

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215973Orig1s000

215974Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



FDA U.S. FOOD & DRUG
ADMINISTRATION

IND 136260
IND 138311

**MEETING REQUEST-
WRITTEN RESPONSES**

Gilead Sciences, Inc.
Attention: Grace Gill, PharmD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Gill:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lenacapavir GS-6207.

We also refer to your March 25, 2021, correspondence, received March 25, 2021, requesting a meeting to share and discuss Phase 2/3 clinical data in people with HIV-1 (PWH) (comprising of data from GS-US-200-4625 and GS-US-200-4334) in advance of the NDA filing. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

Further reference is made to our Meeting Granted letter dated April 6, 2021, where we determined that written responses to your questions would be the most appropriate means for responding to the meeting request

The enclosed document constitutes our written responses to the questions contained in your April 29, 2021 background package.

If you have any questions, call me at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD; BCPS AQ-ID
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious
Diseases
Office of Infectious Diseases

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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Center for Drug Evaluation and Research

Enclosure:

- Written Responses

APPEARS THIS WAY ON ORIGINAL

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WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Breakthrough Therapy-Other

Application Number: 136260
138311

Product Name: GS-6207

Indication: Treatment for heavily treatment-experienced patients with multi-drug resistant HIV-1 infection

Sponsor/Applicant Name: Gilead Sciences, Inc

Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Gilead Sciences, Inc has developed lenacapavir, a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid for the treatment of HIV-1 infection. Lenacapavir inhibits the proper assembly of mature capsid protein in extracellular HIV-1 particles in the late stage of HIV-1 replication cycle and at the same time also reduces virus production through specific binding interactions with the capsid domain of intracellular p24 and gag/gag-pol precursor proteins in the early stage of HIV-1 replication. Lenacapavir is currently being developed by Gilead for the treatment of HIV-1 infection, including for heavily treatment-experienced (HTE) adults. Gilead is currently evaluating two dosage forms of LEN, solution for injection (IND 136260) and oral tablets (IND 138311), which are intended to be used in conjunction. Lenacapavir was granted Fast Track Designation for both dosage forms on March 23, 2018 (IND 136260) and September 19, 2018 (IND 138311) respectively. Lenacapavir was also granted Breakthrough Therapy Designation for the treatment of HIV-1 in HTE patients with multi-drug resistance (MDR) on May 30, 2019.

On March 25, 2021, Gilead submitted a Type B meeting written responses only request to share topline data from their Phase 2/3 clinical data in people with HIV-1 (PWH) (comprising of data from GS-US-200-4625 and GS-US-200-4334) in advance of the planned NDA filing. The Agency granted the request on April 6, 2021 and Gilead submitted a meeting package on April 29, 2021.

QUESTIONS AND RESPONSES

DISCUSSION

Question 1: Does the Agency agree that the top line data summary from Studies GS-US-200-4625 and GS-US-200-4334 support the proposed indication for LEN?

FDA Response to Question 1: We agree that the preliminary data from Studies GS-US-200-4625 and GS-US-200-4334 are appropriate to submit to support your proposed initial NDAs. The language of the proposed indication and proposed patient population will be a review issue. In the initial NDA submission, please include a rationale or further discussion for the following:

- a) Imbalance of baseline HIV-1 RNA and CD4 categories between treatment arms in the functional monotherapy cohort of study GS-US-200-4625. We note that planned subgroup analyses include these two baseline factors. Please also discuss the impact of baseline imbalance on the efficacy outcomes.
- b) Adequacy of the durability of response with LEN based on Week 26 results, including the lack of a concurrent comparator for this portion of the study and complete resistance information for LEN after the functional monotherapy period.
- c) Discussion of the following potential AEs of special interest: injection site reactions and creatine kinase (CK) elevations/rhabdomyolysis.
- d) (b) (4)
- e) Representation of baseline resistance and prior ARV regimen to support the proposed indication of treatment for "multidrug-resistant HIV-1 infection".

In addition, please ensure the responses and additional comments provided in our Pre-NDA Preliminary Meeting Comments (sent January 13, 2021) are adequately addressed in the NDA submissions.

ADDITIONAL COMMENTS:

Clinical Pharmacology:

We recommend submitting the following summary documents and supporting datasets to the NDA.

1. Please provide a summary of in vitro ADME and in vivo PK studies using the attached table template and submit as a MS Word document file (.doc or .docx).
2. Please submit all pharmacokinetic (PK) and/or pharmacodynamic (PD) bioanalytical method validation reports and bioanalytical study reports for PK and/or PD assessments used in clinical studies. In addition, we recommend you submit tables summarizing the bioanalytical methods and the life-cycle

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information using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document (<https://go.usa.gov/xVsdJ>) and submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

Attachment: Clinical Pharmacology In Vitro and In Vivo Study Table Template

In Vitro ADME Studies

Report Title	
Study Type	
Test Drug(s) and concentrations	
Positive control(s) and concentrations	
Negative control(s) and concentrations	
Report Number (with hyperlink to the full report)	
Study System (for example whole blood, plasma, recombinant enzymes, transfected cells, cryopreserved hepatocytes etc)	
Method	Note: Include a very brief description of the methods. For drug interaction studies, please use cutoff criteria recommended in FDA drug interaction guidance.
Results	Note: Include a brief description of the major findings of the study. Also include the results of the
Discussion/Conclusion	Provide a succinct discussion of the results and their clinical relevance. Please indicate if a follow up in vivo trial was conducted to confirm the in vitro findings. If yes, please include the hyperlink to the complete study report. If not, please indicate why a follow up in vivo trial was not conducted.

