CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215973Orig1s000
215974Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215973
Applicant Name	Gilead
Drug Product Name	Lenacapavir injection
Dosage Form.	Injection
Proposed Strength(s)	463.5 mg/ 1.5 ml (309 mg/ml)
Route of Administration	Subcutaneous
Maximum Daily Dose	927 mg SC injection, together with 600 mg loading oral dose using tablets (NDA 215974)
Rx/OTC Dispensed	Rx
Proposed Indication	Lenacapavir is a selective inhibitor of HIV-1 capsid function indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Drug Product Description	Lenacapavir Injection is a sterile, preservative-free solution for subcutaneous administration, packaged in a glass vial with (b) (4) mL (overfill of (b) (4) mL) to allow withdrawal of 1.5 mL.
Co-packaged product information	Vial kit includes two vials of Lenacapavir injection, two vial access devices, two disposable syringes and two injection safety needles
Device information:	Vial access device: (b) (4) Disposable syringe: (b) (4) Injection safety needle: 22G ½ inch (b) (4)
Storage Temperature/ Conditions	20° - 25°C (68° - 77°F)

	Discipline	Primary	Secondary
Review Team	*Drug Substance*	Karina Zuck	Paresma Patel
	Drug Product/ Labeling	Shalini Anand	Peter Guerrieri
	Manufacturing	David Acevedo	Steve Rhieu
	Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
	Microbiology	Sallie Crenshaw	Erika Pfeiler
	RBPM	Erica Keafer	
	ATL	Pete Guerrieri	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C - 25 °C (68°F - 77°F)

b. Additional Comments for Action

Post Market Commitments (PMCs)

4351-4 Complete the vial compatibility study (i.e., [redacted] (b) (4)) for the remaining time points of the registration stability batches and three production batches and submit the report as a CBE-0 supplement.

The timetable you submitted on December 14, 2022, states that you will conduct this study according to the following schedule:

Interim Report: 03/30/2023
Interim Report: 03/30/2024
Final Report Submission: 11/30/2024

[redacted]

4351-5 Evaluate the upcoming stability time points of the registration batches and first three production batches (at release and over stability studies) of lenacapavir injection using the proposed instructions for use (IFU) for (b) (4) particulates in both visible and subvisible size ranges (i.e., 10 µm to 25 µm; 25 µm to 50 µm; 50 µm to 100 µm; 100 µm to 150 µm and >150 µm). Submit the optical microscopy and SEM-EDX analysis data for the vials stored in both inverted and upright orientations. Report any trend or increase in particulates with vial orientation, time etc. and provide explanation including details of any investigation into the source of the increase. Also, submit optical microscopy and SEM-EDX data from multiple batches (e.g., three batches) of the control vials (filled with polyethylene glycol and water mixture) prepared using both vial decrimping and proposed instructions for use (IFU) procedures. Submit the interim and final study reports as CBE-0 supplements.

The timetable you submitted on December 9, 2022, states that you will conduct this study according to the following schedule:

Interim Report: 03/30/2023
Interim Report: 03/30/2024
Final Report Submission: 11/30/2024

4351-6 Evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, which consistently reduces the presence of (b) (4) particulates in the drug product solution (b) (4) per 12 vials as measured by optical microscopy, (b) (4)

Provide supporting data (e.g., optical microscopy, SEM-EDX, USP <788> sub-visible particulates data etc.) from multiple drug product batches (e.g., three batches) tested at release and multiple time points over stability studies (long-term and accelerated storage conditions) under both upright and inverted orientation to support the alternative device/procedure.

The timetable you submitted on December 9, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/30/2023

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Lenacapavir sodium is a new molecular entity. It is an inhibitor of HIV-1 capsid function and is proposed for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Lenacapavir (LEN) Injection, 309 mg/mL is a sterile, preservative-free, yellow solution for subcutaneous administration. The formulation composition is of (b) (4)% active ingredient (b) (4)% water and (b) (4) polyethylene glycol (PEG) 300. The pH of the proposed drug product is around 10, and the dug product manufacturing process involves (b) (4) .

The proposed dosing regimen of LEN includes (Option 1) an initial dose of 927 mg of LEN by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 LEN tablets, NDA 215974 drug product) on Day 1; 600 mg orally (2 LEN tablets) on Day 2, followed by a maintenance doses of 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months; or (Option 2) starting dose of 600 mg orally on Days 1 and 2, 300 mg orally on Day 8, and 927 mg by subcutaneous injection (2×1.5 mL injections) on Day 15 followed by 927 mg by subcutaneous maintenance doses and every 6 months. After administration the drug (b) (4) release lenacapavir to the circulatory system over time. This application was submitted simultaneously with NDA 215974, the submission for a tablet formulation of lenacapavir proposed for initial loading doses, both originally and in this resubmission.

This is the second CMC review of this NDA. Refer to review #1 for additional details. In the original submission, Gilead proposed borosilicate and aluminosilicate glass vials for the packaging of lenacapavir injection. However, the proposed drug product formulation was found incompatible with borosilicate glass vials, leading to the generation of glass lamellae. Due to the lack of sufficient data to support the compatibility of lenacapavir injection with aluminosilicate vials, a Complete Response was issued.

The delamination is suspected to occur (b) (4) of the formulation (b) (4). Significant pitting was observed with the originally proposed borosilicate vials, (b) (4). SEM and optical microscopy images were submitted late in the previous review cycle to support the use of the aluminosilicate vials; however, unexplained particles were observed and

the data was not sufficient to mitigate concerns for the potential interaction of the formulation with the vials.

In addition, the stability data submitted in the first review cycle for the aluminosilicate vials only included nine months long-term (and six months accelerate) results, which did not allow final assessment of the proposed drug product expiry period.

In the re-submission, Gilead submitted the vial compatibility data (optical microscopy, SEM and ICP-MS) data for three registration batches stored in aluminosilicate glass vials for up to 18 months under long term storage conditions (30ºC/75% RH). The data do not show any evidence of glass incompatibility of lenacapavir formulation with the proposed aluminosilicate glass vials. In addition, the FDA OTR lab analysis (report no- FY22-114-OTR-DPQR-T) of registration and clinical batches also demonstrated the compatibility of proposed vials with lenacapavir injection. The proposed analytical methods were also found acceptable. The additional data from registration stability batches and three production batches will be reviewed as it will be submitted post-approval as CBE-0 supplements to further confirm the suitability of the proposed vials with the lenacapavir injection solution.

During the review, (b) (4) . The safety risk of these subvisible/visible (b) (4) particulates was discussed with the OND Clinical and Pharm Tox review team as well as OND leadership, and found to be acceptable based on nonclinical and clinical studies and the overall risk-benefit profile of the product for the particular indication of heavily treatment experienced patients with multi-drug resistance. However, a PMC was requested and agreed by the applicant to evaluate an alternative device/procedure for withdrawal of the vial contents to reduce the generation of (b) (4) particulates. Two additional PMCs have been agreed with the applicant for post-approval submission of additional vial compatibility data and (b) (4) particulates data on additional registration stability time points and future production batches.

Based upon the 18-month long term storage data, Gilead proposed the shelf life of 24-months for the drug product. The proposed shelf life is acceptable. The proposed storage condition for drug product is “Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), protect from light.” The photostability data demonstrates that the secondary

packaging ([redacted] (b) (4) tray with paperboard carton) protects LEN injection from photodegradation. The supporting in-use stability data confirm the stability of lenacapavir injection during the proposed in-use period in the clear glass vials and syringe is provided in the NDA. The proposed drug product label also includes a statement in section 16, i.e. 'keep the vials in the original carton until just prior to preparation of the injections, in order to protect from light'.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments:

N/A

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 12/19/2022 03:49:09PM
GUID: 54eb8ba100062ea99cbaab7c64143df3

RECOMMENDATION

☐ Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215973
Assessment #2

Drug Product Name	Lenacapavir Injection
Dosage Form	Injection
Strength	463.5 mg/ 1.5 ml (309 mg/ml)
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Gilead

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD SN 0036	06/27/2022	All
eCTD SN 0038	07/20/2022	Quality
eCTD SN 0039	08/23/2022	Quality
eCTD SN 0040	08/25/2022	Labeling
eCTD SN 0041	09/02/2022	Quality
eCTD SN 0042	09/06/2022	Quality
eCTD SN 0047	09/30/2022	Quality
eCTD SN 0048	10/07/2022	Quality
eCTD SN 0049	10/21/2022	Quality
eCTD SN 0055	11/03/2022	Quality
eCTD SN 0058	11/15/2022	All
eCTD SN 0060	11/22/2022	Quality
eCTD SN 0061	11/30/2022	Quality
eCTD SN 0062	12/01/2022	All
eCTD SN 0066	12/09/2022	Quality
eCTD SN 0069	12/14/2022	Quality/Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Paresma Patel
Drug Product	Shalini Anand	Peter Guerrieri
Manufacturing	David Acevedo	Steve Rhieu

Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Microbiology	Sallie Crenshaw	Erika Pfeiler
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Pete Guerrieri	
Laboratory (OTR)	Charudharshini Srinivasan	Muhammad Ashraf
Environmental	N/A	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 215973 is recommended for approval from the product quality perspective, with three post marketing commitments to provide additional (b) (4) compatibility testing data, (b) (4) particulates testing data and evaluation of an alternate device/procedure to reduce the presence of (b) (4) particulates when following the labeling instructions for use (IFU).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Lenacapavir sodium is a new molecular entity. It is an inhibitor of HIV-1 capsid function and is proposed for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Lenacapavir (LEN) Injection, 309 mg/mL is a sterile, preservative-free, yellow solution for subcutaneous administration. The formulation composition is of (b) (4) active ingredient (b) (4) water and (b) (4) polyethylene glycol (PEG) 300. The pH of the proposed drug product is around 10, and the dug product manufacturing process involves (b) (4).

The proposed dosing regimen of LEN includes (Option 1) an initial dose of 927 mg of LEN by subcutaneous injection (2×1.5 mL injections) and 600 mg orally (2 LEN tablets, NDA 215974 drug product) on Day 1; 600 mg orally (2 LEN tablets) on Day 2, followed by a maintenance doses of 927 mg by subcutaneous injection (2×1.5 mL injections) every 6 months; or (Option 2) starting dose of 600 mg orally on Days 1 and 2, 300 mg orally on Day 8, and 927 mg by subcutaneous injection (2×1.5 mL injections) on Day 15 followed by 927 mg by subcutaneous maintenance

doses and every 6 months. After administration the drug (b) (4) release lenacapavir to the circulatory system over time. This application was submitted simultaneously with NDA 215974, the submission for a tablet formulation of lenacapavir proposed for initial loading doses, both originally and in this resubmission.

This is the second CMC review of this NDA. Refer to assessment #1 (01/12/2022) for additional details. In the original submission, Gilead proposed (b) (4) aluminosilicate glass vials for the packaging of lenacapavir injection. (b) (4) Due to the lack of sufficient data to support the compatibility of lenacapavir injection with aluminosilicate vials, a Complete Response was issued.

The delamination is suspected to occur as a result (b) (4) of the formulation . Significant pitting was observed with the originally proposed borosilicate vials, (b) (4). SEM and optical microscopy images were submitted late in the previous review cycle to support the use of the aluminosilicate vials; however, unexplained particles were observed and the data was not sufficient to mitigate concerns for the potential interaction of the formulation with the vials.

In addition, the stability data submitted in the first review cycle for the aluminosilicate vials only included nine months long-term (and six months accelerate) results, which did not allow final assessment of the proposed drug product expiry period.

Deficiency included in Complete Response for vial incompatibility:

Your data demonstrate that the drug product solution is incompatible with the proposed commercial borosilicate glass vials. The data provided in support of the compatibility of the alternative aluminosilicate glass vials are incomplete and ambiguous. As evidenced by your data and glass particles found in the clinical batches, glass containers are generally incompatible (b) (4) (b) (4) *. In order to resolve this deficiency, we require a comprehensive study report with unambiguous data and fully validated methods to demonstrate the compatibility of the drug product solution with your proposed primary container closure system.*

In the re-submission, Gilead submitted the vial compatibility data (optical microscopy, SEM and ICP-MS) data for three registration batches stored in aluminosilicate glass vials for up to 18 months under long term storage conditions (30ºC/75% RH). The data do not show any evidence of glass incompatibility of lenacapavir formulation with the proposed aluminosilicate glass vials. In addition, the FDA OTR lab analysis (report no- FY22-114-OTR-DPQR-T) of registration and clinical batches also demonstrated the

compatibility of proposed vials with lenacapavir injection. The proposed analytical methods were also found acceptable. The additional data from registration stability batches and three production batches will be reviewed as it will be submitted post-approval as CBE-0 supplements to further confirm the suitability of the proposed vials with the lenacapavir injection solution.

During the review, [redacted] (b) (4) The safety risk of these [redacted] (b) (4) particulates was discussed with the OND Clinical and Pharm Tox review team as well as OND leadership, and found to be acceptable based on nonclinical and clinical studies and the overall risk-benefit profile of the product for the particular indication of heavily treatment experienced patients with multi-drug resistance. However, a PMC was requested and agreed by the applicant to evaluate an alternative device/procedure for withdrawal of the vial contents [redacted] (b) (4). Two additional PMCs have been agreed with the applicant for post-approval submission of additional vial compatibility data and [redacted] (b) (4) particulates data on additional registration stability time points and future production batches.

Based upon the 18-month long term storage data, Gilead proposed the shelf life of 24-months for the drug product. The proposed shelf life is acceptable. The proposed storage condition for drug product is "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), protect from light." The photostability data demonstrates that the secondary packaging ([redacted] (b) (4) tray with paperboard carton) protects LEN injection from photodegradation. The supporting in-use stability data confirm the stability of lenacapavir injection during the proposed in-use period in the clear glass vials and syringe is provided in the NDA. The proposed drug product label also includes a statement in section 16 i.e. '*keep the vials in the original carton until just prior to preparation of the injections, in order to protect from light*'.

Proposed Indication(s) including Intended Patient Population	Lenacapavir is a selective inhibitor of HIV-1 capsid function indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Duration of Treatment	Chronic

Maximum Daily Dose	927 mg SC injection, together with 600 mg loading oral dose using tablets (NDA 215974)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance review was adequate in the previous review cycle (see review #1), and no new drug substance information was provided in the resubmission. The NDA is recommended for approval from the drug substance perspective.

Drug Product: Adequate

Lenacapavir Injection is a sterile, preservative-free, for subcutaneous administration. Marketing of a single strength is proposed 463.5 mg/ 1.5 ml (309 mg/ml) in a glass vial. The dosage strength is based on the lenacapavir free acid. Each vial contains a nominal 1.5 ml clear, yellow (b) (4) solution consisting of 473.1 mg of lenacapavir sodium, 896.3 mg polyethylene glycol 300 and (b) (4) water for injection. Each vial contains sufficient volume ((b) (4) mL with (b) (4) mL overfill) to allow withdrawal of 1.5 mL.

Drug product kit: The proposed container closure system for the drug product consists of a single-dose, clear glass vial. Each vial is sealed with an elastomeric closure and aluminum overseal with flip off cap. The drug product is supplied as a co-packaged kit which includes all the components needed for healthcare professionals to administer the injection i.e., two lenacapavir filled vials, two vial access devices, two disposable syringes, and two injection safety needles.

