hyperglycemia, Nonfasting	45	43	39	18	88	127
Grade 3 or 4	2 (4.4%)	1 (2.3%)	0	1 (5.6%)	3 (3.4%)	3 (2.4%)
Grade 3	2 (4.4%)	0	0	1 (5.6%)	2 (2.3%)	2 (1.6%)
Grade 4	0	1 (2.3%)	0	0	1 (1.1%)	1 (0.8%)
Urinalysis						
Glycosuria (Dipstick)	52	53	52	25	105	157
Grade 3 or 4	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)
Grade 3	2 (3.8%)	1 (1.9%)	1 (1.9%)	1 (4.0%)	3 (2.9%)	4 (2.5%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIC, B = bictegravir; BVY = bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF; coformulated; Biktarvy); DVY = emtricitabine/tenofovir alafenamide (F/TAF; coformulated; Descovy); eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LEN = lenacapavir; N = number of participants; SC = subcutaneous; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TAF = tenofovir alafenamide
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017.
For summary over all laboratory tests, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from baseline at any time postbaseline up to and including the date of last exposure date.
The fourth generation LDL is derived from Friedewald formula: total cholesterol-HDL- triglyceride/5.
For Urinalysis (eg, urine glucose), the highest grade is up to Grade 3.
Source: GS-US-200-4334 Interim Week 54 CSR Addendum, Table 15.11.6.4.2

Integrated Summary of Safety

Grade 3 or 4 laboratory abnormalities that were reported in greater than 2% of participants in any treatment group included AST (increased), CPK (increased), creatinine (increased), creatinine clearance (decreased) (using Cockcroft-Gault)/estimated glomerular filtration rate (eGFR), total cholesterol (fasting, hypercholesterolemia), serum glucose (fasting, hypoglycemia), low-density lipoprotein (LDL; fasting, increased), triglycerides (fasting, increased), lipase (increased), and urine occult blood (dipstick).

The 3 participants with Grade 3 or 4 AST (increased) laboratory abnormalities (All LEN 1, placebo 2) all had isolated events that improved to Grade 0.

Among the 15 participants with Grade 3 or 4 CPK (increased) laboratory abnormalities, 9 had Grade 3 events (All LEN 6, placebo 3), and 6 had Grade 4 events (All LEN 4, placebo 2). These were mostly isolated events that improved to Grade 0 or 1 at a subsequent visit. One Grade 4 event occurred in a participant in the IV LEN group who also had an SAE of rhabdomyolysis.

Among the 7 participants with Grade 3 or 4 creatinine (increased) laboratory abnormalities, 4 had Grade 3 events (All LEN 2, placebo 2), and 3 had Grade 4 events (All LEN 2, placebo 1). Graded predose values were reported for 1 participant (SC LEN group) with a postdose Grade 3 event that improved to a Grade 2 and 2 participants (1 each in the All LEN and placebo groups) with postdose Grade 4 events that fluctuated with Grade 3 events. Among those who did not have graded predose creatinine (increased) (2 each in the All LEN and placebo groups), the events were isolated and improved to a Grade 2 or better at a subsequent visit for 3 participants; 1 participant who received placebo had a Grade 2 creatinine (increased) at 3 visits and a Grade 3 event at the last visit.

Among the 10 participants with Grade 3 or 4 creatinine clearance (decreased) (using Cockcroft-Gault)/eGFR laboratory abnormalities, 8 had Grade 3 events (All LEN 6, placebo 2), and 2 had Grade 4 events (All LEN 1, placebo 1). Graded predose values were reported for 6 participants (All LEN 5, placebo 1) with a postdose Grade 3 or 4 event. Among those who did not have graded predose creatinine clearance/eGFR, 1 participant who received LEN and 2 participants who received placebo had persistent postdose Grade 2 events at most visits.The Grade 3 or 4 total cholesterol (fasting, hypercholesterolemia) laboratory abnormalities were all Grade 3 events in 5 participants (All LEN 4, placebo 1), who all had graded predose values and had improved to a Grade 1 or 2 event at a subsequent visit.

The Grade 3 or 4 LDL (fasting, increased) laboratory abnormalities were all Grade 3 events in 18 participants (All LEN 15, placebo 3), who all had graded predose values. Most were isolated events that improved to Grade 2 or better at a subsequent visit. Three participants who received LEN and 1 participant who received placebo had multiple Grade 3 LDL (fasting, increased) events and a final assessment of Grade 3.

All 11 participants with Grade 3 or 4 triglycerides (fasting, increased) laboratory abnormalities had received LEN (9 Grade 3, 2 Grade 4), and all except for 1 of these participants had graded predose values. Isolated events occurred in 7 participants (6 Grade 3, 1 Grade 4) and improved to Grade 2 or better in subsequent visits. The other Grade 4 triglycerides (fasting, increased) event occurred at the last visit in a participant with normal predose values and 2 isolated Grade 2 triglycerides (fasting, increased). Three other participants had Grade 3 triglycerides (fasting, increased) at their last visits, which were preceded by Grade 1, 2, or 3 triglycerides (fasting, increased) events at all visits from predose onward.

The Grade 3 or 4 serum glucose (fasting, hypoglycemia) laboratory abnormalities were both isolated Grade 3 events in 2 participants who had received LEN and had improved to Grade 0 or 1 at a subsequent visit.

Among the 3 participants with Grade 3 or 4 lipase (increased) laboratory abnormalities, the values returned to normal for 1 participant who received placebo and had a Grade 3 event and 1 participant who received LEN and had a Grade 4 event. An additional participant who received placebo had 2 Grade 4 lipase (increased) events on Days 57 and 281. There were no AEs of pancreatitis.

Among the 15 participants with Grade 3 urine occult blood, all were female and the abnormalities reported were due to menses or considered not clinically significant by the investigator.