In vivo PK Studies

Location	Study # with hyperlink

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Title	
Brief Description of Trial Design	
PK sample collection times	
Results	For each analyte, please include a table with PK parameters (for example, AUC, C _{max} , C _{trough} (if applicable), t _{1/2}). For each comparison of PK parameters between groups, include a table of statistical comparisons (if applicable) of the PK parameters, including (GLSMs, GLSM ratio, 90%

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

SECURE EMAIL COMMUNICATIONS

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Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

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/

ANDREW A GENTLES
05/25/2021 10:17:36 AM



IND 136260
IND 138311

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Grace Gill, PharmD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Gill:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lenacapavir (GS-6207).

We also refer to your November 16, 2020, correspondence, received November 16, 2020, requesting a meeting to discuss the plan for submission of two NDAs for LEN (injection and oral tablets) in July 2021 and obtain FDA agreement on key aspects related to content and format of the NDAs, and obtain feedback on anticipated activities to occur during application review, including the proposed content of the NDA safety update.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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If you have any questions, call me at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious
Diseases
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments



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PRELIMINARY MEETING COMMENTS

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: January 22, 2021
2:00 PM - 3:30 PM, EST

Meeting Location: TCON

Application Number: 136260
138311

Product Name: Lenacapavir (GS-6207)

Indication: Treatment of HIV in Heavily Treatment-Experienced (HTE) adults

Sponsor/Applicant Name: Gilead Sciences, Inc

FDA ATTENDEES

John Farley, MD, MPH, Director, Office of Infectious Diseases
Debra Birnkrant, MD, Director, Division of Antivirals (DAV)
Jeffrey Murray, MD, MPH, Deputy Director, DAV
Poonam Mishra, MD, Deputy Director for Safety, DAV
Sarah Connelly, MD, Clinical Team Lead, DAV
Benjamin Lorenz, MD, Clinical Reviewer, DAV
Hanan Ghantous, PhD, DABT, Director, Division of Pharmacology/Toxicology for Infectious Diseases (DPT-ID)
Deacqunita Diggs, PhD, Pharmacology/Toxicology reviewer, DPT-ID
Karen Winestock, Chief Project Management Staff, Division of Regulatory Operations for Infectious Diseases, DROID
Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, DROID
Julian O'Rear, PhD, Lead Clinical Virology, DAV
Lisa Naeger, PhD, Virology Reviewer, DAV
Vikram Arya, PhD, Clinical Pharmacology Team Lead, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Infectious Disease Pharmacology (DIDP)
Jenny Zheng, PhD, Pharmacology Reviewer, OTS/OCP/DIDP
Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)

Hengrui Sun, PhD, Biometrics Reviewer, DBIV
Erika Englund, PhD, Acting CMC Team Lead, OPQ

SPONSOR ATTENDEES

Diana Brainard, MD (Senior Vice President, Virology Clinical Research)
Moupali Das, MD, MPH (Executive Director, Virology Clinical Research)
Lijie Zhong, PhD (Executive Director, Biostatistics)
Jan de Jong, PhD (Senior Director, Clinical Pharmacology)
Anne Chester, PhD, DABT (Executive Director, Nonclinical Safety and Pathobiology)
Anna Chiu, PhD (Senior Director, Process Development)
Mae J. Lai, BS (Executive Director, Regulatory Affairs)
Garland Lee, PharmD (Senior Manager, Regulatory Affairs)
Kate Lawrence, PhD (Manager, Regulatory Affairs)

Introduction

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 22, 2021 between Gilead Sciences, Inc and the Division of Antivirals. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gilead Sciences, Inc has developed lenacapavir, a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid for the treatment of HIV-1 infection. Lenacapavir inhibits the proper assembly of mature capsid protein in extracellular HIV-1 particles in the late stage of HIV-1 replication cycle and at the same time also reduces virus production through specific binding interactions with the capsid domain of intracellular

p24 and gag/gag-pol precursor proteins in the early stage of HIV-1 replication. Lenacapavir is currently being developed by Gilead for the treatment of HIV-1 infection, including for heavily treatment-experienced (HTE) adults. Gilead is currently evaluating two dosage forms of LEN, solution for injection (IND 136260) and oral tablets (IND 138311), which are intended to be used in conjunction. Lenacapavir was granted Fast Track Designation for both dosage forms on March 23, 2018 (IND 136260) and September 19, 2018 (IND 138311) respectively. Lenacapavir was also granted Breakthrough Therapy Designation for the treatment of HIV-1 in HTE patients with multi-drug resistance (MDR) on May 30, 2019. The LEN Phase 2/3 development program and proposed registration plan to support an indication for treatment of HIV-1 infection in HTE people with HIV-1 (PWH) with MDR was discussed at a Type B meeting held with the Agency and Gilead on August 6, 2019. On November 16, 2020, Gilead submitted a meeting request for a Type B, Pre-NDA meeting to discuss the plan for submission of two NDAs for LEN (injection and oral tablets) in July 2021 and obtain FDA agreement on key aspects related to content and format of the NDAs, and obtain feedback on anticipated activities to occur during application review, including the proposed content of the NDA safety update. The Agency granted the request on December 2, 2020 and Gilead submitted a meeting package on December 21, 2020.