Devices

All components (devices) of the proposed kit are 510(k) cleared; therefore, the CDRH determined that no additional review is needed. Gilead had previously submitted the device validation studies in section 3.2.R, thus DMEPA team was also consulted during the first review cycle and determined that a HF study and results were not required for NDA submission. There is no change in the device design since that determination (2/2021), thus no additional review was need from DMEPA team and their review will be limited to the labeling. Refer the drug product review #1 and 2 for additional details.

Specifications

In the current review cycle, Gilead updated drug product specifications to include controls for [redacted] apparent pH and tighten the acceptance criterion for the appearance test. The pH measurement is reported to be distorted [redacted] The applicant originally did not include a pH specification as a result. However, USP <791> allows the usage of term 'apparent' for pH values of partially aqueous solutions, which applies to the lenacapavir injection. Therefore, the specification for "apparent pH" was requested, and the applicant complied, adding a test and acceptance limits of [redacted] based on batch history.

Compatibility of drug product solution with container closure components

The available optical microscopy, SEM and elemental analysis data from registration and clinical batches indicate that the proposed aluminosilicate glass vials are compatible with lenacapavir injection up to 18-months under long term storage conditions. The OTR lab analysis and inspection by the FDA team of the Gilead La Verne site also support the vial compatibility.

The proposed vial compatibility test methods were found acceptable, however as Gilead made significant updates to the proposed test methods during current review cycle, and limited data is available as per the revised procedures, Gilead was requested to provide the vial compatibility data for upcoming stability time points for three registration batches and first three production batches as CBE-0 supplement/s, per an agreed PMC. [redacted]. Gilead agreed to the above requests and included agreement in Section 3.2.P.8.2.

During the course of the resubmission review, [redacted] particulates were reported in the filtrate of samples used to evaluate for glass compatibility. However, these were determined to be generated as a result of the sample preparation, [redacted] Therefore, [redacted] particles should not be present at any point in the product nor pose any patient safety concerns.

During the review, for the studies evaluating the compatibility of the product with the glass vials, [redacted]

(b) (4)

No visible particulates were observed in 21-month long-term stability samples of the registration batches when following the IFU. In addition, no (b) (4) particles due to storage of LEN injection vials in the inverted orientation was observed, and no apparent relationship between storage time was observe in data from two (5.5 month, 21 month) stability time points, which indicate that (b) (4) does not appear to be occurring. Since data are limited, additional stability data was agreed by Gilead per PMC to be provided post-approval.

(b) (4) These considerations were discussed with the OND review team, including Clinical and Pharm Tox functions as well as OND leadership.

In addition to the above, the discussions highlighted the following relevant factors for consideration:

1) Nonclinical studies were performed using container closures using borosilicate vials with a (b) (4) and demonstrated injection site reactions (chronic granulomatous inflammations) for dose groups but not vehicle control groups in the same (b) (4). This suggests that (b) (4) particulates are not responsible for the ISRs in animal studies, although it does not rule out that glass lamellae could have contributed. To note, the studies used a needle to withdraw the vial contents.

2) Phase 1 clinical studies, although some were conducted with a different formulation/pH and not all subjects were followed to resolution, were all performed with a (b) (4) with a (b) (4) and demonstrated a decreased frequency and duration of injection site nodules and induration in

patients who received placebo versus in patients who received lenacapavir. This again suggests that (b) (4) particulates may not be responsible for the ISRs. Likewise, if (b) (4) is responsible for the glass delamination observed in borosilicate vials, the ISRs may not be related to glass lamellae but rather drug depot formation or other characteristics of the formulation.

3) Although evidence of foreign body reaction were obtained in available biopsy results, the above studies indicate that the subcutaneous depot of the drug may be responsible.

4) The intended population for the product is treatment of HIV-1 infection in heavily treatment experienced patients with multi-drug resistance, for which the product has breakthrough designation.

Based on the above considerations, (b) (4) does not represent unacceptable risk to patients. Therefore, a PMC was requested and agreed by Gilead to evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, (b) (4)

Labeling

(b) (4) inspection of the syringe during administration was included in the following statement in the dosage and administration section (section 2.3) of the USPI and instructions for use (IFU) i.e., "visually inspect the solution in the vials and prepared syringe for particulate matter and discoloration prior to administration... Do not use SUNLENCA injection if the solution is discolored or if it contains particulate matter." Gilead submitted the revised labelling documents with suggested text on 12-08-2022.

Post-Marketing Commitments

PMC #1

Submit the vial compatibility data (i.e., (b) (4)) for the remaining stability time points of the three registration batches and first three production batches of lenacapavir injection.

PMC #2

Evaluate the upcoming stability time points of the registration batches and first three production batches (at release and over stability studies) of

lenacapavir injection using the proposed instructions for use (IFU) for (b) (4) particulates in both visible and sub-visible size range. Submit the optical microscopy and SEM-EDX analysis data for the vials stored in both inverted and upright orientations. Report any trend for increase in particulates with vial orientation, time etc. and provide explanation including details of any investigation into the source of the increase. Also, submit optical microscopy and SEM-EDX data from multiple batches (e.g., 3 batches) of the control vials (filled with polyethylene glycol and water) prepared using vial decrimping and proposed instructions for use. Submit the interim and final study reports as CBE-0 supplements.

PMC #3

Evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, which consistently reduces the presence of (b) (4) particulates in the drug product solution (b) (4) per 12 vials as measured by optical microscopy, (b) (4) Provide supporting data (e.g., optical microscopy, SEM-EDX, USP <788> sub-visible particulates data etc.) from multiple drug product batches (e.g., three batches) tested at release and multiple time points over stability studies (long-term and accelerated storage conditions) under both upright and inverted orientation to support the alternative device/procedure.

Labeling: Adequate

Recommendations have been conveyed to OND for consideration during labeling revisions. For additional details, see Dr. Shalini Anand's Labeling Review, below.

Manufacturing: Adequate

Two testing facilities were added in the resubmission. Gilead Sciences Inc (FEI: 3013189568) is proposed as stability tester facility (physical – glass lamellae and glass corrosion) of Lenacapavir injection drug product. A pre-approval inspection was performed on 9/12 – 9/16/2022 and a one-item form FDA 483 was issued. The recommendation from the pre-approval inspection was to approve the site to support NDA 215973. Based on the pre-approval inspection recommendation, the facility is found acceptable to perform the proposed responsibilities. (b) (4) is proposed as release and stability tester (chemical – (b) (4)) of the drug product. The firm has

significant experience with chemical testing responsibilities of similar drug product and adequate compliance history. Hence, the firm is found acceptable to perform the proposed responsibilities as release/stability tester of the drug product. There are no changes related to process and previously approved facilities.

(b) (4)

As for Gilead Sciences Inc (FEI 3013189568), (b) (4) particles in samples were observed during SEM sample preparation. Refer to the DP review for more details. Verification of SEM sample preparation is recommended to ensure no foreign particles (e.g., (b) (4)) are introduced to samples.

Information from original review (#1):

The proposed manufacturing process involves (b) (4)

No scale-up is proposed; the applicant manufactured ten clinical and stability batches with batch sizes ranging from (b) (4) kg - (b) (4) kg while the proposed commercial manufacturing scale is (b) (4) kg.

(b) (4)

(b) (4)

The drug product manufacturing facility, (b) (4)), is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance history. Gilead Alberta ULC (FEI: 3001027806, CSN) is found acceptable to perform the proposed responsibilities as drug substance manufacturer and tester based on district recommendation. (b) (4) is proposed as secondary packager (kitting, labeler of co-package kit) and it is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance status. The following testing sites are found acceptable to perform the proposed responsibilities in support of NDA 215973: (b) (4) LCP & LMS) and Gilead Sciences, Inc (FEI: 1000523075, LCP).

The overall manufacturing recommendation is Adequate from manufacturing perspective. For additional details, see Dr. David Acevedo's review below.

Biopharmaceutics: Adequate

No new biopharmaceutics information was included in the resubmission. NDA 215973 remains approvable from the biopharmaceutics perspective.

Microbiology: Adequate

In the CR dated 02/28/2022 of the original submission, the microbiology deficiency below was included:

The information request response provided on December 29, 2021, regarding the Container Closure Integrity Testing (CCIT) performed with aluminosilicate vials with batches GB2007B, GB2008B, and GB2009B is acknowledged. However, this response is incomplete and additional information is needed to assess acceptability of aluminosilicate vials: a) Provide the spectrophotometric data with all results from the CCIT dye ingress studies reported to be performed with 20 intact vials sourced from each of three batches GB2007B, GB2008B, and GB2009B respectively.

The applicant provided a response to this deficiency in the resubmission, provided evaluation of three registration batches of the DP (lots GB2007B, GB2008B, and GB2009B) for container closure integrity after 12 and 15 months storage at 30°C/75% RH in the inverted orientation. Two process validation batches exposed to target (b) (4) conditions (lots P112406PV and P112407PV) and three development batches exposed

to worst-case (b) (4) conditions (lots P112409PV/DV-B, P112409PV/DV-M, and P112409PV/DV-E) were also evaluated for container closure integrity. The results met acceptance criteria and are acceptable. The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product. The NDA is adequate from a microbiology perspective. For additional details, refer to Dr. Sallie Crenshaw's review below and review #1.

C. Risk Assessment

See review #1

D. List of Deficiencies for Complete Response

N/A

Application Technical Lead Name and Date:

Pete Guerrieri, PhD

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Notes –

- Gilead accepted all the CMC labelling recommendations communicated in the last review cycle. No major updates to CMC related sections are proposed in the current review cycle.
- For NDA 215973- The Applicant only included 'apparent pH' information in section 11 of PI and updated injection appearance (yellow color) in the current review cycle.
- For NDA 215974- The Applicant submitted 5-count blister pack (new packaging configuration) container and carton label in the current review
- The updated information submitted in the current review cycle is captured in blue text.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	SUNLENCA® Tablets SUNLENCA® Injection	Adequate
Established name(s)	Lenacapavir Tablets Lenacapavir Injection	Adequate.
Route(s) of administration	Tablet: For oral use Injection: For subcutaneous use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 300 mg Injection: 463.5 mg/1.5 mL (309 mg/mL) in single-dose vials.	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A Injection: The term 'single-dose vial' is included	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Tablet: N/A Injection: Once the solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible.	Adequate Lenacapavir injection is photosensitive and significant degradation was observed for the DP primary-packaged in clear glass vials (without secondary packaging). (b) (4) (b) (4) No further reconstitution or dilution is required for Lenacapavir injection, prior to administration.

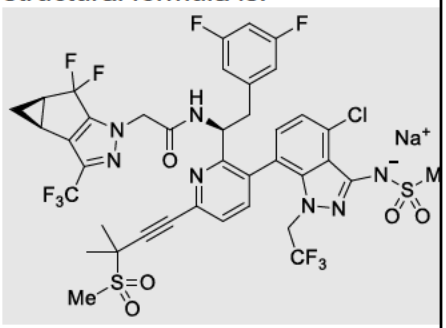
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	SUNLENCA® tablets [SUNLENCA® Injection	Adequate
Strength(s) in metric system	Tablets: Each tablet contains 300 mg of lenacapavir (present as 306.8 mg of lenacapavir sodium) Injection: Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Tablets: Each tablet contains 300 mg of lenacapavir (present as 306.8 mg of lenacapavir sodium) Injection: Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Tablets: The tablets are beige, capsule-shaped, film-coated, debossed with 'GSI' on one side of the tablet and '62L' on the other side of the tablet. Injection: The lenacapavir injectable solution is sterile, preservative-free, clear, and yellow solution with no visible particles.	Adequate As per the CMC comment issued during drug product review of NDA 215973, Gilead tighten the acceptance criterion for injection from '(b) (4) ' to 'yellow solution' only in section 3 of the PI, as well.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Injection: Single- dose Vial	Adequate

1.2.3 Section 11 Description

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	SUNLENCA® tablets SUNLENCA® Injection	Adequate
Dosage form(s) and route(s) of administration	Lenacapavir tablets: for oral administration Lenacapavir Injection: for subcutaneous administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Tablet: Each SUNLENCA® tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium) Injection: Each vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium)……	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Tablet: inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and poloxamer 407. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Injection: inactive ingredients: polyethylene glycol 300 and water for injection.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Injection: … following inactive ingredients: polyethylene glycol 300 and water for injection.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Sterile, preservative- free, clear, yellow (b) (4) solution	Adequate

Pharmacological/ therapeutic class	Capsid inhibitor	Adequate
Chemical name, structural formula, molecular weight	The chemical name of lenacapavir sodium is: Sodium (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-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)-1H-indazol-3-yl)(methylsulfonyl)amide. Its empirical formula is $C_{39}H_{31}ClF_{10}N_7NaO_5S_2$, with a molecular weight of 990.3,. Its structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	The apparent pH range of the injection is 9.0-10.2.	Adequate The Applicant included controls for 'apparent pH' in drug product release and stability specifications. (b) (4) .

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	SUNLENCA® tablets SUNLENCA® Injection	Adequate.

Strength(s) in metric system	Tablets: 300 mg Injection: 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir	Adequate.
Available units (e.g., bottles of 100 tablets)	Tablets: Blister pack containing 4 tablets. Blister pack containing 5 tablets Injection: Single-dose vial	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablet: Beige, capsule-shaped, and film-coated with "GSI" debossed on one side and "62L" on the other side. Injection: Sterile, preservative-free, clear, yellow with no visible particles	As per the CMC comment issued during drug product review of NDA 215973, Gilead tighten the acceptance criterion for appearance test from '(b) (4)' to 'yellow solution' only in DP specifications and section 3 of the PI, as well.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A Injection: Single-dose vial	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Tablet: Dispense only in original blister pack. Injection: Keep the vials in the original carton until just prior to preparation of the injections in order to protect from light. Once the solution has been drawn into the syringes, the injections should be administered as soon as possible. Discard any unused portion of the solution.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and	Packaged with silica gel desiccant in a sealed child-resistant flexible laminated pouch.	Adequate: Section 3.2.P.7 include following information: The desiccant is (b) (4)

desiccant has a warning such as "Do not eat."		(b) (4) Sachet with Silica Gel and printed with the 'DO NOT EAT' statement.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Tablets- Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted 15 °C to 30 °C (59 °F to 86 °F). Injection: "Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted 15 °C to 30 °C (59 °F to 86 °F), protect from light.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Injection: The vial stoppers are not made with natural rubber latex.	Adequate
Include information about child-resistant packaging	Tablets: … packaged with silica gel desiccant in a sealed child-resistant flexible laminated pouch. Injection: N/A	Tablet: Adequate Injection: The product will be used only in the clinical settings.

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured and distributed by: Gilead Sciences, Inc.	Adequate.

Reviewer's Assessment of Package Insert: Adequate

The Applicant updated the CMC sections of prescribing information as per the recent updates submitted to the quality sections of the NDA. The CMC information on the PI is adequate.