Table 79 Laboratory Abnormalities

Maximum Postbaseline Toxicity Grade	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Participants with Postbaseline Value	142	18	221	14	365	49
Any Grade 3 or Above	36 (25.4%)	3 (16.7%)	19 (8.6%)	3 (21.4%)	61 (16.7%)	15 (30.6%)
Grade 3	32 (22.5%)	2 (11.1%)	15 (6.8%)	3 (21.4%)	52 (14.2%)	12 (24.5%)
Grade 4	4 (2.8%)	1 (5.6%)	4 (1.8%)	0	9 (2.5%)	3 (6.1%)
Hematology						
Hemoglobin (Decreased)	142	18	221	14	365	49
Any Grade 3 or Above	1 (0.7%)	0	0	0	1 (0.3%)	0
Grade 3	1 (0.7%)	0	0	0	1 (0.3%)	0
Grade 4	0	0	0	0	0	0
Lymphocyte	142	18	221	14	365	49
Any Grade 3 or Above	2 (1.4%)	0	0	0	2 (0.5%)	0
Grade 3	2 (1.4%)	0	0	0	2 (0.5%)	0
Grade 4	0	0	0	0	0	0
Chemistry						
ALT (Increased)	142	18	221	14	365	49
Any Grade 3 or Above	1 (0.7%)	0	0	0	1 (0.3%)	0
Grade 3	1 (0.7%)	0	0	0	1 (0.3%)	0
Grade 4	0	0	0	0	0	0
Amylase (Increased)	112	18	180	0	310	49
Any Grade 3 or Above	0	0	0	0	0	1 (2.0%)
Grade 3	0	0	0	0	0	1 (2.0%)
Grade 4	0	0	0	0	0	0
AST (Increased)	142	18	221	14	365	49
Any Grade 3 or Above	1 (0.7%)	0	0	0	1 (0.3%)	2 (4.1%)
Grade 3	1 (0.7%)	0	0	0	1 (0.3%)	1 (2.0%)
Grade 4	0	0	0	0	0	1 (2.0%)
CPK (Increased)	142	18	221	14	365	49
Any Grade 3 or Above	5 (3.5%)	1 (5.6%)	3 (1.4%)	1 (7.1%)	10 (2.7%)	5 (10.2%)
Grade 3	4 (2.8%)	0	1 (0.5%)	1 (7.1%)	6 (1.6%)	3 (6.1%)
Grade 4	1 (0.7%)	1 (5.6%)	2 (0.9%)	0	4 (1.1%)	2 (4.1%)

Maximum Postbaseline Toxicity Grade	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Creatinine (Increased)	142	18	221	14	365	49
Any Grade 3 or Above	3 (2.1%)	0	1 (0.5%)	0	4 (1.1%)	3 (6.1%)
Grade 3	2 (1.4%)	0	0	0	2 (0.5%)	2 (4.1%)
Grade 4	1 (0.7%)	0	1 (0.5%)	0	2 (0.5%)	1 (2.0%)
Creatinine Clearance (using Cockcroft-Gault equation)/eGFR	62	18	211	14	275	29
Any Grade 3 or Above	3 (4.8%)	0	4 (1.9%)	0	7 (2.5%)	3 (10.3%)
Grade 3	2 (3.2%)	0	4 (1.9%)	0	6 (2.2%)	2 (6.9%)
Grade 4	1 (1.6%)	0	0	0	1 (0.4%)	1 (3.4%)
Total Cholesterol (Fasting, Hypercholesterolemia)	142	18	209	14	353	49
Any Grade 3 or Above	1 (0.7%)	0	2 (1.0%)	1 (7.1%)	4 (1.1%)	1 (2.0%)
Grade 3	1 (0.7%)	0	2 (1.0%)	1 (7.1%)	4 (1.1%)	1 (2.0%)
Grade 4	0	0	0	0	0	0
Serum Glucose (Fasting, Hypoglycemia)	142	18	209	14	353	49
Any Grade 3 or Above	1 (0.7%)	1 (5.6%)	0	0	2 (0.6%)	0
Grade 3	1 (0.7%)	1 (5.6%)	0	0	2 (0.6%)	0
Grade 4	0	0	0	0	0	0
LDL (Fasting, Increased)	142	18	209	14	353	49
Any Grade 3 or Above	8 (5.6%)	0	6 (2.9%)	1 (7.1%)	15 (4.2%)	3 (6.1%)
Grade 3	8 (5.6%)	0	6 (2.9%)	1 (7.1%)	15 (4.2%)	3 (6.1%)
Grade 4	0	0	0	0	0	0
Triglycerides (Fasting, Increased)	142	18	209	14	353	49
Any Grade 3 or Above	4 (2.8%)	1 (5.6%)	5 (2.4%)	1 (7.1%)	11 (3.1%)	0
Grade 3	2 (1.4%)	1 (5.6%)	5 (2.4%)	1 (7.1%)	9 (2.5%)	0
Grade 4	2 (1.4%)	0	0	0	2 (0.6%)	0
Lipase (Increased)	30	0	42	14	56	2
Any Grade 3 or Above	0	0	1 (2.4%)	0	1 (1.8%)	2 (100.0%)
Grade 3	0	0	0	0	0	1 (50.0%)
Grade 4	0	0	1 (2.4%)	0	1 (1.8%)	1 (50.0%)

Maximum Postbaseline Toxicity Grade	SC LEN (N = 142[a])	IV LEN (N = 18[b])	Oral LEN (N = 221[c])	SC + Oral LEN (N = 14[d])	All LEN (N = 365)	Placebo (N = 49)
Urinalysis						
Urine Occult Blood (Dipstick)	80	0	0	0	80	20
Any Grade 3 or Above	11 (13.8%)	0	0	0	11 (13.8%)	4 (20.0%)
Grade 3	11 (13.8%)	0	0	0	11 (13.8%)	4 (20.0%)
Grade 4	0	0	0	0	0	0
Urine Glucose (Glycosuria)	142	18	221	14	365	49
Any Grade 3 or Above	1 (0.7%)	0	1 (0.5%)	0	2 (0.5%)	0
Grade 3	1 (0.7%)	0	1 (0.5%)	0	2 (0.5%)	0
Grade 4	0	0	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; IV = intravenous; LDL = low-density lipoprotein; LEN = lenacapavir (GS-6207); SC = subcutaneous
Severity grades were defined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
For maximum postdose toxicity grade, the most severe graded abnormality from all tests was counted for each participant.
For each individual laboratory test, the most severe graded abnormality for that test was counted for a participant.
A treatment-emergent laboratory abnormality was defined as an increase of at least 1 toxicity grade from predose.

a. n = 32 from Study GS-US-200-4070, n = 80 from Study GS-US-200-4538, and n = 30 from Study GS-US-200-5709 (Cohort 1, SC period only)
b. n = 18 from Study GS-US-200-4329
c. n = 88 from Study GS-US-200-4071, n = 10 from Study GS-US-200-4330, n = 10 from Study GS-US-200-4331, n = 82 from Study GS-US-200-4333, and n = 31 from Study GS-US-200-5709 (Cohort 1, oral lead-in period only)
d. n = 14 from Study GS-US-200-5709 (Cohort 2 only)

Source: LEN Phase 1 ISS, Table 13338.14

Creatine kinase (CK)

Among the 15 participants with Grade 3 or 4 CPK (increased) laboratory abnormalities reported in the ISS, 9 had Grade 3 events (All LEN 6, placebo 3), and 6 had Grade 4 events (All LEN 4, placebo 2). These were mostly isolated events that improved to Grade 0 or 1 at a subsequent visit. One Grade 4 event occurred in a participant in the IV LEN group who also had an SAE of rhabdomyolysis.