DISCUSSION

Question 1: Submission Strategy Questions-Clinical/Safety

- (a) Does the Agency agree that the proposed indication for LEN is supported by the clinical studies described in Table 1?
- (b) Does the Agency agree that the proposed safety database is adequate and appropriate to support initial registration of LEN for the treatment of HIV-1 infection in HTE PWH?

FDA Response to Question 1: We agree that the clinical studies described in Table 1 and the proposed safety database are appropriate to submit initial NDAs. The language of the proposed indication and proposed patient population will be a review issue. In the initial NDA submission, please include a rationale, with supporting data, for (b) (4)

Question 2: Does the Agency agree that the absence of acute hypersensitivity reactions or other safety issues to date merit simplification, in the initial NDA, of LEN initiation from a 2-week oral lead-in to oral loading on Day 1 and Day 2 with an injection administered on Day 1, given the potential convenience benefit to patients of dosing simplicity?

FDA Response to Question 2: The acceptability of the LEN dosing regimen is contingent upon the availability of adequate PK, safety and efficacy data and will be a

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review issue. In order for us to continue our assessment of the feasibility of the proposed simplified regimen, please address the following when pertinent information becomes available:

- 1) Provide a comparison of the simulated concentration-time profile and PK parameters (indicate whether the parameter is based on observed data or simulated data) of LEN after administration of the regimen proposed for commercialization (Days 1 and 2: 2 × 300 mg oral LEN once daily; Day 8: 300 mg oral LEN once daily; Day 15 and every 6 months thereafter: 2 × 1.5 mL of 309 mg/mL LEN S.C. injection) and the proposed simplified regimen (Day 1: 2 × 1.5 mL LEN S.C. injection + 2 × 300 mg oral LEN once; Day 2: 2 × 300 mg oral LEN once, and 2 × 1.5 mL of 309 mg/mL LEN S.C. injection starting at month 6 and every 6 months thereafter). Further, once the observed PK data from trial GS-US-200-5709, Cohort 2 become available, please revise the aforementioned PK profile comparison by overlaying the observed PK data after administration of the simplified regimen and submit the revised PK profile comparison and updated PK parameters table.
- 2) If the results of the simulations (as requested in point #1) suggest higher exposures with the proposed simplified regimen as compared with the regimen proposed for commercialization, please provide adequate safety data to support these higher exposures with the simplified regimen.
- 3) Please indicate how much observed PK data of LEN will be available from trial GS-US-200-5709 Cohort 2 beyond Week 2 to help with comparison of the LEN PK profile after administration of the regimen proposed for commercialization and the simplified regimen.
- 4) The current drug-drug interaction assessment of LEN (as a perpetrator and a victim) is based on the concentrations expected with the LEN regimen proposed for commercialization. Please comment on whether the same assessment applies to the simplified regimen if the results of the simulations suggest higher exposures with the proposed simplified regimen as compared with the regimen proposed for commercialization.

NDA Structure and Content Questions

Question 3:

- (a) Does the Agency agree with the proposed NDA Table of Contents for the lenacapavir injection NDA and the lenacapavir oral tablet NDA?
- (b) Does the Agency agree with the proposed approach to cross-referencing for Modules 1 - 5?

FDA Response to Question 3:

In general, we agree with the proposed NDA Table of Contents and approach to cross-referencing.

Please submit a study report describing EC₅₀ values determined for GS-6207 inhibition for both the early and late stage replication steps. In the study report on assessment of GS-6207 resistant variants, please include assessments of cross-resistance to other ARVs.

We acknowledge the 1/6/2021 IND amendment describing the change in the proposed commercial strength from the 7/24/2020 to the 12/21/2020 meeting package from 300 mg/mL to 309 mg/mL. In the NDA submission, include a detailed description of the change in calculated strength.

Question 4: Does the Agency agree that the proposed USPI plan for LEN injection and LEN oral tablets is appropriate?

FDA Response to Question 4:

We agree that having a single USPI for both dosage forms could be appropriate.

Question 5: Does the Agency agree with the proposal for provision of the documentation in Modules 1 and 5 described below and in Table 2? For the purposes of financial disclosures and BIMO documentation, does the Agency agree that only Studies GS-US-200-4625 and GS-US-200-4334 are considered covered studies?

FDA Response to Question 5:

We agree. However, if you plan to propose the simplified regimen, Study 5709 should also be considered as a covered study.

We agree with your proposal regarding the BIMO Items in Table 2.

Question 6: Does the Agency agree with this proposal for provision of referenced documents?