2.0 CARTON AND CONTAINER LABELING- NDA 215973

Lenacapavir Injection:

2.1 Container Label - IMAGES OF LABEL AND LABELING RECEIVED ON Nov-14-2022

(b) (4)

2.2 Carton Labeling - IMAGES OF LABEL AND LABELING RECEIVED ON June 27-2022

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label(s)	Information provided in the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	Sunlenca™ (lenacapavir) injection	Sunlenca™ (lenacapavir) injection
Dosage strength	463.5 mg/1.5 mL (309 mg/mL)	463.5 mg/1.5 mL (309 mg/mL)
Route of administration	For subcutaneous injection	For subcutaneous injection
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not included (most likely because of the space constrains, included in the carton label)	Each single-dose vial contains 463.5 mg/1.5 mL of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium)
Net contents (e.g. tablet count)	1.5 mL Single-Dose Vial	2X 1.5 mL Lenacapavir Single-dose vials
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 61958-3004-1	NDC 61958-3002-1
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Protect from light. Store at 20 °C to 25 °C (68 °F to 77 °F), (b) (4)	- Store at 20 ºC - 25 ºC (68 ºF - 77 ºF). - Sunlenca vials must be stored in the original carton, prior to the preparation of the injection.
Bar code	Yes	Yes
Name of manufacturer/distributor	Gilead Sciences, Inc. Manufactured in Canada	Gilead Sciences, Inc. Manufactured in Canada
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	-Single-dose vial. Discard unused portion.	Single-dose vial. (b) (4)

Assessment of Carton and Container Labeling: Adequate

3.0 Lenacapavir Tablets: NDA 215974

IMAGES OF LABEL AND LABELING RECEIVED ON June-27-2022 (4-count blister) and Oct-28-2022 (5-count blister)

3.1 Blister label: 4-count Blister

(b) (4)

5-count Blister

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Item	Information provided in the Blister label(s)	Information provided in the Pouch label(s)	Information provided in the Carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	Sunlenca™ (lenacapavir) tablets	Sunlenca™ (lenacapavir) tablets	Sunlenca™ (lenacapavir) tablets
Dosage strength	300 mg per tablet	300 mg per tablet	300 mg per tablet
Route of administration	Oral	Oral	Oral
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)
Net contents (e.g. tablet count)	-	4 tablets per pouch 5 tablets per pouch	4 tablets per pouch 5 tablets per pouch
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 61958-3001-1 NDC 61958-3001-2	NDC 61958-3001-1 NDC 61958-3001-2	NDC 61958-3001-1 NDC 61958-3001-2
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not Included	Store at 20 ºC - 25 ºC (68 ºF - 77 ºF)	Store at 20 ºC - 25 ºC (68 ºF - 77 ºF)
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345 Made in Canada	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345 Made in Canada
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	N/A

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A	N/A
And others, if space is available	None	Dispense only in original carton. Keep out of the reach of children.	Dispense only in original carton. Keep out of the reach of children.

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 1; ONDP Division of New Drug Products I; OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Peter Guerrier, PhD, SPQA; ONDP Division of New Drug Products I; OPQ

Shalini Anand

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Peter Guerrieri

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number/Type	215973 Type 1 (NME)
Assessment Cycle	2
Drug Product Name/Strength	SUNLENCA® (lenacapavir) injection, for subcutaneous (SC) administration, 463.5 mg/1.5 mL (309 mg/mL)
Dosage and Administration	• Recommended dosage – Initiation followed by once every 6-months maintenance dosing. Tablets may be taken without regard to food. <table><tr><td colspan="2">Initiation</td></tr><tr><td>Day 1</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 tablets)</td></tr><tr><td>Day 2</td><td>600 mg orally (2 tablets)</td></tr><tr><td colspan="2">Maintenance</td></tr><tr><td colspan="2">927 mg by subcutaneous injection (2 x 1.5 mL injections) (26 weeks) every 6 months (26 weeks) +/-2 weeks.</td></tr></table>• Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue, restart initiation from Day 1. • Two 1.5 mL subcutaneous injections are required for complete dose.
Applicant	Gilead Sciences, Inc.
OND Division	OND/OID/DAV
Proposed Indication	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Assessment Recommendation: **Adequate**

Assessment Summary:

On June 27, 2022, Gilead Sciences, Inc. submitted a class 2 resubmission to NDA 215973 (SDN 038). This resubmission was in response to the FDA's Complete Response Letter dated February 28, 2022. No new biopharmaceutics was included in SDN 038. NDA 215973 remains approvable from the biopharmaceutics perspective.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Resubmission (SDN 038)	2022-06-27

Highlight Key Issues from Last Cycle and Their Resolution:

- None.

Concise Description of Outstanding Issues:

- None

Primary Biopharmaceutics Assessor's Name and Date:
Qi Zhang, Ph.D. (11/18/2022)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Elsbeth Chikhale, Ph.D. (11/18/2022)

Qi Zhang

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Elsbeth Chikhale

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215973
Assessment Cycle Number	2
Drug Product Name / Strength	Lenacapavir (309 mg/mL)
Route of Administration	Subcutaneous
Applicant Name	Gilead Sciences, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: **N/A**

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
CRL Response document SD#00038	6/27/2022

Highlight Key Issues from Last Cycle and Their Resolution: Additional information was requested for container closure integrity testing.

Remarks: The drug product is indicated for the treatment of HIV-1 infection.

Concise Description of Outstanding Issues: N//a

Supporting Documents: N/A

Select Number of Approved Comparability Protocols: 0

Product Quality Microbiology Assessment

This review covers the amendment submitted June 27, 2022 in response to the Complete Response letter dated February 28, 2022. The microbiology deficiency is italicized below.

1. *The information request response provided on December 29, 2021, regarding the Container Closure Integrity Testing (CCIT) performed with aluminosilicate vials with batches GB2007B, GB2008B, and GB2009B is acknowledged. However, this response is incomplete and additional information is needed to assess acceptability of aluminosilicate vials:*

   a) Provide the spectrophotometric data with all results from the CCIT dye ingress studies reported to be performed with 20 intact vials sourced from each of three batches GB2007B, GB2008B, and GB2009B respectively.

Response dated 6/27/2022

The applicant provided spectrophotometric data from CCIT using their previously validated method (submitted on 1/21/2022) which included system suitability and method verification data using a sensitivity solution (a solution prepared at the proposed LOD – 10 µL of 1:2.5 dye solution [equivalent dye ingress of 4 µL of undiluted dye]).

Three registration batches of the DP (lots GB2007B, GB2008B, and GB2009B) were evaluated for container closure integrity after 12 and 15 months storage at 30°C/75% RH in the inverted orientation. Two process validation batches exposed to target (b) (4) conditions (lots P112406PV and P112407PV) and three development batches exposed to worst-case (b) (4) conditions (lots P112409PV/DV-B, P112409PV/DV-M, and P112409PV/DV-E) were also evaluated for container closure integrity.

All samples tested met the acceptance criterion for container closure integrity of no visual evidence of dye ingress observed in any of the test samples, and with the absorbance of each test sample solution less than the system sensitivity solution, equivalent to 4 µL of undiluted dye.

a. *Provide details of the CCIT protocol used to include the date the study was performed. Additionally, confirm the dye ingress CCIT was conducted using units exposed to worst case* (b) (4) *conditions prior to CCIT and confirm that both pressure and vacuum conditions were applied during CCIT. These conditions may be necessary to ensure that debris, dried product, and/or particulate matter are completely removed from potential leak paths. In the absence of vials exposed to* (b) (4) *and both pressure and vacuum conditions being applied please provide a new CCIT.*

Response dated 6/27/2022

The applicant provided a complete description of the CCIT method utilized. Twenty intact samples were utilized for each lot:

Three registration batches of the DP (lots GB2007B, GB2008B, and GB2009B) were evaluated for container closure integrity after 12 (12/24/2021) and 15 (3/23-3/28/2022) months storage at 30°C/75% RH in the inverted orientation. Two process validation batches (4/5/2022) exposed to target (b) (4) conditions (lots P112406PV and P112407PV) and three development batches (5/17/2022) exposed to worst-case (b) (4) conditions (lots P112409PV/DV-B, P112409PV/DV-M, and P112409PV/DV-E)

One negative control (not tested) was included per lot as well as three positive control vials each with a 20 µm capillary inserted through the stopper tested). A sensitivity vial was also included for each lot which is one vial spiked with 10 µL of a 1:2.5 dilution of 10% v/v crystal violet and 0.1% v/v tween 80 solution, equivalent to 4 µL of undiluted dye. A system suitability vial was also included which is one vial spiked with 20 µL of a 1:2.5 dilution of solution.

Samples were submerged in the dye solution and exposed to a vacuum of 10 inches Hg and maintained for 30 minutes. The vacuum was released and

samples submitted to a pressure of 15 psi for 30 minutes. The pressure was released and vials were removed and wiped. The following acceptance criteria were utilized:

-The Positive Controls must have visible evidence of dye ingress and must have an absorbance greater than or equal to System Sensitivity Solution.
-The absorbance of the System Sensitivity Solution must be between 25% and 75% of the mean absorbance of the System Suitability Solution.
-The %RSD of the 6 measurements of the System Suitability Solution must be less than or equal to 15%.

All acceptance criteria were met for all samples.

Assessment: *Adequate*

The applicant's verification of container closure integrity is consistent with regulatory expectations for a sterile pharmaceutical product.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: Sallie Crenshaw, Ph.D., 7/1/2022
Secondary Assessor Name and Date: Erika Pfeiler, Ph.D., 7/1/2022

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Sallie Crenshaw

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/s/

PETER P GUERRIERI
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NDA Executive Summary

1. Application/Product Information

NDA Number.	215974		
Applicant Name	Gilead		
Drug Product Name	Lenacapavir tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	300 mg		
Route of Administration	Oral		
Maximum Daily Dose	600 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated as a loading dose for Lenacapavir injection which is subject of referenced NDA 215973.		
Drug Product Description	Lenacapavir tablet is an immediate-release dosage form containing 300 mg lenacapavir present as 306.8 mg lenacapavir sodium.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C - 25°C (68°F - 77°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Karina Zuck	Paresma Patel
	Drug Product/ Labeling	Shalini Anand	Peter Guerrieri
	Manufacturing	Abdollah Koolivand	Hang Guo
	Biopharmaceutics	Qi Zhang	Elsbeth Chikhale

	Microbiology	N/A
	RBPM	Erica Keafer
	ATL	Pete Guerrieri
Consults	N/A	

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C - 25°C (68°F - 77°F)

b. Additional Comments for Action

N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The drug product is a 300 mg strength immediate release lenacapavir tablet proposed as the initial loading dose for lenacapavir injection – subject of the concurrent NDA 215973. The original submission for NDA 215974 was recommended for approval from an OPQ perspective, but the application was not approved due to the CR in the original review cycle for NDA 215973.

Lenacapavir tablets are beige, capsule-shaped, film-coated tablets, debossed with “GSI” on one side and “62L” on the other side, packaged as a 4-count or 5-count blister pack. During the drug product manufacturing process, (b) (4) [redacted] . (b) (4) [redacted]

(b) (4)

Based on the available stability data, a 24-month shelf life of the drug product is acceptable. The proposed drug product storage conditions are "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F)"".

In the first review cycle, the applicant's proposal to measure the drug product expiry period from (b) (4) was found acceptable. In the current review cycle, Gilead agreed to submit a post approval supplement for any future extensions of shelf life (b) (4) via a post-approval supplement based upon (b) (4) (up to the maximum proposed shelf life). The applicant also submitted the five-count blister pack (new packaging configuration) container and carton label in the current review, with appropriate stability data to support the pack, in addition to the previously approved four-count configuration.

All facilities remain compliant and in approved status. The overall recommendation remains as approvable.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments: N/A

Peter Guerrieri

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RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215974
Assessment #2

Drug Product Name	Lenacapavir tablets
Dosage Form	Tablets
Strength	300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD SN 0027	06/27/2022	All
eCTD SN 0030	08/25/2022	Labeling
eCTD SN 0035	10/06/2022	Quality
eCTD SN 0041	11/04/2022	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Paresma Patel
Drug Product	Shalini Anand	Peter Guerrieri
Manufacturing	Abdollah Koolivand	Hang Guo
Microbiology	N/A	
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Pete Guerrieri	
Laboratory (OTR)	N/A	
Environmental	N/A	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 215974 is recommended for approval from the product quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product is a 300 mg strength immediate release lenacapavir tablet proposed as the initial loading dose for lenacapavir injection – subject of the concurrent NDA 215973. The original submission for NDA 215974 was recommended for approval from an OPQ perspective, but the application was not approved due to the CR in the original review cycle for NDA 215973.

Lenacapavir tablets are beige, capsule-shaped, film-coated tablets, debossed with "GSI" on one side and "62L" on the other side, packaged as a 4-count or 5-count blister pack. During the drug product manufacturing process, (b) (4)

Based on the available stability data, a 24-month shelf life of the drug product is acceptable. The proposed drug product storage conditions are "Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F)".

In the first review cycle, the applicant's proposal to measure the drug product expiry period from (b) (4) was found acceptable. In the current review cycle, Gilead agreed to (b) (4)

The applicant also submitted the five-count blister pack (new packaging configuration) container and carton label in the current review, with

appropriate stability data to support the pack, in addition to the previously approved four-count configuration.

All facilities remain compliant and in approved status. The overall recommendation remains as approvable.

Proposed Indication(s) including Intended Patient Population	Indicated as a loading dose for Lenacapavir injection which is subject of referenced NDA 215973.
Duration of Treatment	2 or 3 doses
Maximum Daily Dose	600 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance review was adequate in the previous review cycle (see review #1), and no new drug substance information was provided in the resubmission. The NDA is recommended for approval from the drug substance perspective.

Drug Product: Adequate

Lenacapavir tablet is an immediate-release dosage form containing 300 mg lenacapavir, present as 306.8 mg lenacapavir sodium. The drug substance is (b) (4)

The proposed container closure system for the drug product consists of blister card with four (4) or five (5) tablets, fitted between two (2) paperboard cards, (b) (4) . The blister cards are packaged in a sealed (b) (4) -laminated pouch with three (3) grams of silica gel desiccant. The packaging materials are identical for the proposed commercial 4-count and 5-count configurations

Stability results through 18 months long term and 6 months accelerated storage for three drug product batches packaged with 5-count blister packaging configuration, along with three-month stability data for three DP batches packaged with 4-count blister pack is provided in section 3.2.P.8.

In addition, 12-18 months of long-term stability data for two drug product batches (b) (4) is also provided.

Based on the available stability data, a 24-month shelf life of the drug product is acceptable. The proposed drug product storage conditions are "Store at 25°C, excursions permitted to 15 – 30 °C". (b) (4)

(b) (4)

The NDA remains approvable from a drug product perspective. For additional details, refer to Dr. Shalini Anand's review below.

Labeling: Adequate

The Applicant submitted 5-count blister pack (new packaging configuration) container and carton label in the current review. The NDA is approvable for labeling. For additional details, refer to Dr. Shalini Anand's review below.

Manufacturing: Adequate

The drug product is an immediate-release tablet containing 300 mg lenacapavir (LEN), equivalent to 306.8 mg LEN sodium. The LEN API is (b) (4)

(b) (4)

(b) (4)

The facilities involved in the current submission are as follow:

- Gilead Alberta ULC, FEI: 3001027806: DS manufacture
- (b) (4): release/stability testing for DS/DP
- Gilead Sciences, Inc, FEI: 1000523075: release/stability testing for DS/DP
- (b) (4)
- (b) (4): DP manufacture
- (b) (4): DP packaging

All sites have experience with the proposed responsibilities and thus, no PAI was recommended for any of these facilities. All facilities currently remain compliant.