In study Study GS-US-200-4625 no participants had Grade 3 or higher increase in creatine kinase (CK) or CK-associated AEs such as rhabdomyolysis during the study.

In study GS-US-200-4334, Grade 3 or higher laboratory abnormalities regarding CK were reported for 12 participants (11 lenacapavir (7 %), 1 comparator (4%)). However, Grade 3 or higher abnormalities of high CK were isolated and infrequent, improved on subsequent visits despite continued exposure to the study drug and were attributed to strenuous activity, dehydration, or use of creatine according to the investigators.

According to the applicant's investigation there appears to be no clear exposure-dependence.

Triglycerides

In the pooled analysis of Studies GS-US-200-4538 and GS-US-200-5709 in the original MAA, Grade 3 or above increased triglycerides (fasting) were reported for 5 of 55 participants (9.1%) (2 participants in Study GS-US-200-4538 and 3 participants in Study GS-US-200-5709 (ISS) in the LEN group and no participants in the placebo group. Also in the updated ISS imbalance was reported (11/353 (3.1 %) vs. 0/49 (0%). Imbalance was not observed in studies GS-US-200-4625 and GS-US-200-4334.

Follow-up of graded laboratory abnormalities that could not be considered transient as no follow-up data were available

In the original MAA, a total of 12 participants experienced 18 Grade 3 or 4 laboratory abnormalities at their latest visit in Studies GS-US-200-4625 at Week 26 (2 participants), GS-US-200-4334 at Week 28 (6 participants), and the GS-US-200-4538 and GS-US-200-5709 ISS (4 participants).

In Study GS-US-200-4625, additional data (Week 52 data cut) confirmed that 3 Grade 3 or 4 laboratory abnormalities in 2 participants improved at subsequent visits. One participant returned to Grade 1 at the latest visit date. The other participant continued to have a Grade 3 creatinine clearance at the latest visit which was likely related to prior and ongoing use of tenofovir disoproxil fumarate 300 mg.

In Study GS-US-200-4334, additional data (Week 54 data cut) confirmed that 8 Grade 3 or 4 laboratory abnormalities in 6 participants improved at subsequent visits.

One participant continued to have Grade 3 or 4 laboratory abnormalities at the last visit date and was likely related to their preexisting conditions or an intercurrent event. Four participants returned to Grade 2 at the latest visit date.

In the ISS (Studies GS-US-200-4538 and GS-US-200-5709), there were a total of 4 participants with 3 Grade 3 and 1 Grade 4 laboratory abnormalities at their last visit. In Study GS-US-200-4538, the last data points for the 3 participants were already included in the original submission, as this study had finished when it was included in the ISS. Throughout the study, the low-density lipoprotein and triglyceride levels had transient increases to Grade 3 with subsequent decreases to Grade 1, while study drug continued. One participant in Study GS-US-200-5709 had Grade 3 increased triglycerides at the data cut, which then returned to Grade 2 as the latest value.

In summary, the participants who had a Grade 3 or 4 laboratory abnormality at the latest time point in the original submission were reviewed with the available follow-up data and no safety concerns were identified. The majority of Grade 3 or 4 laboratory abnormalities were explained by underlying conditions and/or returned to Grade 2 or below while the participants remained on study drug.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

In the primary study that supports the safety (GS-US-200-4625) and in the supportive study (GS-US-200-4334) there were a total of 7 subjects aged 65 years and above of which 1 aged 75 years and above.

2.6.8.7. Immunological events

Hypersensitivity Reactions

During the functional monotherapy period of Study GS-US-200-4625, Grade 1 AEs of rhinitis allergic and rash were reported for 1 participant each (4.2%) in the LEN group. Neither AE was considered related to study drug.

Adverse events that occurred in more than 1 participant at Week 52 were rash (6.9%, 5 participants), rhinitis allergic (2.8%, 2 participants), and rash pruritic and rash papular (2.8%, 2 participants each).

No TEAEs of hypersensitivity were reported. Treatment-emergent adverse events considered related to study drug were rash macular and rash papular reported for 1 participant each (1.4%) and rash for 2 participants (2.8%), all of which resolved and did not recur with ongoing LEN exposure.

All TEAEs were Grade 1 or 2 in severity except for a Grade 3 AE of rash in 1 participant, reported as general maculopapular exanthema, itchy when touched, covering chest and back, occurring concurrently with Grade 2 AEs of pyrexia and influenza like illness. All events started on Day 11 and resolved with ongoing LEN exposure and after a switch from Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate [TDF]) to Truvada (emtricitabine/TDF) in the OBR. The investigator suspected that the allergic reaction occurred due to the OBR, in particular doravirine, and the participant proceeded to receive SC LEN on Day 15 with no recurrence of the rash.

None of the reported TEAEs led to discontinuation of study drug or the study.

Since the Week 26 Interim analysis, 1 additional participant experienced an unrelated Grade 1 AE of rash (reported term "rash on nose"). Study drug was continued.

In the LEN total group of Study GS-US-200-4334, AEs that occurred in more than 1 participant at Week 54 were hypersensitivity (3.2%, 5 participants), rhinitis allergic (2.5%, 4 participants), rash (2.5%, 4 participants), and rash macular (1.3%, 2 participants).

Since the Week 28 analysis, 2 additional participants experienced AEs of hypersensitivity (reported terms "allergy in body" and "allergy"), and 1 additional participant experienced the AE of rash (reported term "skin rash"). None of the additional rash or hypersensitivity AEs were considered related to study drug by the investigator, or led to discontinuation, and all AEs were Grade 1 and resolved during continued exposure to study drug.