FDA Response to Question 6:

We agree that it is not necessary to submit referenced guidelines and other similar documents within the application. Hyperlinked URLs for any such references, however, would be helpful to facilitate the review process. The prescribing information should be included in both NDA submissions.

Non-Clinical Questions

Question 7:

(a)  (b) (4)

(b) [REDACTED] (b) (4)

FDA Response to Question 7: We do not agree. The transgenic mouse study and SEND datasets should be submitted once they are finalized either with the NDA or after approval similar to the 2-years rat carcinogenicity study.

Statistical Questions

Question 8: Does the Agency agree with the proposed analysis strategy for the Clinical and Safety data evaluation across these studies?

FDA Response to Question 8:

We agree with the proposed efficacy evaluation for the Studies 4625 and 4334. Given the difference in study populations (heavily treatment-experienced versus treatment-naïve), we agree that no pooled safety analysis will be done with these patient populations. We also agree with an integrated safety analysis of Studies 4538 and 5709 since these studies were both conducted in people without HIV-1.

Question 9: Does the Agency agree with the provision of study narratives and CRFs as described above?

FDA Response to Question 9:

We agree. Please also provide narratives and CRFs for any Snapshot failures in Studies 4625 and 4334.

Question 10:

(a) Does the Agency agree with the scope of datasets to be submitted to the LEN NDA?

(b) Does the Agency agree with the proposed list and naming of variables provided in Attachment 8 and Attachment 9?

FDA Response to Question 10:

We agree with the scope of datasets to be submitted to the LEN NDA.

Attachment 8

We agree with the proposed list and naming of variables in Attachment 8.

Attachment 9

The general time structure of the proposed ADEG and ADPC datasets appear to differ from the intended proposal in the Technical Specifications Document (TSD) for QT studies. Specifically, for a parallel study with a nested cross-over the TSD recommends

using ANL01FL and ANL02FL to flag the data from the parallel and cross-over parts, respectively. This way, the general structure for QT data would be uniform regardless of the design being a cross-over, parallel or parallel with nested cross-over. We refer the sponsor to Table 9 in the appendix of the TSD (page 22) or the SBIA Webinar (<https://www.fda.gov/drugs/news-events-human-drugs/technical-specifications-submitting-dataqt-studies-webinar-nov-8-2019-11082019>, starting slide 24). This appendix and referenced slides discuss this specific design and provide additional information on how to encode data from such a design following the QT TSD. We also have the following comments and responses to the included clarifying questions, which are provided by column or grouped as appropriate:

- TRTSEQP: The suggestion of representing placebo either as “PTM MOXI” or “PLACEBO” in this column is reasonable.
- AVISIT/AVISITN: It is acceptable to drop these two columns.
- APERIOD/APERDAY: These columns are not consistent with the QT TSD, see above for additional details and slides 25 and 33 in the presentation referenced above.
- NRRLT: This column is a required column because it is a reserved column to represent the nominal time relative to ATPTREF using RRLTU units, whereas ATPTN is not required to represent nominal time.
- ATPTREF: This column appears to be derived differently for ADEG and ADPC, which is acceptable. However, the ATPTREF column values for ADEG and ADPC must be consistent to allow joining of the datasets.
- APERDAYC, NRRLTC: These columns were missing and should be added.
- PARAMCD: We recommend that you consider a PARAMCD value such as INTP instead of INTPSG, because the contents of this column must not exceed 4 characters. More detailed information can be included in the PARAM column. The 4 character limit is imposed to allow for construction of analysis-ready datasets to support analysis such as concentration-QTc where the dataset will be transposed and a limit of 4 characters is required to not exceed 8 character column names.
- PARAM: This column should not include the units (AVALU) and we recommend considering omitting “, Single beat” for ADEG.
- EGREFID: This is a required column for ADEG and allows for locating the associated ECG Waveform. Please include this column in your ADEG dataset. Please also note the additional comments below for information about ECG waveform submission updates.
- BASETYPE: The definition of this column suggests that the baseline will be the same for the parallel and cross-over part of the study as the key is defined as “Baseline at day x hr”. We recommend considering redefining to identify if associated baseline is from the parallel or nested crossover part.

In addition, we also have the following comments for you to consider:

- To support the use of QTcI, the datasets included with the study report should include the individual subject parameters for QT correction as well as the source data used to derive the individual QT correction unless the source data is already included in ADEG.
- When you submit your QT evaluation report, please include a completed version of the most recent “QT Evaluation Report Submission Checklist” located at the IRT website (<https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt>).
 - o FDA expects that by March 2021, ECG waveforms submitted to the agency to support the QT assessment will be received via the Electronic Submissions Gateway. Before March 2021, ECG waveforms should be submitted to the FDA ECG Warehouse (www.ecgwarehouse.com) and can be submitted additionally through the Electronic Submissions Gateway on a voluntary basis.

Virology Questions

Question 11: Does the Agency agree with the proposal for provision of virology data and datasets?

FDA Response to Question 11:

The proposal for submitting virology resistance reports and datasets is acceptable. We are requesting NGS datasets be submitted.