Biopharmaceutics: Adequate

No new biopharmaceutics was included in SDN 029. NDA 215974 remains approvable from the biopharmaceutics perspective. For additional details, see Dr. Qi Zhang's review.

Microbiology: N/A

C. Risk Assessment

See review #1.

D. List of Deficiencies for Complete Response
N/A

Application Technical Lead Name and Date:

Pete Guerrieri, PhD

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Notes –

- Gilead accepted all the CMC labelling recommendations communicated in the last review cycle. No major updates to CMC related sections are proposed in the current review cycle.
- For NDA 215973- The Applicant only included 'apparent pH' information in section 11 of PI and updated injection appearance (yellow color) in the current review cycle.
- For NDA 215974- The Applicant submitted 5-count blister pack (new packaging configuration) container and carton label in the current review
- The updated information submitted in the current review cycle is captured in blue text.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	SUNLENCA® Tablets SUNLENCA® Injection	Adequate
Established name(s)	Lenacapavir Tablets Lenacapavir Injection	Adequate.
Route(s) of administration	Tablet: For oral use Injection: For subcutaneous use	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 300 mg Injection: 463.5 mg/1.5 mL (309 mg/mL) in single-dose vials.	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A Injection: The term 'single-dose vial' is included	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Tablet: N/A Injection: Once the solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible.	Adequate Lenacapavir injection is photosensitive and significant degradation was observed for the DP primary-packaged in clear glass vials (without secondary packaging). (b) (4) (b) (4) No further reconstitution or dilution is required for Lenacapavir injection, prior to administration.

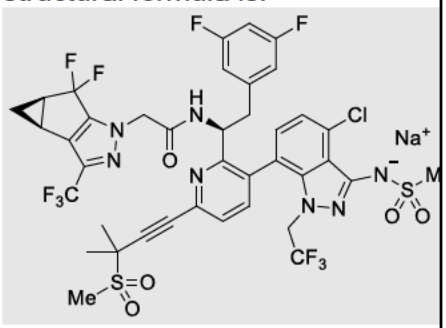
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	SUNLENCA® tablets [SUNLENCA® Injection	Adequate
Strength(s) in metric system	Tablets: Each tablet contains 300 mg of lenacapavir (present as 306.8 mg of lenacapavir sodium) Injection: Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Tablets: Each tablet contains 300 mg of lenacapavir (present as 306.8 mg of lenacapavir sodium) Injection: Each single-dose vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium.	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Tablets: The tablets are beige, capsule-shaped, film-coated, debossed with 'GSI' on one side of the tablet and '62L' on the other side of the tablet. Injection: The lenacapavir injectable solution is sterile, preservative-free, clear, and yellow solution with no visible particles.	Adequate As per the CMC comment issued during drug product review of NDA 215973, Gilead tighten the acceptance criterion for injection from '(b) (4) ' to 'yellow solution' only in section 3 of the PI, as well.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Injection: Single- dose Vial	Adequate

1.2.3 Section 11 Description

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
Proprietary and established name(s)	SUNLENCA® tablets SUNLENCA® Injection	Adequate
Dosage form(s) and route(s) of administration	Lenacapavir tablets: for oral administration Lenacapavir Injection: for subcutaneous administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Tablet: Each SUNLENCA® tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium) Injection: Each vial contains 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium)……	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Tablet: inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, and poloxamer 407. The tablets are film-coated with a coating material containing iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Injection: inactive ingredients: polyethylene glycol 300 and water for injection.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Injection: … following inactive ingredients: polyethylene glycol 300 and water for injection.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Sterile, preservative- free, clear, yellow (b) (4) solution	Adequate

Pharmacological/ therapeutic class	Capsid inhibitor	Adequate
Chemical name, structural formula, molecular weight	The chemical name of lenacapavir sodium is: Sodium (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-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)-1H-indazol-3-yl)(methylsulfonyl)amide. Its empirical formula is $C_{39}H_{31}ClF_{10}N_7NaO_5S_2$, with a molecular weight of 990.3,. Its structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	The apparent pH range of the injection is 9.0-10.2.	Adequate The Applicant included controls for 'apparent pH' in drug product release and stability specifications. (b) (4) [redacted] .

1.2.4 Section 16 HOW SUPPLIED/STORAGE AND HANDLING section

Item	Information Provided in the NDA	Assessor's Comments
Available dosage form(s)	SUNLENCA® tablets SUNLENCA® Injection	Adequate.

Strength(s) in metric system	Tablets: 300 mg Injection: 463.5 mg/1.5 mL (309 mg/mL) of lenacapavir	Adequate.
Available units (e.g., bottles of 100 tablets)	Tablets: Blister pack containing 4 tablets. Blister pack containing 5 tablets Injection: Single-dose vial	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablet: Beige, capsule-shaped, and film-coated with "GSI" debossed on one side and "62L" on the other side. Injection: Sterile, preservative-free, clear, yellow with no visible particles	As per the CMC comment issued during drug product review of NDA 215973, Gilead tighten the acceptance criterion for appearance test from '(b) (4)' to 'yellow solution' only in DP specifications and section 3 of the PI, as well.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Tablet: N/A Injection: (b) (4)	Adequate
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Tablet: Dispense only in original blister pack. Injection: Keep the vials in the original carton until just prior to preparation of the injections in order to protect from light. Once the solution has been drawn into the syringes, the injections should be administered as soon as possible. Discard any unused portion of the solution.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and	Packaged with silica gel desiccant in a sealed child-resistant flexible laminated pouch.	Adequate: Section 3.2.P.7 include following information: The desiccant is 3-Gram, (b) (4)

desiccant has a warning such as "Do not eat."		(b) (4) Sachet with Silica Gel and printed with the 'DO NOT EAT' statement.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Tablets- Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted 15 °C to 30 °C (59 °F to 86 °F). Injection: "Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted 15 °C to 30 °C (59 °F to 86 °F), protect from light.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Injection: The vial stoppers are not made with natural rubber latex.	Adequate
Include information about child-resistant packaging	Tablets: … packaged with silica gel desiccant in a sealed child-resistant flexible laminated pouch. Injection: N/A	Tablet: Adequate Injection: The product will be used only in the clinical settings.

1.2.3 Other Sections of Labeling

1.2.4 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured and distributed by: Gilead Sciences, Inc.	Adequate.

Reviewer's Assessment of Package Insert: Adequate

The Applicant updated the CMC sections of prescribing information as per the recent updates submitted to the quality sections of the NDA. The CMC information on the PI is adequate.

2.0 CARTON AND CONTAINER LABELING- NDA 215973

Lenacapavir Injection:

2.1 Container Label - IMAGES OF LABEL AND LABELING RECEIVED ON Nov-14-2022

(b) (4)

2.2 Carton Labeling - IMAGES OF LABEL AND LABELING RECEIVED ON June 27-2022

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Item	Information provided in the container label(s)	Information provided in the carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	Sunlenca™ (lenacapavir) injection	Sunlenca™ (lenacapavir) injection
Dosage strength	463.5 mg/1.5 mL (309 mg/mL)	463.5 mg/1.5 mL (309 mg/mL)
Route of administration	For subcutaneous injection	For subcutaneous injection
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not included (most likely because of the space constrains, included in the carton label)	Each single-dose vial contains 463.5 mg/1.5 mL of lenacapavir (present as 473.1 mg/1.5 mL of lenacapavir sodium)
Net contents (e.g. tablet count)	1.5 mL Single-Dose Vial	2X 1.5 mL Lenacapavir Single-dose vials
"Rx only" displayed on the principal display	Yes	Yes
NDC number	NDC 61958-3004-1	NDC 61958-3002-1
Lot number and expiration date	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Protect from light. Store at 20 °C to 25 °C (68 °F to 77 °F), (b) (4) .	- Store at 20 ºC - 25 ºC (68 ºF - 77 ºF). - Sunlenca vials must be stored in the original carton, prior to the preparation of the injection.
Bar code	Yes	Yes
Name of manufacturer/distributor	Gilead Sciences, Inc. Manufactured in Canada	Gilead Sciences, Inc. Manufactured in Canada
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	Yes	Yes

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	-Single-dose vial. Discard unused portion.	Single-dose vial. (b) (4)

Assessment of Carton and Container Labeling: Adequate

3.0 Lenacapavir Tablets: NDA 215974

IMAGES OF LABEL AND LABELING RECEIVED ON June-27-2022 (4-count blister) and Oct-28-2022 (5-count blister)

3.1 Blister label: 4-count Blister

(b) (4)

5-count Blister

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Item	Information provided in the Blister label(s)	Information provided in the Pouch label(s)	Information provided in the Carton label(s)
Proprietary name, established name, and dosage form (font size and prominence	Sunlenca™ (lenacapavir) tablets	Sunlenca™ (lenacapavir) tablets	Sunlenca™ (lenacapavir) tablets
Dosage strength	300 mg per tablet	300 mg per tablet	300 mg per tablet
Route of administration	Oral	Oral	Oral
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)	Each tablet contains 300 mg of lenacapavir (present as 306.8 mg lenacapavir sodium)
Net contents (e.g. tablet count)	-	4 tablets per pouch 5 tablets per pouch	4 tablets per pouch 5 tablets per pouch
"Rx only" displayed on the principal display	Yes	Yes	Yes
NDC number	NDC 61958-3001-1 NDC 61958-3001-2	NDC 61958-3001-1 NDC 61958-3001-2	NDC 61958-3001-1 NDC 61958-3001-2
Lot number and expiration date	Yes	Yes	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Not Included	Store at 20 ºC - 25 ºC (68 ºF - 77 ºF)	Store at 20 ºC - 25 ºC (68 ºF - 77 ºF)
Bar code	Yes	Yes	Yes
Name of manufacturer/distributor	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345 Made in Canada	Manufactured for: Gilead Sciences, Inc. Foster City, CA 12345 Made in Canada
Medication Guide (if applicable)	N/A	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A	N/A

When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A	N/A
And others, if space is available	None	Dispense only in original carton. Keep out of the reach of children.	Dispense only in original carton. Keep out of the reach of children.

Assessment of Carton and Container Labeling: Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Refer to discussion above and recommendations in OND labeling.

Primary Labeling Reviewer Name and Date:

Shalini Anand, PhD, Branch 1; ONDP Division of New Drug Products I; OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Peter Guerrier, PhD, SPQA; ONDP Division of New Drug Products I; OPQ

Shalini Anand

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Peter Guerrieri

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	215974 Type 1 (NME)
Assessment Cycle	2
Drug Product Name/Strength	SUNLENCA® (lenacapavir) tablets, for oral use, 300 mg
Dosage and Administration	Recommended dosage – Initiation with one of two options followed by once every 6-months maintenance dosing. Initiation Option 1 Day 1: 927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 tablets) Day 2: 600 mg orally (2 tablets) Initiation Option 2 Day 1: 600 mg orally (2 tablets) Day 2: 600 mg orally (2 tablets) Day 8: 300 mg orally (1 tablet) Day (b) (4): 927 mg by subcutaneous injection (2 x 1.5 mL injections) Maintenance 927 mg by subcutaneous injection (2 x 1.5 mL injections) (b) (4) every 6 months (26 weeks) +/-2 weeks.
Applicant Name	Gilead Sciences, Inc.
OND Division	OND/OID/DAV
Proposed Indication	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Assessment Recommendation: **Adequate**

Assessment Summary:

On June 27, 2022, Gilead Sciences, Inc. submitted a class 2 resubmission to NDA 215974 (SDN 029). This resubmission was in response to the FDA's Complete Response Letter dated February 28, 2022. No new biopharmaceutics was included in SDN 029. NDA 215974 remains approvable from the biopharmaceutics perspective.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Resubmission (SDN 029)	2022-06-27

Highlight Key Issues from Last Cycle and Their Resolution:

- None.

Concise Description of Outstanding Issues:

- None

Primary Biopharmaceutics Assessor's Name and Date:
Qi Zhang, Ph.D. (11/18/2022)

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Elsbeth Chikhale, Ph.D. (11/18/2022)

Qi Zhang

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Elsbeth Chikhale

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/s/

PETER P GUERRIERI
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 215973
Assessment #1

Drug Product Name	Lenacapavir injection
Dosage Form	
Strength	463.5 mg/ 1.5 ml (309 mg/ml)
Route of Administration	Subcutaneous
Rx/OTC Dispensed	
Applicant	Gilead
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD: 1,8, 13, 17, 20, 21, 23, 24, 25, 26, 27, 28 (carton labels), 30		
SD 31 and 32 were not evaluated in this review cycle.		

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Paresma Patel
Drug Product	Shalini Anand	David Claffey
Manufacturing	David Acevedo	Steve Rhieu
Microbiology	Jonathan Burgos	Paul Dexter
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Environmental	James Laurenson	
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	David Claffey	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Recommend that this application not be approved from a product quality perspective at this time. One of the proposed commercial vial containers (borosilicate) proved incompatible with the drug product solution with degradation of the vial surface and glass particles found in the solution. Considering the high pH of the drug product solution, the (b) (4) and a history of glass particle contamination, approval of the proposed alternative aluminosilicate glass vial will require a comprehensive validated study rather than the piecemeal ambiguous data provided by the applicant to-date. Further, data supporting the container closure integrity testing remains outstanding despite numerous information requests.

As stated in II.A, the OND review team were notified about the atypical nature of this product –no intrinsic release controls and first subcutaneous product with pH >9.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Lenacapavir sodium is a new molecular entity. It is an inhibitor of HIV-1 capsid function and is proposed for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. It is formulated as a (b) (4) a single strength injection product – composed (w/w) (b) (4) % active ingredient (b) (4) % water and (b) (4) % polyethylene glycol (PEG) 300. The role of PEG is to solubilize (b) (4). This application was submitted simultaneously with NDA 215974, which is a tablet formulation of lenacapavir proposed for initial loading doses.

The drug product will be dosed subcutaneously every six months. After administration the drug (b) (4) release lenacapavir to the circulatory system over a six-month period. (b) (4) No extended-release claim was made, which was found acceptable by the biopharmaceutics team. (b) (4) The clinical review team was notified that there are no CMC data to support the six-monthly dosing – (b) (4) will need to rely wholly on clinical data – which were not evaluated by OPQ. Further, the OND team were alerted to the high pH of the drug product solution – pH 9 to 10. There is no precedence for approval of a subcutaneous product with pH >9 (response to Comment 5b, SD 16). (b) (4) (b) (4) . (b) (4)

Although lenacapavir sodium has low solubility in aqueous media, characterization of its solubility in serum or blood could have provided information on the risk of dose dumping if it came in contact with blood during or after administration (e.g., broken capillaries).

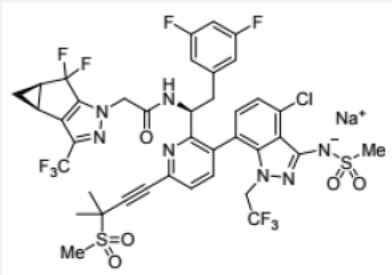
Such data were requested from the applicant by OND, but the applicant indicated (#4e, SD 16) that they had difficulty in carrying out this determination.