Immune reconstitution syndrome

One participant (2.8%) in Study GS-US-200-4625 experienced a Grade 3 increase in ALT and a Grade 4 increase in AST, which were reported as an AE of immune reconstitution inflammatory syndrome considered as associated with an ongoing medical history of chronic hepatitis B.

2.6.8.8. Safety related to drug-drug interactions and other interactions

LEN is a substrate of cytochrome P450 enzyme 3A (CYP3A), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Strong inducers of CYP3A, P-gp, and UGT1A1, such as rifampin, may significantly decrease plasma concentrations of LEN. As such, rifampin is contraindicated with LEN. Moderate inducers of CYP3A and P-gp, such as efavirenz, may also significantly decrease plasma concentrations of LEN, and as such, are not recommended with LEN.

Strong CY3A4 inhibitors alone (e.g., voriconazole) or strong inhibitors of CYP3A4 and P-gp together (e.g., cobicistat) do not result in a clinically meaningful increase in LEN exposures. Strong inhibitors of CYP3A, P-gp and UGT1A1 together (i.e., all 3 pathways), such as atazanavir/cobicistat, may significantly increase plasma concentrations of LEN, and as such, are not recommended with LEN.

LEN is a moderate inhibitor of CYP3A. Caution is advised if LEN is co-administered with a sensitive CYP3A substrate with a narrow therapeutic index (e.g., midazolam). LEN is not a clinically meaningful inhibitor of P-gp and BCRP and does not inhibit OATP.

2.6.8.9. Discontinuation due to adverse events

Study GS-US-200-4625

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

Study GS-US-200-4334
Three of 105 participants (2.9%) in the SC LEN total group discontinued study drug due to AEs (injection site induration, injection site erythema, and injection site swelling). All were nonserious and Grade 1 in severity.

Since the Week 28 analysis, 1 participant in the SC LEN total group had experienced AEs of injection site erythema and injection site swelling that led to premature discontinuation of study drug after the week 52 LEN SC injection. Both occurrences were nonserious and Grade 1 in severity.

Integrated Summary of Safety

The only AE that led to the premature discontinuation of study drug was a Grade 1, nonserious, and non-study drug-related AE of SARS-CoV-2 test positive with onset on Day 9 and resolution on Day 32 in a participant in Cohort 1 in Study GS-US-200-5709.

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The safety profile of LEN has mainly been established from one phase 2/3 study (GS-US-200-4625), one phase 2 study (GS-US-200-4334) and an integrated summary of safety (ISS) presenting pooled analyses of 8 Phase 1 studies.

The primary study that supports the safety and efficacy of LEN is the Phase 2/3 study in HTE PWH (Study GS-US-200-4625). Of the 72 participants in Cohorts 1 and 2 who received oral LEN, 72 participants received SC LEN on Day 1 SC, 70 participants (Cohort 1: 36 participants, Cohort 2: 34 participants) received a second dose of SC LEN at Week 26, and 36 participants (Cohort 1: 34 participants, Cohort 2: 2 participants) received a third dose of SC LEN at Week 52. The median (first quartile [Q1], third quartile [Q3]) duration on study was 484 (411, 559) and 317 (267, 352) days for Cohorts 1 and 2, respectively.

The primary study is supported by a Phase 2 study of LEN in treatment-naive PWH (Study GS-US-200-4334). By Week 54, 89.2% of participants in the LEN total group (140 of 157 participants) and 96.0% of those in the BVY group (24 of 25 participants) had been exposed to study drug for at least 54 weeks.

In the Integrated Summary of Safety (ISS), a pooled analysis is presented from the 8 Phase 1 studies, in healthy participants who were dosed with lenacapavir (LEN) (n = 365) or placebo (n = 49), regardless of the route, dose, or formulation.

The safety database is at a size that could be acceptable for a novel product that may be able to address an unmet medical need. However, the limited number of patients and healthy subjects

somewhat hampers the isolation of the safety profile. Only common or very common adverse reactions are expected to be detected. Moreover, as LEN is a first-in-class medicinal product, there is no experience regarding the safety profile within this class.

The initially proposed posology (without an oral lead in phase) has not been investigated in the target population of MDR PWH and is mainly supported by a population PK data analysis. Based on this analysis, the regimen is considered acceptable since it led to Ctrough values that are well above the IQ4 and reached values above IQ4 earlier. During the oral lead-in phase of the studies, no subjects discontinued, which is reassuring. However, omission of the oral lead-in seems premature, especially considering the limited safety data available and the long-acting nature of Lenacapavir. A conservative approach of including the oral lead-in is preferred. If more experience is gained with the simplified dosing regimen this position may be reconsidered**.** The indication statement included in the SmPC of the LEN tablets should reflect their use in combination with LEN SC during oral lead-in. This approach is acknowledged by the applicant.

In certain patient populations higher exposures are observed. The MAH has agreed to follow long-term safety (considered missing information in the RMP), especially with regards to patients with moderate to severe renal and hepatic impairment, who experience higher exposure, in the PSURs. Additionally, in order to support the long-term safety profile in patients with higher exposure to LEN, the MAH plans to provide a safety-exposure analysis with the final clinical study reports from Studies GS-US-200-4625 and GS-US-200-4334 comparing the safety in participants with high exposures versus the safety in participants with lower exposures.

In study GS-US-200-4625 (MDR HIV), 37.5% versus 25% of patients reported a TEAE in the placebo-controlled phase. 3/24 (12.5%) of LEN patients reported nausea, versus 0/12 patients on placebo. Study drug-related injection site reactions (ISRs) occurred in 41 participants (56.9%) at Day 15, 29 participants (41.4%) at Week 26, and 15 participants (41.7%) at Week 52. Among all patients receiving a LEN injection, 28-38% of patients reported each of the items injection site swelling, erythema and pain.

There was one death from malignancy at day 90, in a patient previously treated for non-Hodgkin's lymphoma. This was likely not related to study therapy.

In Study GS-US-200-4334, study drug-related ISRs occurred in 39 participants (37.9%) at Day 15, 42 participants (44.2%) at Week 28, and 23 participants (25.6%) at Week 54, 31% of patients reported injection site erythema, 28 % swelling and 24% pain. None of the ISRs were considered as a SAE.