In the resistance dataset, variables and column headings should be included to be able to determine:

- what the failing regimen is
- resistance to the failing regimen (genotype/phenotype of failing drugs)
- prior genotypic and phenotypic resistance (including historical data)
- number of agents and classes that subject is resistant to (both at study entry and historically)
- what the new OBT regimen is
- Also, must identify agents that are intolerable or contraindicated for each subject in the dataset.

Please identify the dataset, column headings and variable names that can be used to determine the above information for the reviewer.

Regulatory Review Questions

Question 12: Does the Agency agree that the currently available safety information for LEN does not warrant inclusion of a REMS?

FDA Response to Question 12: At this time, the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) have insufficient information to conclusively determine whether a REMS will be necessary. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Question 13: Does the Agency agree with the provision of topline data from the secondary efficacy endpoint (26 weeks after initial SC injection) and safety data from Study GS-US-200-4625, and a summary of efficacy and safety data from GS-US-200-4334, in June 2021 (NDA submission anticipated to occur in July 2021)?

FDA Response to Question 13:

We agree. Unless there are specific questions related to the topline results (e.g., unexpectedly discordant results or unanticipated safety issue), an additional Type B meeting may not be needed.

Question 14: Given the Breakthrough Therapy designation for LEN, does the Agency anticipate an expedited review of the LEN marketing applications?

FDA Response to Question 14: As long as the clinical data continue to support the potential for LEN to meet the unmet medical need in HTE patients with limited treatment options, the Agency anticipates an expedited review of the NDAs for this indication.

Question 15: Does the Agency agree with the proposed list of studies and cutoff date for additional safety data to be included with the required NDA Safety Update?

FDA Response to Question 15: We agree.

Question 16: Based on the nonclinical and clinical data provided to IND 136260 and IND 138311, does the Agency anticipate that the NDAs for LEN for the treatment of HIV-1 infection in HTE PWH will be the subject of an FDA Advisory Committee Meeting?

FDA Response to Question 16:

Based on the available data, we currently do not anticipate an Advisory Committee Meeting. We will revisit this issue pending availability of topline data, including safety and secondary efficacy endpoint of Study 4625 (26 weeks after initial SC injection).

Additional Comments

Clinical Pharmacology:

Please use quantitative methodologies to address the following scenarios and include the assessment in the NDA submission:

- 1) *Adherence to Injection Schedule:* Please propose a time window ($\pm$ days) within which S.C. administration is not expected to significantly alter the safety or efficacy of LEN relative to when LEN is administered exactly once every 6 months.
- 2) *Missed Injections:* Please assess the impact of missed S.C. injections on the efficacy of LEN. Of note, in case of the proposed simplified regimen, if a patient fails to return to a healthcare facility to receive an injection at month 6, the patient will likely not receive a LEN S.C. dose until approximately a year following the first two days of LEN dosing.
- 3) *Need for another lead in phase:* In case a patient misses the 6-month S.C. dosing, please assess the time since the last injection beyond which the lead in phase would need to be reinitiated.
- 4) *Effect of residual LEN concentrations on the PK of other drugs:* In case a patient decides to discontinue LEN dosing, please assess the potential of residual LEN concentrations on the PK of other drugs, risk of the emergence of resistance, and the potential for other drugs to affect LEN.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 2, 2020 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of

any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.¹

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

Information² and Pregnancy and Lactation Labeling Final Rule³ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/

ANDREW A GENTLES
01/13/2021 04:53:47 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	136260
Request Receipt Date	April 3, 2019
Product	GS-6207 (subcutaneous injection)
Indication	Treatment of HIV-1 infection in the heavily treatment experienced patient population
Drug Class/Mechanism of Action	Selective inhibitor of HIV-1 capsid function
Sponsor	Gilead Sciences, Inc.
ODE/Division	OND/DAVP
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	May 9, 2019 - Internal June 2, 2019 (Sunday)

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

GS-6207 (subcutaneous injection) has requested Breakthrough Therapy designation for the treatment of HIV-1 infection in the heavily treatment experienced patient population.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

YES NO

3. Was the BTDR submitted to a PIND?

YES NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

YES NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- Undetermined
- NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b: N/A

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks CD4⁺ cells and thereby weakens the immune system. Infection with HIV-1 results in chronic, progressive depletion of T-lymphocytes*

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

(CD4+ or helper T-cells) and also affects macrophages and other cells important for immune surveillance. If left untreated or suboptimally treated, HIV infection is characterized by immune destruction with subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death..