Proposed Indication(s) including Intended Patient Population	Lencapavir is a selective inhibitor of HIV-1 capsid function indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Duration of Treatment	Chronic
Dose	Every six months SC injection. Loading oral dose using tablets (NDA 215973)
	The proposed dosing regimen of lenacapavir includes an initial dose of 927 mg of lenacapavir by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 lenacapavir tablets, NDA 215974 drug product) on Day 1; 600 mg orally (2 tablets) on Day 2, followed by a maintenance dose of 927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months.

B. Quality Assessment Overview

Drug Substance: Adequate

Lenacapavir sodium drug substance is a light yellow or yellow (b) (4) solid, slightly hygroscopic. The drug substance is practically insoluble in aqueous media pH 1.8-8.9 and is soluble in several organic solvents. Three (b) (4) polymorphic forms, Form I, II, and III, have been isolated. (b) (4) . Lenacapavir has three stereogenic centers (b) (4) . (b) (4) . (b) (4) impurities are not controlled in the release specification, but their levels are adequately justified based on a risk assessment per ICH Q3D. Class 2 and Class 3 organic solvents (b) (4) are controlled as per ICH Q3C. (b) (4) . Several of the tentative present impurities contain alerting (b) (4) and (b) (4) structural functionalities



which are potential mutagenic impurities, and these impurities are adequately controlled by ICH M7 option 3 or 4. The risk of nitrosamines was summarized and determined to be low for the drug substance manufacture process. The drug substance is adequately characterized by standard spectroscopic techniques used for small molecules (1D and 2D NMR spectroscopy, MS spectrometry, UV and IR spectroscopy, elemental analysis, X-Ray and microcrystal electron diffractometry. The characterization data support its structure. (b) (4) and residual solvents are controlled as per ICH Q3A and ICH Q3C, respectively. The proposed acceptance criteria for the impurities were found below the qualifying toxicologic level by the P/T reviewer Dr. Diggs. Lenacapavir sodium is stable throughout 12 months at long term (30°C/75%RH) stability conditions. The proposed retest period of (b) (4) months was found acceptable under the storage conditions (b) (4).

Drug Product: Inadequate

Lenacapavir Injection is a sterile, preservative-free, for subcutaneous administration. Marketing of a single strength is proposed 463.5 mg/ 1.5 ml (309 mg/ml) in a glass vial. The dosage strength is based on the lenacapavir free acid. Each vial contains a nominal 1.5 ml clear, yellow (b) (4) solution consisting of 473.1 mg of lenacapavir sodium, 896.3 mg polyethylene glycol 300 and (b) (4) water for injection. Each vial contains sufficient volume ((b) (4) mL with (b) (4) mL overfill) to allow withdrawal of 1.5 mL.

Drug product kit: The proposed container closure system for the drug product consists of a single-dose, clear glass vial. Each vial is sealed with an elastomeric closure and aluminum overseal with flip off cap. The drug product is supplied as a co-packaged kit which includes all the components needed for healthcare professionals to administer the injection i.e., two lenacapavir filled vials, two vial access devices, two disposable syringes, and two injection safety needles.

Vial issue: In the original submission, Gilead proposed to market the product with two different vials: borosilicate glass vials and aluminosilicate glass vials. However, significant pitting of the borosilicate glass vials was observed (b) (6) (b) (4) Also, glass-like particles were observed in the drug product samples of five clinical batches stored up to 22 months in borosilicate glass vials. Multiple t-cons were held between Agency (CMC and clinical review team) and Gilead. The Applicant was requested to justify the marketing of borosilicate glass vials for the commercial packaging as data indicated that they were incompatible with the drug product solution and manufacturing process. The Applicant proposed to withdraw the borosilicate glass vials in the submission dated 12/29/2021. However, due to its submission late in this review cycle, time and resources did not allow for its review.

To support the aluminosilicate glass vials, Gilead submitted the SEM images and optical microscopic images of the vial surfaces of the developmental batches after (b) (4) and 6-month storage under accelerated and long-term storage conditions. The SEM images of these developmental lots showed significant number of particulate matter or consistent changes on the vial surface after (b) (4) and during stability studies compared to unfilled vials (submission dated 11-22-2021 and 12-15-2021). In response to an IR, Gilead justified that the observed particulates are extrinsic particles present in a laboratory environment, as these lab batches were manufactured and tested under non-cGMP environment.

Gilead was also asked to submit the SEM images, optical microscopy images of the solution and vial surfaces of the registration stability batches packaged with aluminosilicate vials for registration stability batches. The SEM and optical microscopic images of the vial surfaces of the registration batches at 11.5-month time point were submitted in the submission dated 12-29-2021. Due to its timing, this submission was not reviewed in the current review cycle, but on face the data did not appear sufficient, to support the use of the aluminosilicate vials. Note that the issue of glass compatibility with either vial was not raised by the applicant and was only addressed by the applicant after several rounds of IRs by the review team. Data supporting the aluminosilicate vials were provided in a piecemeal manner and the applicant indicated that they did not have a comprehensive study report to address this issue. Considering the drug product solutions unusually high pH coupled with (b) (4) and the clear incompatibility of the borosilicate vials with the drug product solution, this application can not be approved without a comprehensive report for the SEM and optical microscopy analysis of the stability batches over the period of time to unambiguously demonstrate that the aluminosilicate glass vials are compatible with proposed high pH and (b) (4) of lenacapavir injection formulation.

Drug product stability: The data for 12-month stability time points to support aluminosilicate glass vials will be submitted in mid-Jan 2022 – after completion of the OPQ review. Lenacapavir injection is sensitive to light and significant degradation was observed for the drug product samples primary-packaged in the clear glass vials – though it remained stable while stored within the secondary packaging.

Stability results through 12 months long term and six months accelerated storage for three drug product batches packaged with borosilicate glass vials, along with nine months long-term (and six months accelerated) stability data for three drug product batches packaged with aluminosilicate glass vials is provided in section 3.2.P.8. A final assessment of the proposed drug product expiry period could not be made due to the proposed withdrawal of the borosilicate vials and the pending stability and compatibility data for the aluminosilicate vials.

Labeling: Choose an item.

As per the Agency's recommendations, Gilead revised the storage condition for drug product to USP controlled room temperature, protect from light."

Manufacturing: Adequate

The proposed manufacturing process involves (b) (4) . (b) (4) in the LEN injection, 309mg/mL formulation. The proposed in-process controls include (b) (4) . No scale-up is proposed; the applicant manufactured ten clinical and stability batches with batch sizes ranging from (b) (4) kg while the proposed commercial manufacturing scale is (b) (4) kg.

Various process issues were identified and resolved during this review cycle, such as lack of environmental controls (b) (4) but the applicant supported the lack of control based on development studies. (b) (4)

The drug product manufacturing facility, (b) (4) is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance history. Gilead Alberta ULC (FEI: 3001027806, CSN) is found acceptable to perform the proposed responsibilities as drug substance manufacturer and tester based on district recommendation. (b) (4) is proposed as secondary packager (kitting, labeler of co-package kit) and it is found acceptable to perform the proposed responsibilities based on district recommendation, experience with the proposed operations, and adequate compliance status. The following testing sites are found acceptable to perform the proposed responsibilities in support of NDA 215973: (b) (4), LCP & LMS) and Gilead Sciences, Inc (FEI: 1000523075, LCP).

Biopharmaceutics: Adequate

Based on the Biopharmaceutics assessment of the provided information, the following is concluded:

In Vitro Drug Release Test: Since the proposed drug product is a solution formulated without any release controlling excipients and the in vivo drug release is expected to be determined by the intrinsic properties of the API and controlled by the *in-situ* environment at the site of injection after product's administration, the implementation of an in vitro drug release test (IVRT) for the proposed drug product is deemed not necessary.

Product's Bridging: Bridging is not needed because the pivotal clinical drug product is the same as the proposed to-be-marketed drug product.

Extended-Release Claim: The proposed drug product formulation is not extended release from a Biopharmaceutics perspective; considering that 1) the dosage form is solution; 2) the composition does not contain any release controlling excipients; 3) the long acting nature is not related to the drug product formulation; therefore, an extended-release claim is not required.

Microbiology (if applicable): Inadequate

(b) (4) The microbiology review team recommended a CR action based on the firm's multiple incomplete responses to Container Closure Integrity Test information requests.

D. List of Deficiencies for Complete Response

1. *Your data demonstrate that the drug product solution is incompatible with the proposed commercial borosilicate glass vials. The data provided in support of the compatibility of the alternative aluminosilicate glass vials are incomplete and ambiguous. As evidenced by your data and glass particles found in the clinical batches, glass containers are generally incompatible with highly alkaline solutions, (b) (4) . In order to resolve this deficiency, we require a comprehensive study report with unambiguous data and fully validated methods to demonstrate the compatibility of the drug product solution with your proposed primary container closure system.*

2. The information request response provided on 29 December 2021 regarding the CCIT performed with aluminosilicate vials with batches GB2007B, GB2008B, and GB2009B is acknowledged. However, additional information is needed:

a) Provide the spectrophotometric data with all results from the CCIT dye ingress studies reported to be performed with 20 intact vials sourced from each of three batches GB2007B, GB2008B, and GB2009B respectively.

b) Provide details of the CCIT protocol used to include the date the study was performed. Additionally, confirm the dye ingress CCIT was conducted using units exposed to worst case (b) (4) conditions prior to CCIT and confirm that both pressure and vacuum conditions were applied during CCIT. These conditions may be necessary to ensure that debris, dried product, and/or particulate matter are completely removed from potential leak paths. In the absence of vials exposed to (b) (4) and both pressure and vacuum conditions being applied please provide a new CCIT.

Additional Comment:

1. The proposed acceptance criterion for the appearance test in drug product release and stability specifications is - '*a clear, yellow* (b) (4) *solution, essentially free of visible particle*s.' Clarify whether any drug product batch (es) exhibited (b) (4) color at release or during stability and whether change in color from 'yellow (b) (4)' had any impact on other drug product CQAs. Also, report the exact color for the appearance test for future stability time points of drug product registration batches.

Application Technical Lead Name and Date: David Claffey

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215973
Assessment Cycle Number	1
Drug Product Name/ Strength	Lenacapavir (309 mg/mL)
Route of Administration	Subcutaneous
Applicant Name	Gilead Sciences, Inc.
Therapeutic Classification/ OND Division	Treatment of HIV-1 infection
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Inadequate - Minor**

The DMA recommendation is for CR based on the firm's multiple incomplete responses to Container Closure Integrity Test IRs.

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received

eCTD Sequence 0001	06/28/2021
eCTD Sequence 0016	10/29/2021
eCTD Sequence 0019	11/12/2021
eCTD Sequence 0020	11/22/2021
eCTD Sequence 0025	12/15/2021
eCTD Sequence 00026	12/17/2021
eCTD Sequence 0029	12/23/2021
eCTD Sequence 00030	12/29/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A.

Remarks: Six additional submissions were issued to the Agency on 06/28/2021, 07/22/2021, 08/05/2021, 08/09/2021, 08/13/2021, 08/17/2021. None of the subsequent submissions require a microbiological review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):

Supporting Documents:

Review Document (Date)	Review Status	Referenced Information
D021723M16R01 (04/01/2021)	Adequate	For review of 3 mL Borosilicate Glass Vial (b) (4) depyrogenation data
D030807M01R01 (11/15/2021)	Adequate	For review of 3 mL Aluminosilicate Glass Vial (b) (4) depyrogenation data
D10953M55R01 (06/07/2021)	Adequate	For review of Stopper (b) (4) data

S DRUG SUBSTANCE

N/A, drug substance is nonsterile, and is sterilized as part of the drug product manufacturing process.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Information Located at: Sequence 0001 [06/28/2021], Modules 3.2.P.1, Description and Composition of Drug Product; 3.2.P.3.3, Description of Manufacturing Process and Process Controls [Page 4]; 3.2.P.7, Summary of Container Closure System, Page 1; 3.2.R.1, Executed Batch Record, Batch Record GB1905B1, Page 64)

Lenacapavir (LEN) injection is a single-use, preservative-free, sterile solution in 309 mg/mL strength filled in 3 mL vials (target fill weight (b) (4) g [(b) (4) mL]). Exact formulation is described in the table below.

Component	Reference to Quality Standard	Function	% w/w	Quantity per 1.5 mL Solution (mg)
LEN sodium[c]	In-house	Active Ingredient	(b) (4)	(b) (4)
Polyethylene glycol 300	NF, Ph. Eur.	Solvent		
Water for injection[c]	USP, Ph. Eur.	(b) (4)		(b) (4)

Description of Container Closure System

CCS Component	Manufacturer	Construction Material	DMF
3 mL Vial ((b) (4))	(b) (4)	Aluminosilicate Glass Vial	(b) (4)
13 mm Rubber Stopper		(b) (4)	
Aluminum Overseal		Seal: Aluminum Plastic Button: (b) (4)	

The applicant indicated the two proposed vials are equivalent and interchangeable. Moreover, the applicant indicated both vials are compatible with the proposed 13 mm rubber stopper and aluminum seal. Diagrams of both proposed vials were provided in Pages 7-8 illustrating identical inner/outer neck diameters. Of note, LEN is co-packaged as a vial kit, which includes the necessary components for administration by a healthcare professional. The kit includes: (1) Two vials of LEN, (2) Two vial access devices, (3) Two disposable syringes, and (4) Two injection safety needles.

Note to Reviewer: While the applicant proposed both borosilicate ((b) (4)) and aluminosilicate ((b) (4) vials in the original submission (e.g., 06/28/2021), in the 29 December 2021 communication, the applicant informed the Agency that only the aluminosilicate vials will be used as a primary drug product container. The applicant revised Module 3.2.P.7 (Container Closure System) to reflect this change. This change was also addressed in the proposed CCIT studies detailed below. Consequently, the CCS table above only includes the proposed aluminosilicate vial.

The applicant indicated the drug product kit components have been registered in the US under the 510(k) numbers shown in the table below. Moreover, the applicant proposed to sterilize the various kit components per ISO 11137 (see table below).