Nausea was reported in 15/105 (14.3%) of patients treated with SC LEN, compared to 1/25 (4%) of patients treated with biktarvy. Depression was reported in 7/105 (6,7%) patients on SC LEN versus 1/25 (4%) patients treated with biktarvy.

One participant experienced an AE of immune reconstitution inflammatory syndrome. The applicant provided a narrative regarding this AE and agreed to include immune reconstitution inflammatory syndrome in table 4.8 in SmPC.

Overall, the safety profile of LEN appears favourable. Injection site reactions including e.g. pain, erythema and swelling, were the most common AEs. Notably nausea, which was the only adverse drug reaction (ADR) proposed to be included in the product information (in addition to injection site reactions), was more frequently observed for LEN compared with in the comparator group receiving bictegravir / emtricitabine / tenofovir alafenamide.

Because of the numerically higher number of patients with depression, the applicant was asked to make a separate analysis of adverse events in the SOC of psychiatric disorders. The safety database is limited. However, the psychiatric disorder data do not indicate that lenacapavir treatment has impact

on the incidence of psychiatric disorders other than could be expected. As presented by the applicant high rates of psychiatric comorbidities have been reported in the literature comparable to the rates in studies GS-US-200-4625 and GS-US-200-4334. Routine pharmacovigilance is considered sufficiently.

In both Studies GS-US-200-4625 and GS-US-200-4334, there was a numerically lower percentage of participants with nausea, headache, or depression after the second or third LEN injection compared with the first injection. In Study GS-US-200-4625 the median duration (Q1, Q3) for nausea, headache, or depression was 95 (18, 329), 9 (2, 31) and 12 (12, 12) days. In Study GS-US-200-4334 the median duration (Q1, Q3) for nausea, headache, or depression was 11 (2, 22), 15 (1, 46), and 218 (17, 315) days.

Two participant receiving LEN developed rhabdomyolysis. The first subject had received a single dose of LEN 20 mg intravenously. The time of onset was 21 days after the C_{max} of LEN was reached (within 1 hour of dosing). Symptoms from muscles were however present already on day 7 possibly indicating rhabdomyolysis but CK was normal at day 8 and 15 indicating that these symptoms likely had another explanation. It is agreed with the applicant that this late debut appears unusual for a drug-induced rhabdomyolysis. However, there are no alternative obvious explanation.

The second participant receiving LEN developing rhabdomyolysis after the Study GS-US-200-4334 Week 54 data cut was a less than 30 years-old male in the daily oral LEN + emtricitabine/tenofovir alafenamide (coformulated; Descovy®) (DVY) group. He experienced a serious adverse event (SAE) of rhabdomyolysis at Day 586, which resulted in hospitalisation. Approximately 48 hours after beginning an exercise routine, the participant developed severe muscle pain and dark urine. The investigator considered that the event was due to exercise and not related to study drug. The participant continued with study drug.

The provided safety update does not support a causality between lenacapavir and rhabdomyolysis. It is agreed with the applicant not to include rhabdomyolysis in the RMP but to keep rhabdomyolysis under close monitoring and to present any relevant new safety information in LEN PSUR/PBRERs.

The applicant was requested to perform an analysis to investigate if there are any correlations of CK elevations and plasma concentrations of lenacapavir. There appears to be no clear exposure-dependence.

Grade 3 or above abnormalities regarding triglycerides were more frequent among LEN exposed subjects also in the updated ISS (11/353 (3.1%) vs. 0/49 (0%)). However, imbalance was not observed in Studies GS-US-200-4625 and GS-US-200-4334. Overall, currently it is acceptable to consider causality as unlikely according to the safety data base.

Participants who had a Grade 3 or 4 laboratory abnormality at the latest time point in the original submission were reviewed with the available follow-up data and no safety concerns were identified. The majority of Grade 3 or 4 laboratory abnormalities were explained by underlying conditions and/or returned to Grade 2 or below while the participants remained on study drug.

No clinically meaningful conclusions can be made based regarding safety in subgroups or special populations due to the low number of participants in each group. The number of participants aged 65 years and above were limited and precludes analysis of a potential age-related risk of adverse events.

Hypersensitivity reactions were sporadic and mostly reported as Grade 1 to 2. One Grade 3 AE of rash, reported as "exanthema", occurring concurrently with Grade 2 AEs of pyrexia and influenza like illness, all starting on Day 11 and resolving with ongoing LEN exposure and switch from Delstrigo (doravirine /lamivudine /tenofovir disoproxil fumarate [TDF]) to Truvada (emtricitabine/TDF) was observed.

Five participants discontinued study drug due to adverse events, all Grade 1.

MAH was requested to design a real-world Drug Utilisation Study (DUS). It is likely that a DUS could provide additional data. However, it is considered by the applicant that a DUS in this small patient population would not add significantly to the safety data for LEN. As such, the applicant proposes to monitor adherence, discontinuations, virologic failure, and resistance through the use of a targeted questionnaire to follow-up on cases in the post marketing setting. The applicant believes that the routine and additional pharmacovigilance activities already proposed in the LEN EU-risk management plan (RMP), supplemented with the use of targeted follow-up (including a questionnaire) will be sufficient to gather the information requested by the CHMP. This approach would align with that taken for the other recently approved products for the treatment of HTE PWH for which a DUS was not required. The proposed follow up is considered acceptable.

Finally, regarding the weight increase shown in the studies, in the All Lenacapavir Analysis for Study GS-US-200-4625, the overall median change in weight (Q1, Q3) at Week 52 was 2.2 (−1.6, 3.6) kg. In Study GS-US-200-4334, the overall median change (Q1, Q3) in weight at Week 54 was 2.6 (0.2, 6.8) kg, compared with 2.3 (−3.1, 7.3) kg in the Biktarvy arm. Therefore, it remains unclear whether Lenacapavir exerts a specific effect on body weight, beyond return to health effect. The ongoing PreP study where LEN is used as monotherapy in individuals/subjects without HIV, is anticipated to further inform on this. The applicant will monitor this issue within the routine pharmacovigilance activities.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The overall safety profile of LEN appears favourable although the limited safety database somewhat hampers the complete characterisation of the safety profile.