- In the U.S., 1.1 million people were living with HIV at the end of 2015, and 38,739 people were newly diagnosed with HIV in 2017 (Centers for Disease Control and Prevention 2019).
- The goals of HIV treatment are to durably suppress HIV viral load, preserve and restore the immune system, reduce HIV-associated morbidity, and ultimately improve long-term survival. Effective viral load suppression can also provide the additional public health benefit of decreased HIV-1 transmission.
- The current approach to therapy is the use of a combination of antiretroviral drugs (ARVs) from two or more of the six available ARV classes: nucleos(t)ide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (INI), fusion inhibitors, and attachment inhibitors. For the majority of patients, combination antiretroviral therapy (ART) has effectively changed HIV infection from a disease associated with reduced life expectancy to a chronic disease requiring life-long treatment.
- HIV-1 continues to be a significant public health concern, both globally and domestically. Despite the availability of a multitude of ARVs, treatment failure still occurs and places patients at risk for disease progression and death. The principle reasons for treatment failure include the development of viral resistance, non-adherence, and intolerance to the available medications. Treatment failure may result in selection of an HIV-1 strain that is resistant to one or more ARV, necessitating transition to a second or third line ART regimen that may be less convenient and less tolerable. Hence, new ARVs are needed to provide treatment options that are potent, durable, well-tolerated, and convenient. This is especially true for Highly Treatment Experienced (HTE) patients who, by definition, have failed multiple ARV classes/regimens and have no more than two fully active ARVs available to be combined in a suppressive regimen. This is the population for which GS-6207 is being developed.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.
 - The primary endpoint in the Phase 1b (proof-of-concept) trial was the maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) from Day 1 through Day 10 in HIV-1 infected adult subjects who are antiretroviral treatment naïve (TN) or are treatment-experienced (TE) but not currently taking ARV treatment. A mean decline of at least 0.5 $\log_{10}$ HIV-1 RNA copies/mL over 10-14 days is associated with a reduction in clinical disease progression.
- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
 - Decrease in HIV-1 RNA level (viral load) is now considered a validated surrogate for predicting the efficacy of antiretrovirals. The paradigm of accelerated approvals based on HIV-1 RNA levels at 24 weeks followed by traditional approvals based on levels at 48 weeks is no longer necessary. At present, approval is dependent on the timing of HIV-1 RNA assessments in the population under study. For HTE patients, the Division is now assessing virologic response (proportion of patients with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ viral copies/mL) at 2 weeks plus virologic and safety follow-up at 24 weeks. Of note, trials evaluating short-term virologic response in the HTE population would support only a limited treatment indication for use in patients who cannot construct a viable regimen without a new antiretroviral drug.
 - The first, Phase 1b (proof-of-concept) trial in HIV-infected patients should be a study that allows for short-term (e.g., several days to 2 weeks depending on the drug class, resistance profile in cell culture, potency, and pharmacokinetics) evaluation of a drug's effect on reducing HIV-1 RNA levels from baseline and also provides for evaluation of safety for a short duration. Mean changes in HIV-1 RNA from baseline should be the primary

endpoint. The trial duration depends on the anticipated resistance barrier of the drug based on cell culture studies. Some drugs with an anticipated low genetic barrier to resistance would not be appropriate candidates for study in a monotherapy trial of any duration. Drugs with a presumed high barrier to resistance emergence generally can be studied for up to 2 weeks.

- The primary endpoint in Phase 2 studies conducted to date has been short-term (7-14 day) reduction in HIV-1 RNA from baseline. HIV-1 RNA at Week 24 was another key efficacy endpoint to assess for the durability of the initial antiviral response. The Division accepts this surrogate endpoint as a clinically significant endpoint for HIV-1 treatment trials in HTE patients because HIV-1 viral suppression has been associated with reduced morbidity and all-cause mortality.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

- Change in CD4⁺ cell count is also an important surrogate marker that is followed in all HIV-1 treatment trials. Restoration of a normal CD4⁺ cell count is associated with decreased risk of morbidity and mortality associated with opportunistic infections.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- Treatment of HTE HIV patients is challenging. The goal is to construct an optimized regimen containing at least two fully-active antiretroviral drugs, which are identified by genotypic and phenotypic resistance profiles. Unlike first-line ARV regimens, which typically consist of a dual NRTI “backbone” plus one “anchor drug” – usually a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI) – regimens for HTE patients often consist of two or more “anchor” drugs. In order to effectively reduce viral load to undetectable levels, these anchor drugs must have potent and durable antiviral activity with a high barrier to resistance and minimal cross-resistance within and between ARV class.
- Table 1 summarizes ARV drugs that are currently approved for treatment-experienced subjects. Please note that this list is not all-inclusive, as any ARV can theoretically be used in HTE patients based on the individual’s resistance profile. For the same reason, not all drugs on this list may be active for HTE patients, who are a subset of the “treatment experienced” subjects enrolled in the clinical trials and who often carry more extensive resistance-conferring substitutions than the overall “treatment experienced” population.

Table 1: FDA-approved ARVs for Treatment-Experienced Subjects, by ARV Class

ARV Class/Drug Name	Clinical Trial Name	Number of Subjects (study drug/comparator)	Key Inclusion Criteria	Comparator Drug*	% of Subjects meeting the Primary Endpoint
NNRTI					
Etravirine	DUET 1 and 2	1203 (599/604)	HIV-1 RNA > 5000 copies/mL despite >8 weeks of ART AND 1 or more protocol-specified NNRTI/PI resistance substitutions	Placebo + OBR (all had DRV/r [#] + 2 ARVs)	60% vs. 38% HIV-1 RNA <50 copies/ml at Week 48 (investigational drug vs. comparator), FDA Snapshot algorithm