Proposed LEN Kit component 510(k) Registration Numbers

Kit Component	FDA 510(k) Clearance	Relevant Standards
Vial Access Device	(b) (4)	(b) (4)
Disposable Syringe		
Injection Safety Needle		

Sterilization Method of the Proposed LEN Kit components

Kit Component	Packaging	Terminal Sterilization Method	Sterility Assurance Level (SAL)
Vial Access Device	(b) (4)		
Disposable Syringe			
Injection Safety Needle			

Notes to Reviewer:

1. Although the applicant provided sterilization information of the various kit components, this review will only cover the drug component.
2. Through personal communication, the PM indicated that a CDRH consult was requested for review of the kit and that the consult was withdrawn because the kit components are all 510(k) cleared.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

(b) (4)

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Jonathan Burgos

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Paul Dexter

Digitally signed by Paul Dexter
Date: 1/11/2022 07:24:50AM
GUID: 508da70c00028f8ef6fc7fb5f60df2ce

CHAPTER VI: BIOPHARMACEUTICS

<table>
<tr><td>NDA Number/Type</td><td>215973; Type 1 (NME); Priority 505(b)(1)</td></tr>
<tr><td>Assessment Cycle</td><td>1</td></tr>
<tr><td>Drug Product</td><td>SUNLENCA™ (lenacapavir) injection, for subcutaneous (SC) administration</td></tr>
<tr><td>Dosage Form/strength</td><td>Injection solution (SC)/ 463.5 mg/1.5 mL (309 mg/mL)</td></tr>
<tr><td>Proposed Dosage and Administration</td><td>• Recommended dosage – Initiation followed by once every 6-months maintenance dosing. Tablets may be taken without regard to food.
<table>
<tr><td colspan="2">Initiation</td></tr>
<tr><td>Day 1</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections) and
600 mg orally (2 tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 tablets)</td></tr>
<tr><td colspan="2">Maintenance</td></tr>
<tr><td colspan="2">927 mg by subcutaneous injection (2 x 1.5 mL injections) (26 weeks) every 6 months (26 weeks) +/-2 weeks.</td></tr>
</table>
• Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue, restart initiation from Day 1.
• Two 1.5 mL subcutaneous injections are required for complete dose.</td></tr>
<tr><td>Applicant</td><td>Gilead Sciences, Inc.</td></tr>
<tr><td>OND Division</td><td>OND/OID/DAV</td></tr>
<tr><td>Associated INDs</td><td>IND 136260, IND 138311</td></tr>
<tr><td>Proposed Indication</td><td>Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.</td></tr>
<tr><td>Primary Reviewer</td><td>Qi Zhang, PhD</td></tr>
<tr><td>Secondary Reviewer</td><td>Elsbeth Chikhale, PhD</td></tr>
<tr><td>Assessment Recommendation</td><td>Adequate</td></tr>
</table>

Background:

Lenacapavir (LEN) is an HIV-1 antiretroviral, new molecular entity (NME) developed under IND 136260 and IND 138311. NDA 215974 for LEN tablets, 300 mg is also currently under review. LEN tablets and SC injection are to be administered together as indicated in the Dosage and Administration section of the product's label. The clinical program in support of both NDAs includes a pivotal phase 2/3 trial (Study GS-US-200-4625), one supportive phase 2 trial (Study GS-US-200-4334), and 2 phase 1 trials in healthy participants (Studies GS-US-200-4538 and GS-US-200-5709).

LEN sodium drug substance is a light yellow to yellow solid ((b) (4) and is practically insoluble in water and aqueous media (pH 1.8 to pH 8.9; refer to Table 2 of 3.2.S.1.3 General Properties). (b) (4)

The composition of the pivotal phase 2/3 clinical and proposed commercial formulation of LEN injection, 309 mg/mL is shown in **Table 1**. The manufacturing process consists of (b) (4) . The final LEN injection product is a sterile, preservative-free, yellow (b) (4) clear solution in a glass vial with no visible particles. The pH of the drug product is between (b) (4) and (b) (4), and the drug product is hypertonic with a calculated osmolarity of 1800 mOsm/L. For detailed information, refer to the Drug Product Review and Process Review.

Table 1: Quantitative Composition of LEN Injection, 309 mg/mL

Component	Reference to Quality Standard	Function	% w/w	Quantity per 1.5 mL Solution[a,b] (mg)
LEN sodium[c]	In-house	Active Ingredient	(b) (4)	
Polyethylene glycol 300	NF, Ph. Eur.	Solvent		
Water for injection[c]	USP, Ph. Eur.			

a Each unit is filled with approximately (b) (4) mL excess volume to allow withdrawal of 1.5 mL of solution.
b Based on formulation density of (b) (4) g/mL at room temperature.
c (b) (4)
d Equivalent to 463.5 mg of LEN

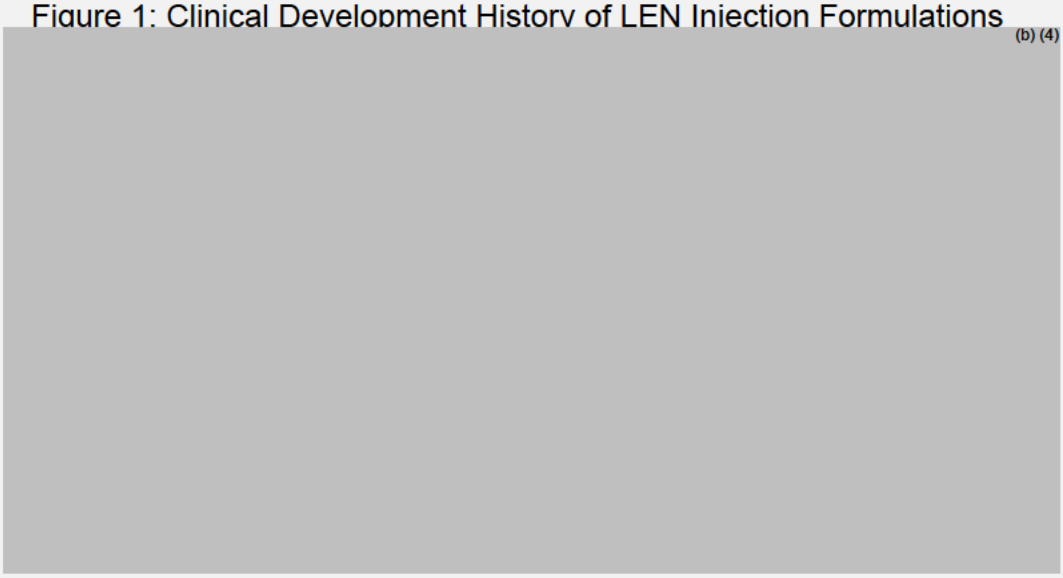
(ref. Table 1 of 3.2.P.1)

Bridging Throughout the Product's Development:

Early clinical studies (Study GS-US-200-4070 and GS-US-200-4072) were conducted with an aqueous suspension formulation of (b) (4) LEN free acid; (b) (4) , solution formulations of (b) (4) LEN sodium salt in PEG 300 and water for injection (b) (4) were used in all the subsequent phase 1 PK characterization (Study GS-US-200-4538 and GS-US-200-5709) and phase 2/3 studies (Study GS-US-200-4625 and GS-US-200-4334) (**Figure 1** and **Table 2**). The suspension and other early formulations do not need to be bridge to the commercial formulation because they were not used in the pivotal clinical studies. The final PEG 300/water formulation shown in **Table 1** was used in the pivotal phase 2/3 clinical studies and is the same formulation as the proposed commercial drug product formulation. The manufacturing site of the clinical product batches is also the proposed commercial site. Thus, bridging between the drug product-formulations used in the pivotal clinical studies and the commercial drug product is not needed.

Figure 1: Clinical Development History of LEN Injection Formulations

(b) (4)



(ref. Figure 1 of 3.2.P.2.2 Drug Product)

Table 2: Clinical Development History of LEN Injection Formulations

(b) (4)

(ref. Table 1 of 3.2.P.2.2 Drug Product)

Extended-Release Claim:

The Applicant does not consider the formulation of the proposed drug product as an extended-release formulation because the drug product is manufactured as a clear solution and does not contain a polymer, nor other rate controlling membranes or excipients. However, it was unclear how the drug is released from the site of injection to achieve and maintain therapeutic levels over a six-month period. Therefore, a multi-disciplinary Information Request (IR dated October 12, 2021) was issued, requesting a detailed explanation of the mechanism of drug release in vivo.

In the Response (SN-15 dated October 26, 2021), the Applicant indicates that (b) (4)

Data submitted as part of the Applicant's Response support their hypothesis. Refer to Figures 1 and 2 below for supportive evidence from an in vitro experiment using simulated SC medium (**Figure 2**) and an in vivo rat MRI imaging study (**Figure 3**).

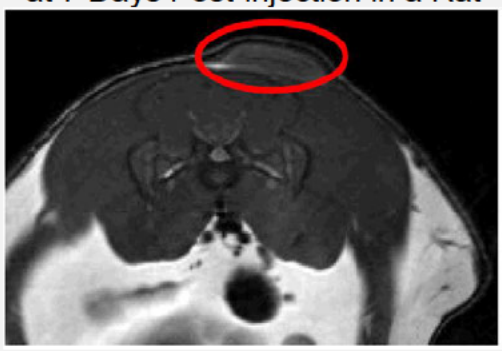
(b) (4)

Figure 2: (b) (4)

(b) (4)

(ref. Figure 1 of Response to the Information Request (SN-15))

Figure 3: Representative MRI Imaging of the SC Injection Site at 7 Days Post-injection in a Rat



(ref. Figure 3 of the Response to the Information Request (SN-15))

In addition, the Applicant claims that nonclinical as well as clinical PK studies showed that the rate of drug release/ PK profile is affected by (b) (4)

(b) (4) .

(b) (4) .

(b) (4)

(b) (4)

(b) (4)

(b) (4) The Applicant stated that the selected formulation of LEN sodium in PEG 300 and water for injection, at 309 mg/mL, (b) (4) release rate, and pharmacokinetic performance.

(b) (4)

It should be noted that the proposed drug product is precedent setting in the sense that the drug product is intended to provide therapeutic drug levels for 6 months after SC injection but there are no conventional quality controls in place to ensure that the drug release rate of the commercial drug product is consistent with the drug release rate of the clinically tested drug product. Conventional quality controls such as in vitro drug release testing, polymorphic form, particle size, and polymer content, do not apply to the proposed drug product because the proposed drug product is not a suspension, and it does not contain any release controlling polymers. Instead, the proposed drug product is a simple solution dosage form containing only the API (b) (4) in PEG 300 and water (b) (4), and the in vivo drug precipitation and subsequent drug release is determined by the inherent properties of LEN and the selected formulation.

Concurrence from both the Biopharmaceutics Branch Chief and Division Director were obtained to conclude that, although the drug product exhibits very slow drug release /long acting properties *in vivo*, from a Biopharmaceutics perspective, the proposed drug product formulation itself is not considered an extended release formulation, because the proposed drug product is a solution and its formulation does not contain a polymer or functional excipient that co-precipitates with the drug substance to control the in vivo extended release profile, nor is the release of the drug controlled by conventional quality standards, which is the case for other approved extended-release drug products; therefore, an extended release claim is not required for the proposed drug product formulation.

Dose Dumping:

If LEN is much more soluble in blood than in a neutral aqueous environment such as the subcutaneous environment, then dose dumping is a potential concern. Therefore, solubility data of LEN in blood were requested in the IR dated October

12, 2021. In the Response dated October 26, 2021, the Applicant stated that they are unable to provide the solubility data of LEN in blood due to the high lipophilicity of LEN and heterogeneous composition of serum. Therefore, the potential effect of the presence of blood at the injection site, on LEN release [redacted] (b) (4) is unknown. Furthermore, the Applicant was asked to provide evidence showing that intrinsic or extrinsic factors (external heat, pressure, exercise etc.) will not result in dose dumping. In response to the IR the Applicant stated that extrinsic factors possibly impacting drug release (external heat, pressure, exercise etc.) were not evaluated in the clinical or non-clinical studies. Therefore, the potential effect of external factors (applied heat, pressure, etc.) on LEN release [redacted] (b) (4) at the site of injection is unknown. The Applicant claims that there is no evidence of dose dumping based on the non-clinical and clinical PK studies. Refer to the Applicant's Responses (SN-15 dated October 26, 2021) for details; Defer to OCP and OND reviews for evaluation of lack of dose dumping in the non-clinical and clinical studies.

Note: *The in vivo drug release, lack of extended release claim, and potential dose dumping issues as described above have been discussed extensively within the OPQ review team and have been communicated to the OND review team.*

Conclusion and Recommendation:

Based on the Biopharmaceutics assessment of the provided information, the following is concluded:

In Vitro Drug Release Test: Since the proposed drug product is a solution formulated without any release controlling excipients and the in vivo drug release is expected to be determined by the intrinsic properties of the API and controlled by the *in-situ* environment at the site of injection after product's administration, the implementation of an in vitro drug release test (IVRT) for the proposed drug product is deemed not necessary.

Product's Bridging: Bridging is not needed because the pivotal clinical drug product is the same as the proposed to-be-marketed drug product.

Extended-Release Claim: The proposed drug product formulation is not extended release from a Biopharmaceutics perspective; considering that 1) the dosage form is solution; 2) the composition does not contain any release controlling excipients; 3) the long acting nature is not related to the drug product formulation; therefore, an extended-release claim is not required.

From a Biopharmaceutics perspective, NDA 215973, SUNLENCA™ (lenacapavir) injection, 463.5 mg/1.5 mL (309 mg/mL) for subcutaneous use, is recommended for approval.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	06/28/2021

Response to Information Request	10/26/2021

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

Qi Zhang

Digitally signed by Qi Zhang
Date: 12/20/2021 10:30:21PM
GUID: 547e178000007695c91eb10380b07939

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 12/21/2021 08:48:00PM
GUID: 50743ccc000031928b54eba1769a5df9

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID J CLAFFEY
01/12/2022 09:16:46 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215974
Assessment #1

Drug Product Name	Lenacapavir tablets
Dosage Form	
Strength	300 mg
Route of Administration	Oral
Rx/OTC Dispensed	
Applicant	Gilead
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD: 1, 7, 13, 18, 21, 22		

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Karina Zuck	Paresma Patel
Drug Product	Shalini Anand	David Claffey
Manufacturing	Abdollah Koolivand	Hang Guo
Microbiology	Jonathan Burgos	Paul Dexter
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	David Claffey	
Laboratory (OTR)		
Environmental	James Laurenson	

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Recommend approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

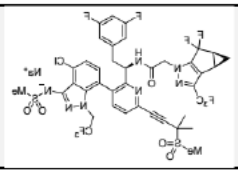
The drug product is 300 mg strength immediate release tablet proposed as the initial loading dose for lenacapavir injection – subject of the concurrent NDA 215974. During the drug product manufacturing process, (b) (4) [redacted] (b) (4)

Proposed Indication(s) including Intended Patient Population	Indicated as a loading dose for Lenacapavir injection which is subject of referenced NDA 215973.
Duration of Treatment	2 or 3 doses
Maximum Daily Dose	600 mg
Alternative Methods of Administration	

B. Quality Assessment Overview

Drug Substance: Adequate

Drug substance information was cross referenced to NDA 215973 which was found adequate by K Zuck on 18 NOV 2021.



Drug Product: Adequate

Lenacapavir tablet is an immediate-release dosage form containing 300 mg lenacapavir, present as 306.8 mg lenacapavir sodium. During manufacturing (b) (4) [redacted]

(b) (4)

The proposed commercial container closure system for the drug product consists of blister card with four tablets, fitted between two paperboard cards, (b) (4) . One 4-count blister card is packaged in a sealed (b) (4)-laminated pouch with 3 grams of silica gel desiccant.

For the clinical and primary stability batches, a 5-count blister pack configuration was developed to satisfy the dosing regimen of the clinical studies; with subsequent progression to 4-count blister configuration to support the simplified commercial dosing regimen (b) (4) are acceptable, and the stability data of 5-count blister pack was found suitable to support the shelf life of commercial 4-count blister configuration.

Stability results through 12 months long term and six months accelerated storage for three drug product batches packaged with 5-count blister packaging configuration, along with three months stability data for three drug product batches packaged with 4-count blister pack is provided. These data supported the proposed 24-month drug product expiry period.

(b) (4)

Labeling: Choose an item.