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. Pharmacovigilance plan

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

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
GS-US-200-4625 Ongoing	To evaluate the safety of LEN in combination with an OBR through 52 weeks of treatment in adults with MDR HIV-1 who are failing their current regimen.	Long-term safety information (missing information)	Submission of Final Clinical Study Report	30 September 2024
GS-US-200-4334 Ongoing	To evaluate the safety and tolerability of LEN-containing regimens through 80 weeks of treatment in treatment-naïve participants with HIV-1.	Long-term safety information (missing information)	Submission of Final Clinical Study Report	30 April 2024
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)

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
None	N/A	N/A
Important potential risk		
None	N/A	N/A
Missing information		
Long-term safety information	Routine risk communication: None Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	• GS-US-200-4625 – safety of LEN in HTE PWH with multidrug resistance • GS-US-200-4334 – safety of LEN in treatment-naïve PWH
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2 Other routine risk minimisation measures beyond the Product Information: Medicine's legal status: restricted medical prescription, whereby therapy should be initiated by a physician experienced in the management of HIV-1 infection Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities Antiretroviral Pregnancy Registry (APR)

2.7.4. Conclusion

The routine risk minimisation measures as proposed in version 1.0 of the RMP is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.

2.9.2. Labelling exemptions

N/A

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lenacapavir Gilead (lenacapavir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The presently sought therapeutic indication is:

Solution for injection:

Sunlenca injection, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV 1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (see sections 4.2 and 5.1).

Film-coated tablets:

Sunlenca tablet, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV 1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, for oral loading prior to administration of long-acting lenacapavir injection (see sections 4.2 and 5.1).

3.1.2. Available therapies and unmet medical need

Advances in combination antiretroviral (ARV) therapy (ART) for HIV-1 have led to durable suppression of viral replication, allowing for preservation and reconstitution of immunologic function and averting disease progression to AIDS, ultimately delivering a normal quality of life and life expectancy.

For most people with HIV-1, these are possible with a well-tolerated once daily therapy. While combination ART for the treatment of HIV-1 infection has largely reduced the morbidity and mortality previously associated with HIV 1 disease, a subset of patients continues to experience virologic and immunologic failure. There remains an unmet medical need for new therapies for individuals failing currently available therapies because of multidrug resistance (MDR).

Key agents for the management of MDR HIV include drugs with high barrier to resistance such as boosted protease inhibitors (primarily darunavir) and the 2nd generation integrase inhibitor dolutegravir. These are used in combination regiments including recycled nucleoside analogues (primarily tenofovir alafenamide or -disoproxil fumarate along with emtricitabine), as well as etravirine and in some cases enfuvirtide or maraviroc.

In the last few years, 2 novel treatments have been approved specifically for MDR HIV:

- Ibalizumab, a monoclonal humanised antibody that targets CD4 cell receptors to prevent HIV entry, for IV infusion every 2 weeks.
- Fostemsavir, an orally administered twice daily attachment inhibitor that selectively inhibits the interaction between HIV and cellular CD4 receptors, thereby preventing viral entry into the host cells.

3.1.3. Main clinical studies

The primary study providing information on the efficacy and safety of LEN is the ongoing Phase 2/3 study in HIV-1 infected patients with multidrug resistance (Study GS-US-200-4625). Interim data from week 26 and 52 has been submitted with this application.

The main efficacy was evaluated during a Functional Monotherapy Period of 14 days where participants were randomised to LEN + failing regimen (N=24) or placebo + failing regimen (N=12).

Thereafter all received LEN in combination with an optimised background regimen (n=36). In a second cohort participants all received LEN+OBR (n=36) from Day 1. The lenacapavir treatment consisted of an oral lead-in and maintenance SC planned for every 6 months.

Participants had to have HIV-1 RNA ≥ 400 copies/mL at screening and HIV resistance reports (at screening or historical) showing resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications.

The primary efficacy endpoint was proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period.

Supportive data is provided with the ongoing Study GS-US-200-4334. This is a randomised, open-label, active-controlled, multicentre study evaluating the safety and efficacy of LEN in combination with other ARV agents in treatment-naive PWH randomised in a 2:2:2:1 ratio to 1 of the 4 treatment groups: (SC LEN + [DVY → TAF]) (N = 52); (SC LEN + [DVY → BIC]) (N = 53); (Oral LEN + DVY) (N = 52); (BVY) (N = 25). Interim data on the proportion of participants with HIV-1 RNA < 50 copies/mL, the change from baseline in log10 HIV-1 RNA and in CD4 cell count through week 54 has been provided.

Study GS-US-200-4625 in MDR HIV patients is designed in accordance with relevant regulatory guidance (EMEA/CPMP/EWP/633/02 Rev. 3). Concerning Study GS-US-200-4334, the following passage from the same document is pertinent: "a new agent of a new class (with no known or suspected cross-resistance to other drug classes) randomised controlled double-blind studies in treatment naïve patients might suffice to support use in HIV-infected subjects regardless of prior treatment history and presence of RAMs relevant for agents of other classes."

Study GS-US-200-4334 is not large enough to support an indication covering patients who are presumed to reach durable virological suppression with presently approved agents. However, it is informative of the barrier to resistance of lenacapavir and is therefore of efficacy to the extent that it may be considered co-pivotal for this application.

3.2. Favourable effects

In patients with MDR HIV-1 a significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period compared than those receiving placebo (87.5% vs 16.7%; P < 0.0001).

Participants in the LEN group Cohort 1 were on a failing regimen and still had a comparable decline in HIV-1 RNA, -1.97 log10 copies/mL, compared to Cohort 2 (-1.90 log10 copies/mL) and the placebo group (-1.92 log10 copies/mL) who received OBR during the oral lead-in period of LEN.

The secondary endpoint was the proportion of participants with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment. Virologic suppression was sustained through Week 26 for 80.6% (29 of 36 participants) with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm. At Week 52 the percentages of participants with HIV-1 RNA < 50 and < 200 copies/mL using the US FDA-defined snapshot algorithm were 77.8% (35 of 45 participants) and 82.2% (37 of 45 participants).

In addition, in the total LEN group the mean decline in HIV-1 RNA was -2.53 log10 copies/mL (95% CI -2.81 to -2.24) at Week 26 and -2.50 (95% CI -2.85 to -2.14) at Week 52.