<i>ARV Class/Drug Name</i>	<i>Clinical Trial Name</i>	<i>Number of Subjects (study drug/comparator)</i>	<i>Key Inclusion Criteria</i>	<i>Comparator Drug*</i>	<i>% of Subjects meeting the Primary Endpoint</i>
PI					
<i>Atazanavir/r[#]</i>	<i>AI424-045</i>	<i>237 (119/118)</i>	<i>Failing ART regimen containing PI + NNRTI + NRTI</i>	<i>Lopinavir/r + OBR (tenofovir + one additional NRTI)</i>	<i>38% vs. 45% HIV-1 RNA <50 copies/ml at Week 48, FDA Snapshot algorithm</i>
<i>Darunavir/r[#]</i>	<i>POWER 1 and 2</i>	<i>255 (131/124)</i>	<i>HIV-1 RNA > 1000 copies/mL despite >8 weeks of PI-based ART AND 1 or more protocol-specified PI resistance substitutions</i>	<i>Placebo + OBR (must contain a PI)</i>	<i>57% vs. 10% $\geq 1 \log_{10}$ decrease in HIV-1 RNA below baseline (Week 96)</i>
<i>Tipranavir/r[#]</i>	<i>RESIST 1 and 2</i>	<i>1483 (746/737)</i>	<i>HIV-1 RNA >1000 copies/mL on a PI-based ART regimen AND 1 or more protocol-specified PI resistance substitutions</i>	<i>Placebo + OBR (containing PI)</i>	<i>34% vs. 15% $\geq 1 \log_{10}$ decrease in HIV-1 RNA below baseline</i>
INSTI					
<i>Dolutegravir</i>	<i>VIKING-3</i>	<i>183</i>	<i>Failing an INSTI-based ART regimen with resistance to raltegravir or elvitegravir</i>	<i>N/A: single-arm trial</i>	<i>1.4 $\log_{10}$ (95% CI 1.3 $\log_{10}$, 1.5 $\log_{10}$) Mean decrease in HIV-1 RNA at Day 8</i>
<i>Elvitegravir</i>	<i>145</i>	<i>702 (351/351)</i>	<i>Treatment experienced</i>	<i>Raltegravir + OBR (containing 1 fully active PI/r + another ARV)</i>	<i>52% vs. 53% HIV-1 RNA <50 copies/ml at Week 48, FDA Snapshot algorithm</i>
<i>Raltegravir</i>	<i>BENCHMARK 1 and 2</i>	<i>699 (462/237)</i>	<i>Documented resistance to at least 1 drug in the NNRTI, NRTI, and PI class</i>	<i>Placebo + OBR</i>	<i>55% vs. 27% HIV-1 RNA <50 copies/ml at Week 48, FDA Snapshot algorithm</i>
Entry Inhibitor					
<i>Enfuvirtide</i>	<i>TORO 1 and 2</i>	<i>997 (663/334)</i>	<i>Either 1. Viremia despite 3 to 6 months ART with NRTI, NNRTI, + PI OR 2. Resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes</i>	<i>Placebo + OBR</i>	<i>46% vs. 18% $\geq 1 \log_{10}$ decrease in HIV-1 RNA below baseline</i>

<i>ARV Class/Drug Name</i>	<i>Clinical Trial Name</i>	<i>Number of Subjects (study drug/comparator)</i>	<i>Key Inclusion Criteria</i>	<i>Comparator Drug*</i>	<i>% of Subjects meeting the Primary Endpoint</i>
<i>CCR5 Antagonist (Attachment Inhibitor)</i>					
<i>Maraviroc</i>	<i>MOTIVATE 1 and 2</i>	<i>635 (426/209)</i>	<i>CCR5-Tropic, Baseline HIV-1 RNA >5000 copies/mL despite >6 months of ART OR documented resistance to at least one agent in each ARV class</i>	<i>Placebo + OBR</i>	<i>46% vs. 17% HIV-1 RNA < 50 copies/ml at Week 48, FDA Snapshot algorithm</i>
<i>CD4-directed post-attachment HIV-1 inhibitor</i>					
<i>Ibalizumab-uiyk</i>	<i>Trial TMB-301</i>	<i>40</i>	<i>Treatment-experienced with multidrug resistance to at least 1 ARV from 3 classes, HIV-1 RNA >1000 copies/mL</i>	<i>N/A: single-arm trial</i>	<i>83% achieved ≥ 0.5 log₁₀ decrease in viral load (67%, 93%)</i>

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

- *Breakthrough designation has been granted to fostemsavir (BMS-663068), an HIV attachment inhibitor for the treatment of HTE adults. Activity of fostemsavir was established in two Phase 2 trials, which demonstrated ≥ 1 log₁₀ reduction in HIV-1 RNA (viral load) after short-term monotherapy: one POC study in treatment-naïve HIV-1 infected subjects followed by an active-controlled trial in 251 treatment-experienced subjects. Virologic activity of this initial response was durable at 24 and 48 weeks.*

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 2: Ongoing Phase 1 Clinical Studies with GS-6207