Not evaluated this review cycle

Manufacturing: Adequate

The drug product is an immediate-release tablet containing 306.8 mg LEN sodium. (b) (4)

(b) (4)

(b) (4)

. Applicant provided several development studies in support of proven acceptable ranges for the critical process parameters of tablet manufacturing.

During the application review, several deficiencies regarding the commercial batch size, manufacturing process, in process controls, shelf life stability, and yields were identified. Applicant response to process deficiencies (SD # 0012, dated 10/21/2021) adequately addressed the process concerns.

(b) (4)

(b) (4)

the shelf-life of the finished drug product is assigned based on the date of manufacturing of the finished drug product. For the assessment of finished product stability studies, see DP review IQA.

(b) (4)

the limited data provided in the current submission for tablets does not indicate a significant polymorphism risk. However, in the absence of adequate stability data for (b) (4), applicant was asked to include the physical form confirmation testing in the release and stability specifications for the finished drug product tablets (for more information see DP review IQA).

The facilities involved in the current submission are as follow:

- Gilead Alberta ULC, FEI: 3001027806: DS manufacture
- (b) (4) release/stability testing for DS/DP
- Gilead Sciences, Inc, FEI: 1000523075: release/stability testing for DS/DP
- (b) (4)
- (b) (4) DP manufacture
- (b) (4) DP packaging

All sites have experience with the proposed responsibilities and thus, no PAI was recommended for any of these facilities. All facilities currently remain compliant.

Biopharmaceutics: Adequate

The proposed dissolution method and acceptance criterion were determined to be adequate for the routine QC testing at batch release and during shelf-life/stability testing, based on the totality of the information and data provided. The proposed to-be-marketed LEN tablets 300 mg have the same formulation, image, manufacturing process and manufacturing site as the drug product used in the pivotal phase 2/3 Study GS-US-200-4625, and primary stability studies. Thus, bridging between the clinical formulations and commercial drug products is not needed.

D. List of Deficiencies for Complete Response

No deficiencies.

Comment for action letter: We note that in 3.2.P.3.4 you proposed to submit at least three months long term and accelerated stability data for a drug product batch (b) (4) . Note that this approach will require full justification and more stability data and batches may be required to support a postmarketing change of this type. We request that you acknowledge this in any subsequent NDA resubmission.

Application Technical Lead Name and Date: *David Claffey*

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CHAPTER VI: BIOPHARMACEUTICS

<table>
<tr><td>NDA Number/Type</td><td>215974; Type 1 (NME); Priority</td></tr>
<tr><td>Assessment Cycle</td><td>1</td></tr>
<tr><td>Drug Product</td><td>SUNLENCA™ (lenacapavir) tablets, for oral use</td></tr>
<tr><td>Dosage Form</td><td>Tablets: 300 mg (free base, equivalent to 306.8 mg of lenacapavir sodium)</td></tr>
<tr><td>Dosage and Administration</td><td>Recommended dosage – Initiation with one of two options followed by once every 6-months maintenance dosing.
<table>
<tr><td colspan="2">Initiation Option 1</td></tr>
<tr><td>Day 1</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections) and
600 mg orally (2 tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 tablets)</td></tr>
<tr><td colspan="2">Initiation Option 2</td></tr>
<tr><td>Day 1</td><td>600 mg orally (2 tablets)</td></tr>
<tr><td>Day 2</td><td>600 mg orally (2 tablets)</td></tr>
<tr><td>Day 8</td><td>300 mg orally (1 tablet)</td></tr>
<tr><td>Day 14</td><td>927 mg by subcutaneous injection (2 x 1.5 mL injections)</td></tr>
<tr><td colspan="2">Maintenance</td></tr>
<tr><td colspan="2">927 mg by subcutaneous injection (2 x 1.5 mL injections) 26 weeks after initial subcutaneous injection, then every 6 months (26 weeks) +/-2 weeks.</td></tr>
</table></td></tr>
<tr><td>Applicant</td><td>Gilead Sciences, Inc.</td></tr>
<tr><td>OND Division</td><td>OND/OID/DAV</td></tr>
<tr><td>Associated INDs</td><td>IND 136260, IND 138311</td></tr>
<tr><td>Proposed Indication</td><td>SUNLENCA, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.</td></tr>
<tr><td>Primary Reviewer</td><td>Qi Zhang, PhD</td></tr>
<tr><td>Secondary Reviewer</td><td>Elsbeth Chikhale, PhD</td></tr>
<tr><td>Assessment Recommendation</td><td>Adequate</td></tr>
</table>

Assessment Summary:

Lenacapavir (LEN) is an HIV-1 antiretroviral, new molecular entity (NME) developed under IND 136260 and IND 138311. NDA 215973 for LEN injection is also currently under review. Products in both NDA 215973 and NDA 215974 are proposed to be indicated together for the treatment of adults and pediatric patients with multidrug resistant HIV-1 infection. The clinical program in support of both

NDAs includes a pivotal phase 2/3 trial (Study GS-US-200-4625), one supportive phase 2 trial (Study GS-US-200-4334), and 2 phase 1 trials in healthy participants (Studies GS-US-200-4538 and GS-US-200-5709).

This Biopharmaceutics review is focused on (i) evaluation of the adequacy of the proposed dissolution method and acceptance criterion and (ii) bridging throughout product development.

- ***Dissolution Method and Acceptance Criterion***

The proposed LEN tablet 300 mg is formulated with [redacted] (b) (4) [redacted]. The proposed dissolution method and acceptance criterion (as tabulated below) are determined to be adequate for the routine QC testing of LEN 300 mg tablets at batch release and during shelf-life/stability testing, based on the totality of the information and data provided.

Acceptable Dissolution Method and Acceptance Criterion for SUNLENCA™ (lenacapavir) tablets, 300 mg				
Apparatus	*Speed*	*Medium*	*Volume/Temp*	*Acceptance Criterion*
USP Apparatus 2 (Paddle) with sinkers	75 rpm	30 mM potassium phosphate, pH 6.0 with 2.0% Cremophor EL	900 mL/37°C	Q= (b) (4) % in 30 minutes

Biopharmaceutics Risk Assessment				
CQAs	**Initial Risk Ranking**	**Comments**	**Updated Risk Ranking After Assessment**	**Comments**
Dissolution	Medium	BCS Class 4 drug; formulation contains (b) (4) [redacted] Tmax (4 h) is not critical. No clinically significant effects of food or antacid on LEN.	Low	Adequate dissolution specification

- ***Product Bridging***

The proposed to-be-marketed LEN tablets 300 mg have the same formulation, image, manufacturing process and manufacturing site as the drug product used in the pivotal phase 2/3 Study GS-US-200-4625, and primary stability studies. Thus,

bridging between the clinical formulations and commercial drug products is not needed.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	06/28/2021

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):
None.

Recommendation:
From a Biopharmaceutics perspective, NDA 215974 SUNLENCA™ (lenacapavir) tablets, 300 mg is recommended for **APPROVAL**.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required.*

The Applicant claimed that LEN is a BCS Class 4 drug. The provided data are consistent with the indicated BCS class as LEN exhibits low and pH dependent solubility, and low permeability based on the results of a Caco-2 cell permeability study and low absolute bioavailability (6.2% to 10%).

In vitro dissolution of LEN tablets is (b) (4) rapid in the proposed QC dissolution medium (with surfactant 2% Cremophor EL).

For oral LEN tablet doses 50 to 1800 mg, LEN exposure increased in a less than dose proportional manner with the median Tmax ranging from 4 and 8 hours, and the median t1/2 ranging from 10 to 13 days.

- ***Solubility***

The drug substance LEN sodium (GS-6207- (b) (4) is a weak acid (pKa 6.8) with a Log P being 5.1 (in octanol/water). The Applicant reported the intrinsic solubility of ≤ 0.1 µg/mL for (b) (4) LEN sodium (b) (4), from pH 1.2 to 6.8 at room temperature, and LEN exhibits pH-dependent solubility over the pH range of 2-12 with increasing solubility when the pH increases > 6.8 (above the pKa) (refer to Table 2 of Section 3.2.S.2.1).

(b) (4) The Applicant reported that the solubility of (b) (4) LEN sodium (b) (4), is < 0.1 mg/mL at pH range from 1.2 to 7.8 as well as in FaSSIF and FeSSIF at 37 ℃ (Table 1). The solubility of LEN (b) (4) increases in the presence of surfactant. (b) (4)

(b) (4)

Therefore, sink conditions (calculated to be >1 mg/mL [3x300 mg/900 mL]) can be anticipated and maintained during dissolution testing of LEN tablet 300 mg in 900 mL of the proposed dissolution medium.

Table 1. Solubility of (b) (4) LEN Sodium (b) (4) at 37 °C Across the Physiologically Relevant pH Range and in FeSSIF and FaSSIF Media

	Solubility (mg/mL)[a]	
pH (Media)	LEN Sodium	(b) (4)
1.2 (HCl)	< 0.1	
2.0 (HCl)	< 0.1	
4.5 (30 mM Acetate Buffer)	< 0.1	
6.0 (30mM Phosphate Buffer)	< 0.1	
6.8 (30mM Phosphate Buffer)	< 0.1	
7.8 (50mM Phosphate Buffer)	< 0.1	
FeSSIF (pH 5.0)[b]	< 0.1	
FaSSIF (pH 6.5)[c]	< 0.1	

Reference: Gilead Electronic Notebook 14547-81, 14545-79
a 24 hrs solubility
b FeSSIF contains 15 mM taurocholate and 3.75 mM lecithin in 144 mM acetate buffer
c FaSSIF contains 3 mM taurocholate and 0.75 mM lecithin in 29 mM phosphate buffer

Source: Table 3 of Report REP-22545

Table 2. Aqueous Solubility of (b) (4) LEN Sodium (b) (4) as a Function of Surfactant Type and Level Maintained at pH 6.0 (30 mM Phosphate) and 37 °C

	Solubility (mg/mL)		Sink Factor[a]	
Surfactant Concentration (% w/v)	(b) (4) LEN Sodium	(b) (4)	(b) (4) LEN Sodium	(b) (4)
No surfactant	< 0.1		< 0.1	
1.0% Cremophor EL	1.27		1.27	
1.5% Cremophor EL	1.56		1.56	
2.0% Cremophor EL[b]	1.75		1.75	
2.5% Cremophor EL	1.96		1.96	
1.0% SDS	0.41		0.41	
1.5% SDS	0.62		0.62	
2.0% SDS	0.82		0.82	
2.5% SDS	1.01		1.01	
1.0% Polysorbate 80	0.19		0.19	
1.5% Polysorbate 80	0.28		0.28	
2.0% Polysorbate 80	0.38		0.38	
2.5% Polysorbate 80	0.48		0.48	
0.5% CTAB	1.71		1.71	
1.0% CTAB	3.10		3.10	
1.5% CTAB	3.41		3.41	

Reference: Gilead Electronic Notebook 15187-10, 11, 14547-81, 14963-65
a Sink factor = [(Solubility, mg/mL) /(300 mg Label Claim / 900 mL Dissolution Medium Volume)]/3.
b Selected medium in the proposed dissolution method condition.

Source: Table 9 of Report REP-22545

➢ ***Permeability***

The absolute bioavailability following oral LEN administration is approximately 6.2% to 10%. In a Caco-2 cell permeability Study AD-200-2009, the bidirectional permeability of LEN at 1.0 µM showed low forward (absorptive) permeability of 0.3 x 10-6 cm/sec and high reverse permeability of 2.5 x 10-6 cm/sec through Caco-2 monolayers with an efflux ratio of 7.8. In a human mass balance Study GS-US-200-4329, 76% of the total radioactivity was recovered from feces and < 1% from urine after a single i.v. dose of radiolabeled-LEN to healthy participants, indicating that fecal elimination is the primary elimination route of LEN and its metabolites.

➢ ***Dissolution***

In 900 mL of buffer media without surfactant, NMT 5% of LEN dissolved within 60 minutes at pH 1.2, 2.0, 4.5, 6.0, 6.8, and FaSSIF, and FeSSIF media.

In 900 mL of buffer media with surfactant, dissolution of LEN tablets followed this rank-order: pH 7.8, pH 6.8 and pH 6.0> pH 4.5> pH 2.0 and pH 1.2.

In the proposed dissolution medium (pH 6.0 buffer with 2% Cremophor EL), LEN tablets exhibit rapid dissolution (85% dissolution at 30 minutes). Refer to Section B.2 below for details.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment*: Adequate*

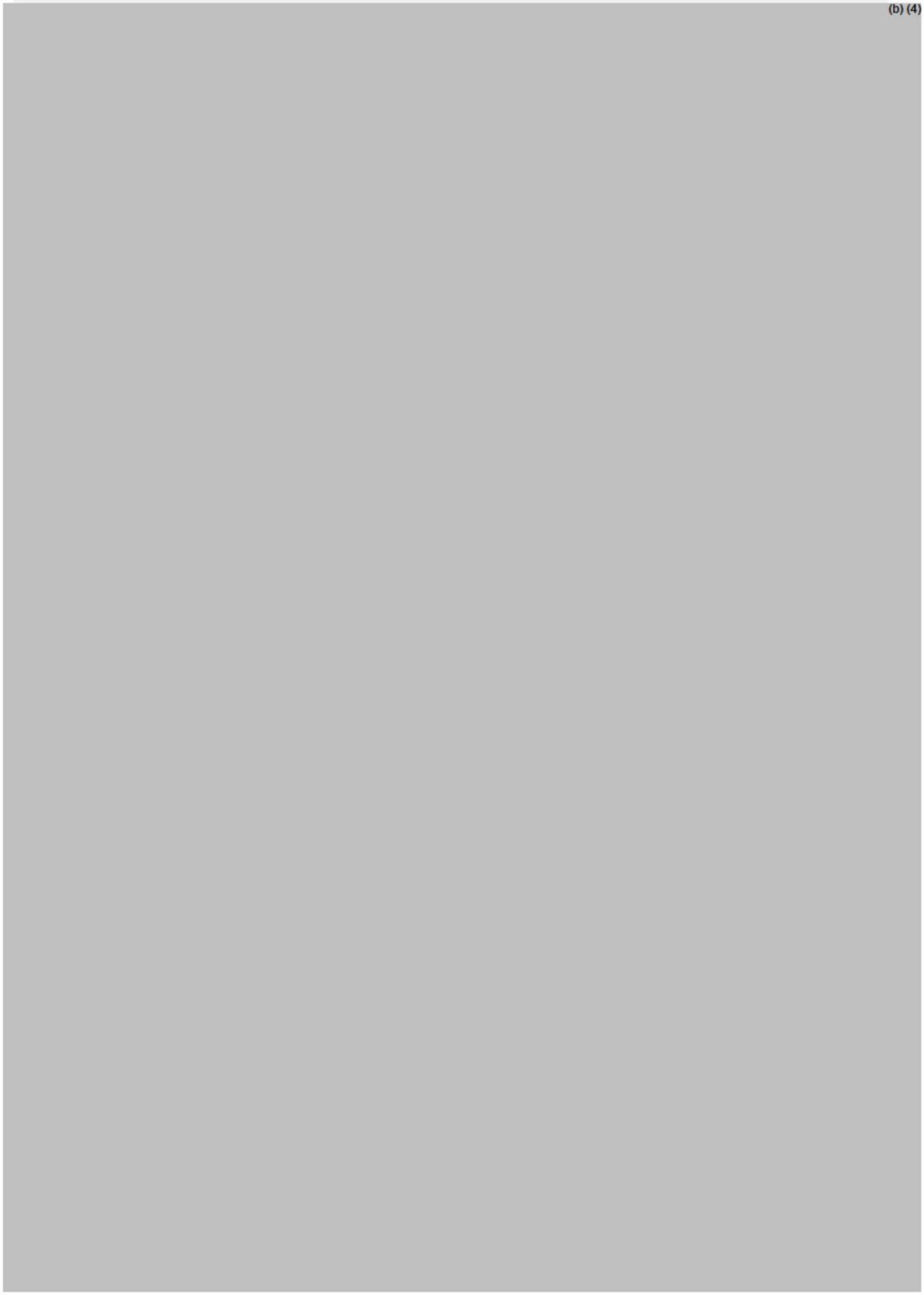
Table 3. Proposed Dissolution Method Parameters

Parameter	Setting
Apparatus	USP Dissolution Apparatus 2 (paddle method)
Volume	900 mL
Sinkers	CAPWHT-XLS
Paddle Speed	75 rpm
Medium pH	6.0
Medium temperature	37 °C
Buffer and Concentration	Potassium Phosphate, 30 mM
Surfactant and Concentration	Cremophor EL, 2.0% w/v

LEN tablets 300 mg are designed as an immediate-release solid oral dosage form and composed of (b) (4) . The acceptance criterion for dissolution of LEN from LEN tablets is Q of (b) (4) % at 30 minutes. The proposed dissolution method parameters (Table 3) are selected based on suitability for routine QC testing (complete and robust dissolution, and discriminating capability) for LEN tablets 300 mg. Refer to the Dissolution Method Development Report REP-22545 for detailed information, additional supporting figures and tables.