In Study GS-US-200-4334, the percentages of participants with HIV-1 RNA < 50 copies/mL at Week 28 using the US FDA-defined snapshot algorithm were 147/157 (93.6%) among lenacapavir treated patients, and 25/25 (100%) among patients randomised to the Biktarvy control. At week 54, 86.6% (136 of 157) of lenacapavir treated and 92% (23 of 25) in the Biktarvy control group had HIV-1 RNA < 50 copies/mL.

3.3. Uncertainties and limitations about favourable effects

The pivotal dataset in the MDR study is very small, and not balanced on all relevant baseline parameters. This includes the OSS of the failing background regimen which was higher in the lenacapavir arm. If study entry improves adherence to the background regimen, this might create some bias in the effect estimate favouring lenacapavir. However, based on previous experiences with the relevant study design, any such effect is anticipated to be minor, and do not impact the overall conclusions from the study.

The second part of the pivotal trial, after the primary endpoint and the optimisation of background therapy lacks a control arm, and therefore does not isolate drug effects. The contribution of lenacapavir to the overall durability of regimen response would need to be inferred based on the presumed activity of the baseline regimen in each case, given the selected agents and the pattern of drug resistance, but there would still remain uncertainties. In up to half of the cases, it appears that the background regimen alone might have been suppressive, if adhered to.

However, the results of Study GS-US-200-4334 are indicative that, while the intrinsic barrier to resistance of lenacapavir is not high, it is sufficient for the drug to successfully support tenofovir alafenamide and emtricitabine and provide durable response over 28 weeks. This inference is based on historical experience indicating that the suppression rates seen in this study, could not have been achieved with two nukes alone. Moreover, the response was maintained after transition at week 28 to a two-agent regimen with lenacapavir and either tenofovir alafenamide or bictegravir up to week 54.

The included population in the pivotal study supports an indication of multidrug resistant PWH for whom it is otherwise not possible to construct a suppressive antiviral regimen, in line with the proposed indication and which is currently available for recently approved medications for multidrug resistant PWH.

It remains unknown whether patients in a real-world setting will be sufficiently adherent to other part(s) of the ART, the visit schedule, and what fraction will at some point be lost to follow-up (either for a short period of time or longer). Such patients would be at great risk of virologic failure and subsequent resistance development. This should be clearly communicated to patients before they start treatment with this long-acting ARV, and reiterated at subsequent visits. This is not a theoretical risk, as already during study GS-US-200-4625 the applicant suggested that 3 participants developed LEN RAMs due to the fact that LEN was essentially a monotherapy in these patients.

3.4. Unfavourable effects

A total of 594 subjects received at least 1 dose of lenacapavir regardless of the route, dose, or formulation. 72 patients with multi-resistant HIV and 103 treatment naïve patients with HIV infection received SC lenacapavir, following an oral lead in. In the 8 Phase 1 studies (ISS), 69 participants were dosed with lenacapavir with comparable exposure as the intended treatment regimen, SC LEN injection 927 mg.

In study GS-US-200-4625 (MDR HIV), 37.5% versus 25% of patients reported a TEAE in the placebo-controlled phase. 3/24 (12.5%) of lenacapavir patients reported nausea, versus 0/12 patients on placebo. Among all patients receiving a lenacapavir injection, 28-38% of patients reported each of the items injection site swelling, erythema and pain. None of the ISRs were considered as a SAE.

There was one death from malignancy at day 90, in a patient previously treated for non-Hodgkin's lymphoma. This was likely not related to study therapy.

In study GS-US-200-4334, 31%, 28% and 24% of patients reported each of the injection site symptoms erythema, swelling and pain. None of the ISRs were considered as a SAE. Nausea was reported in 15/105 (14.3%) of patients treated with SC lenacapavir, compared to 1/25 (4%) of patients treated with biktarvy. Depression was reported in 7/105 (6.7%) patients on SC lenacapavir versus 1/25 (4%) patients treated with Biktarvy.

One participant experienced an AE of immune reconstitution inflammatory syndrome, which is generic to antiretroviral treatment resulting in restored immunity. The applicant agrees to inclusion of immune reconstitution inflammatory syndrome in table 4.8 in SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainty stems from the relatively limited size of the safety database.

The proposed posology (without an oral lead in phase) has not been investigated in the target population of MDR PWH and is mainly supported by a population PK data analysis. Based on this, the regimen is considered acceptable since it led to Ctrough values that are well above the IQ4 and reached values above IQ4 earlier. However, omission of the oral lead-in is considered premature, given the limited safety data available and the long-acting nature of Lenacapavir. A conservative approach of including the oral lead-in is preferred. If more experience is gained with the simplified dosing regimen this position may be reconsidered.

Two participants receiving lenacapavir developed conditions termed rhabdomyolysis.

The first participant receiving lenacapavir that developed rhabdomyolysis had received a single dose of lenacapavir 20 mg intravenously. The time of onset was 21 days after the Cmax of lenacapavir was reached (within 1 hour of dosing). Symptoms from muscles were however present already on day 7

possibly indicating rhabdomyolysis but CK was normal at day 8 and 15 indicating that these symptoms likely had another explanation. It is agreed with the applicant that this late debut appears unusual for a drug-induced rhabdomyolysis. However, there are no evident other explanations

Since the MAA submission, and after the Study GS-US-200-4334 Week 54 data cut, 1 additional AE of rhabdomyolysis was reported. A less than 30 years old male in the daily oral LEN + emtricitabine/tenofovir alafenamide group, experienced a serious adverse event (SAE) of rhabdomyolysis on study day 586, which resulted in hospitalisation. The episode resolved despite ongoing Lenacapavir exposure.

The investigator considered that the event was due to exercise and not related to study drug. The participant continued with study drug.

Overall, causality is not considered established based on provided data. The time to onset as well as prompt resolution under continued drug exposure does not support a causal link to Lenacapavir. However, this cannot be completely excluded. It is agreed with the applicant not to include rhabdomyolysis in the RMP but to keep rhabdomyolysis under close monitoring and to present any relevant new safety information in LEN PSUR/PBRERs.

In the light of the two cases of rhabdomyolysis it is noted that 15 participants with Grade 3 or 4 CPK (increased) laboratory abnormalities was reported in the ISS, 9 had Grade 3 events (All LEN 6, placebo 3), and 6 had Grade 4 events (All LEN 4, placebo 2). These were mostly isolated events that improved to Grade 0 or 1 at a subsequent visit. One Grade 4 event occurred in the participant in the IV LEN group who also had an SAE of rhabdomyolysis.