- ***Justification of Dissolution Method Parameters***

(b) (4)



(b) (4)

- ***Discriminating Ability of Dissolution Method***

(b) (4)

(b) (4)

The Applicant showed that the proposed method using a dissolution medium containing 2% Cremophor EL in pH 6.0 phosphate buffer exhibits discriminating ability towards changes in the critical manufacturing process for (b) (4) formulation variables that could potentially impact drug release and bioavailability of the proposed drug product.

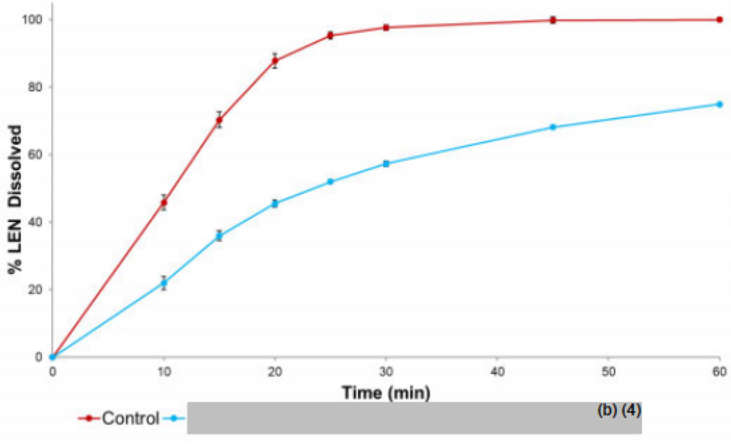
(b) (4)

(b) (4)

Tablet Disintegration

Tablet disintegration is a critical quality attribute for LEN tablets. Tablets manufactured with (b) (4) do not meet Q = (b) (4) % at 30 minutes as compared to the tablets made at the target level ((b) (4) w/w) of the (b) (4) (Figure 5).

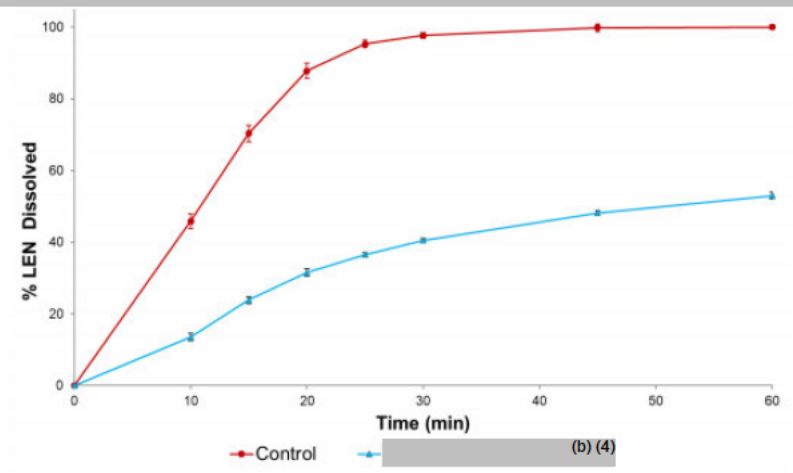
Figure 3. Dissolution of LEN Tablets Manufactured with (b) (4)



Dissolution conditions: USP apparatus 2, 30 mM phosphate buffer pH 6.0 with 2.0% w/v Cremophor EL, 900 mL media, 75 rpm, 37 °C, n = 6

Source: Figure 1 of Section 3.2.P.5.6

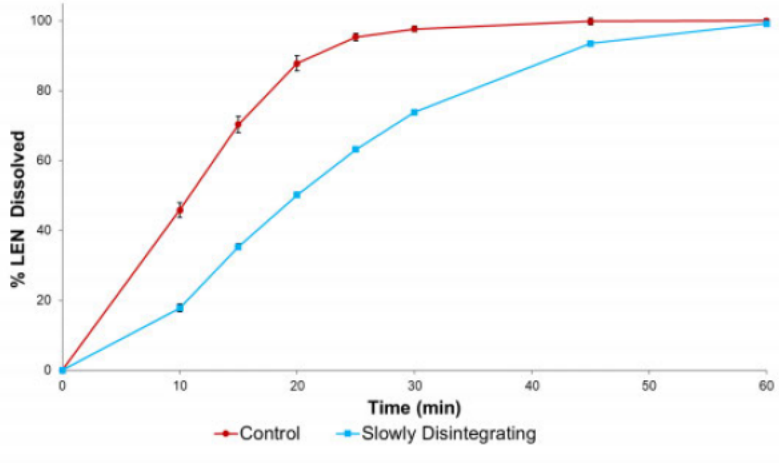
Figure 4. Dissolution of LEN Tablets Manufactured with (b) (4)



Dissolution conditions: USP apparatus 2, 30 mM phosphate buffer pH 6.0 with 2.0% w/v Cremophor EL, 900 mL media, 75 rpm, 37 °C, n = 6

Source: Figure 2 of Section 3.2.P.5.6

Figure 5. Dissolution of Control Tablets (containing (b) (4)) and Slowly Disintegrating Tablets (containing (b) (4))



Dissolution condition: USP apparatus 2, 30 mM phosphate buffer pH 6.0 with 2.0% w/v Cremophor EL, 900 mL media, 75 rpm, 37 °C, n = 6

Source: Figure 3 of Section 3.2.P.5.6

The proposed method was unable to discriminate against tablet manufacturing process variations. As shown in Figure 22 of Report REP-22545, combinations of three process variables ((b) (4)) had no impact on dissolution of LEN tablets.

In addition, there is a potential for (b) (4) during the product manufacturing process or during stability studies. The Applicant did not provide dissolution profiles to show the impact of (b) (4) on

dissolution. The limitation of the dissolution test is acknowledged and does not preclude approval of the proposed dissolution method that was demonstrated to possess sufficient discriminating power for critical bioavailability attributes as discussed above. The evaluation of the adequacy of the control of (b) (4) is deferred to the Drug Product and Process Reviewers.

- ***Validation of Dissolution Method***

An UPLC assay method is used to quantify the drug in the dissolution samples. The Applicant reported that the UPLC method was validated regarding system suitability, linearity, specificity, accuracy, repeatability, precision, (b) (4) solution stability, and robustness with respect to UPLC system changes and dissolution method parameters (b) (4)

Refer to the Drug Product Review, for the evaluation of the adequacy of the analytical method validation (UPLC method used for dissolution sample analysis).

- ***Dissolution Acceptance Criterion***

Based on the dissolution profiles from clinical and registration stability batches (Figure 6; summary of the batch information provided in Table 4), the proposed dissolution acceptance criterion of Q =(b) (4)% at 30 minutes is justified and found acceptable. In addition, the time point and acceptance criterion can discriminate against aberrant tablets with variations to critical manufacturing process with respect to (b) (4) formulation composition that impact the dissolution of the active ingredient.

Table 4. Drug Product Batch Information

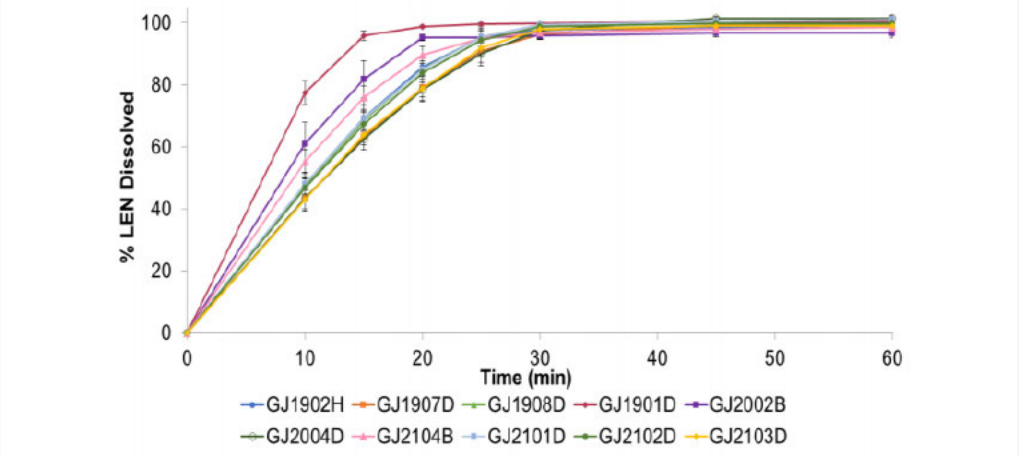
Lot No.	Manufacturer	Date of Manufacture[a]	Batch Size (kg)[b]	Purpose
GJ1901D	(b) (4)	May 2019	18	Clinical
GJ1902H		September 2019	33	Clinical, stability
GJ1907D		November 2019	30	Clinical, stability
GJ1908D		November 2019	30	Clinical, stability
GJ2002B		September 2020	7.8	Clinical, stability
GJ2004D		November 2020	30	Clinical, stability
GJ2101D		February 2021	30	Clinical, stability
GJ2102D		February 2021	30	Clinical, stability
GJ2103D		February 2021	30	Clinical, stability
GJ2104B		February 2021	7.9	Stability

(b) (4)

b Theoretical batch size (b) (4)

Source: Table 1 of Section 3.2.P.5.4

Figure 6. Dissolution Profiles of Clinical and Stability Batches of LEN Tablets



Medium: 30 mM phosphate buffer pH 6.0 with 2.0% w/v Cremophor EL, 900 mL media, 75 rpm USP Type II apparatus, 37 °C
All batches tested with n = 12. Reference: Gilead Electronic Notebook 15187-29

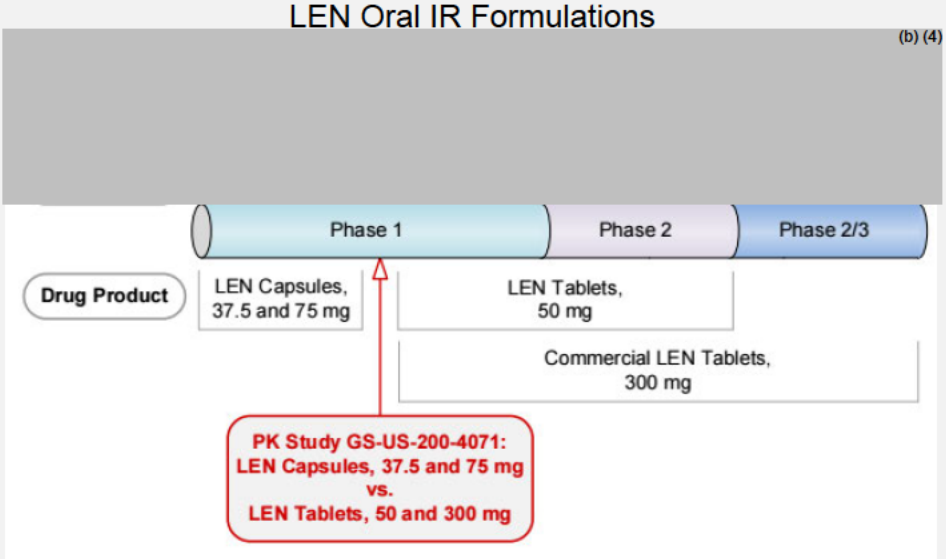
Source: Figure 4 of Section 3.2.P.5.6

B.1 PRODUCT BRIDGING

Assessment: Adequate

Two oral IR formulations of LEN (capsule and tablet) were developed during clinical development (Figure 7; a list of drug products throughout the product development for clinical trials presented in Table 1 Section 3.2.P.2.2.).

Figure 7. Drug Substances and Drug Products Used in Clinical Development of LEN Oral IR Formulations



Source: Figure 1 Section 3.2.P.2.2

The initial formulation was a capsule containing (b) (4) (b) (4) (LEN capsule 37.5 mg and 75 mg). During the Phase 1 clinical trials, (b) (4)

(b) (4)

remained unchanged for the phase 2 and phase 2/3 clinical studies. As shown in Table 5, the phase 1 PK Study GS-US-200-4071, the LEN tablet formulation containing (b) (4) achieved 3- or 6- fold higher exposure than LEN capsules (8 × 37.5 mg or 4 × 75 mg).

Table 5. Plasma PK Parameters of LEN Following Oral Administration of a Single 300 mg Dose of LEN Capsules and LEN Tablets (N = 8 per cohort)

300 mg Dose	Regimen	PK Parameter Mean (%CV)			
		AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$t_{1/2}$ (h)[a] [days]
LEN Capsule	8 × 37.5 mg	2296.0 (51.3)	4.8 (52.4)	6.99 (4.00, 28.00)	318.21 (292.62, 346.16) [13.3]
LEN Capsule	4 × 75 mg	1211.9 (33.3)	2.3 (31.9)	6.00 (4.00, 27.00)	363.18 (303.61, 378.65) [15.1]
LEN Tablet	1 × 300 mg	7692.1 (57.8)	33.7 (96.3)	4.00 (4.00, 6.00)	242.64 (204.37, 281.36) [10.1]

a Median (Q1, Q3)

Source: Table 12 of Section 3.2.P.2.2

The phase 2/3 studies were conducted using the proposed commercial (to be marketed) tablets. All phase 2/3 batches were manufactured at (b) (4), the drug product manufacturing facility where the commercial tablets will be manufactured. Therefore, no additional information is needed to bridge the clinical and commercial drug products.

Qi Zhang

Digitally signed by Qi Zhang
Date: 11/30/2021 10:56:17AM
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Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 11/30/2021 02:32:41PM
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