In study GS-US-200-4625 no participants had Grade 3 or higher increase in creatine kinase (CK) or CK-associated AEs such as rhabdomyolysis during the study.

In study GS-US-200-4334, Grade 3 or higher laboratory abnormalities regarding CK were reported for 12 participants (11 lenacapavir (7 %), 1 comparator BYV (4%)).

Grade 3 or above abnormalities regarding triglycerides were more frequent among LEN exposed subjects 3.1% (11/353) than among subjects receiving placebo 0 % (0/49) in the ISS. Imbalance was not observed in studies GS-US-200-4625 and GS-US-200-4334. Overall causality is not considered as established.

No clinically meaningful conclusions can be made based regarding safety in subgroups or special populations due to the low number of participants in each group. The number of participants aged 65 years and above were limited and precludes analysis of a potential age-related risk of adverse events.

The MAH is has agreed to follow long-term safety (considered missing information in the RMP), especially with regards to patients with moderate to severe renal and hepatic impairment, who experience higher exposure, in the PSURs. Additionally, in order to support the long-term safety profile in patients with higher exposure to LEN, the MAH plans to provide a safety-exposure analysis with the final clinical study reports from Studies GS-US-200-4625 and GS-US-200-4334 comparing the safety in participants with high exposures versus the safety in participants with lower exposures.

3.6. Effects Table

Table 80 Effects Table for Lenacapavir

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HIV-1 RNA reduction	Proportion ≥0.5 log10 copies/mL decline from baseline at Day 14 in HTE MDR PWH	% (n)	87.5 (21/24)	16.7 (2/12)	Demonstrates clinically relevant statistically significant antiviral efficacy.	
HIV-1 RNA reduction	Proportion below 50 copies/mL at Week 26 in HTE MDR PWH	% (n)	78.6% (33/42))	-	Sustained virological control in majority of LEN treated participants. However, this metric does not isolate drug effects in the absence of a control arm	
HIV-1 RNA reduction	Proportion below 50 copies/mL at Week 52 in HTE MDR PWH	% (n)	77.8% (35/45)	-	Sustained virological control in majority of LEN treated participants. However, this metric does not isolate drug effects in the absence of a control arm	
Unfavourable Effects						
ISR	Incidence of injection site induration	%	72.7 [1]	30 [1]	Several ISRs are common	
	Incidence of injection site pain	%	56.4 [1]	25 [1]		
	Incidence of injection site erythema	%	47.3 [1]	0 [1]		
	Incidence of injection site bruising	%	12.7 [1]	40 [1]		
	Incidence of injection site swelling	%	23.6 [1]	10 [1]		
	Incidence of injection site nodule	%	18.2 [1]	0 [1]		
	Incidence of injection site pruritus	%	5.5 [1]	0 [1]		
Nausea	Incidence of nausea	%	12.5 [2]	0 [2]		
Depression	Incidence of depression	%	5.7 [3]	0 [3]		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hypertriglyceridemia	Incidence of hypertriglyceridemia	%	9 (1)	0 (1)		
IRIS	Incidence of IRIS	N	1 (2)	-		
Rhabdomyolysis	Incidence of rhabdomyolysis	N	1 (4)	-		

Abbreviations: HTE= heavily treatment experienced; IRIS= Immune reconstitution inflammatory syndrome; MDR=multi-drug resistant; PWH= people with HIV

Notes:(1) GS-US-200-4538 and GS-US-200-5709 (placebo-controlled); (2) GS-US-200-4625; (3) GS-US-200-4334; (4) GS-US-200-4329

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patients with multidrug resistant HIV-1, it is not always possible to construct an antiretroviral regimen that will be fully suppressive. Therefore, there is a high risk of disease progression and death in these patients. This indicates that there is unmet medical need for novel treatment options for these patients. LEN could potentially address (some of) this unmet medical need, as it has a novel mechanism of action compared to currently available ARVs. Virological data do not indicate any cross resistance with available classes. Dose-ranging monotherapy data in treatment naïve subjects show a drug with antiviral potency in a similar range as the integrase inhibitors.

Study GS-US-200-4334, a traditionally designed phase II study in treatment naïve subjects show that lenacapavir can yield sustained virological suppression as backbone for two nukes. Non-clinical data, however, indicate that the barrier to resistance is relatively low, with high level treatment emergent resistance emerging in case of treatment failure. Adherence to the oral components will be crucial to avoid lenacapavir monotherapy and loss of this treatment option due to resistance.

Efficacy in the target population with MDR HIV may be inferred in two different ways. First, through the fact that cross-resistance with available agents is unlikely, and that the results of GS-US-200-4334 indicate that lenacapavir contributes to the activity and durability of response of a conventionally designed treatment regimens; as well as through the activity shown in the first phase of the GS-US-200-4625 in MDR HIV patients. In the second phase of this study, all patients received an optimised background regimen and lenacapavir. Therefore, data are descriptive and do not conclusively isolate drug effects.

The safety profile appears favourable and appropriate for the proposed use. The safety database is of a size and duration that could be acceptable for a novel product that may be able to address an unmet medical need. However, it remains relatively limited.

The proposed indication is acceptable and the wording in Section 4.2 of the SmPC highlighting the importance of adherence as proposed by the applicant is satisfactory. Based on precedent decisions for long acting injectable antiretrovirals a warning is included in 4.4 regarding the risk of resistance following discontinuation of LEN treatment.

The level of evidence is currently not considered sufficient to remove the oral lead-in phase from the posology, and a conservative approach of including the oral lead-in is preferred. If more experience is gained with the simplified dosing regimen this position may be reconsidered.

3.7.2. Balance of benefits and risks

The B/R balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Sunlenca is positive

4. Recommendations

Outcome

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

Solution for injection:

Sunlenca injection, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug- resistant HIV 1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen (see sections 4.2 and 5.1).

Film-coated tablets:

Sunlenca tablet, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug- resistant HIV 1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen, for oral loading prior to administration of long-acting lenacapavir injection (see sections 4.2 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product

within 6 months following authorisation.

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

- **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.
-

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Lenacapavir is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.