Study Number/Population	Study Title or Description	Formulations evaluated	Subjects who received GS-6207 to date (Planned), N^a
Subcutaneous formulations			
GS-US-200-4070 Healthy volunteers	Randomized, blinded, placebo-controlled, SAD study	SC suspension (free acid)	32
GS-US-200-4538 Healthy volunteers	Randomized, blinded, placebo-controlled, SAD study	SC solution (various formulations)	42 (Up to 192)
GS-US-200-4072 HIV-infected subjects	Randomized, blinded, dose ranging placebo-controlled POC	SC suspension (free acid)	18 (Up to 30)
Oral formulations			
GS-US-200-4071 Healthy volunteers	Randomized, blinded, placebo-controlled, SAD/MAD study	Oral solution in capsule	40 (Up to 56)
Total Number of Subjects Who Received GS-6207 (SC or Oral) to Date^a			132

SAD = single ascending dose; SC = subcutaneous; POC = proof of concept; ^a Excludes subjects who received placebo

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

GS-6207 is the first investigational agent in a new class of ARVs. Regardless of prior treatment history all subjects are likely to be susceptible to this new class of ARVs. Activity was established in the POC trial. Other trials were conducted in HV. Total of 132 subjects received product to date with no safety findings that would preclude ongoing development in HTE population. (b) (4), but based on the doses and volumes evaluated, PK profiles are consistent with sustained delivery that are likely to support convenient dosing intervals.

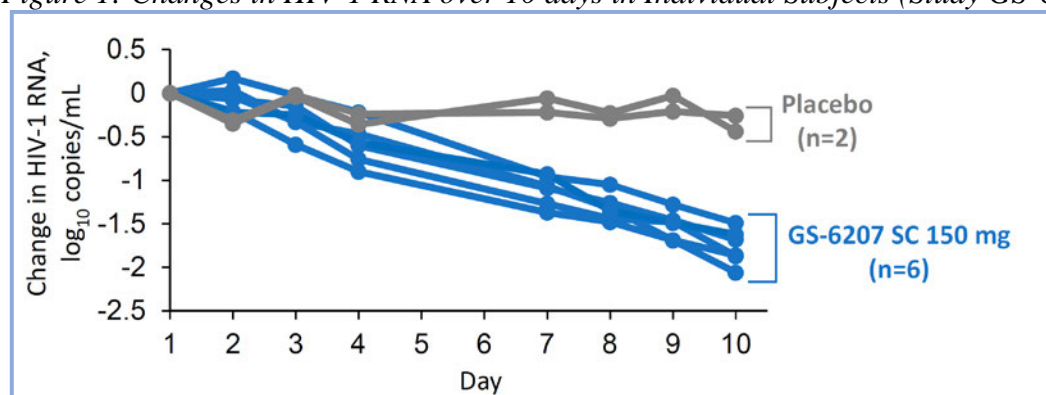
Interim results from one clinical trial (Study GS-US-200-4072) were provided as supporting evidence of clinical efficacy:

- Phase 1b randomized, double-blinded, placebo-controlled, multi-cohort POC study
- Primary objective: short-term antiviral activity of GS-6207 versus placebo
- Primary endpoint: maximum reduction of plasma HIV-1 RNA ($\log_{10}$ copies/mL) through Day 10
- Patient population: Treatment-naïve (or experienced but off ARVs for at least 12 weeks and INSTI-naïve)
- Planned enrollment: 32 subjects, with 8 subjects in 4 cohorts, randomized 3:1 to SC GS-6207 or placebo
- Cohort 1 starting with 150 mg, and up to 450 mg through Cohort 4 (Cohort 5 added: 900 mg)

Table 3: Preliminary results from Cohort 1 with 150 mg (Study GS-US-200-4072)

Log ₁₀ copies/mL	GS-6207 (n=6)	Placebo (n=2)
Mean (SD)	-1.76 (0.203)	-0.38 (0.092)
P-value	< 0.001	
95% CI	(-1.97, -1.55)	(-1.21, 0.45)
Median	-1.77	-0.38
Q1, Q3	-1.87, -1.62	-0.44, -0.31
Min, Max	-2.06, -1.49	-0.44, -0.31

Figure 1: Changes in HIV-1 RNA over 10 days in Individual Subjects (Study GS-US-200-4072)



Note: HIV Guidance recommends $>0.5 \log_{10}$ at an early time point (up to 2 weeks)

In Cohort 1, mean (%CV) GS-6207 concentrations on Day 10 were 12.9 (39.3) ng/mL, which is approximately 3.3 fold higher than the paEC95 for wild type HIV 1 (ie, IQ=3.3).

PK data from additional cohorts are not yet available, but the Sponsor provided the following updates from evaluation of antiviral activity:

Log ₁₀ copies/mL	GS-6207 SC 50 mg (n=6)	GS-6207 SC 150 mg (n=6)	GS-6207 SC 450 mg (n=6)	Placebo (n=6)
Mean (SD)	-1.79 (0.476)	-1.76 (0.203)	-2.20 (0.468)	-0.23 (0.124)
95% CI	-2.29, -1.29	-1.97, -1.55	-2.69, -1.71	-0.36, -0.10
Min, Max	-2.39, -1.16	-2.06, -1.49	-2.86, -1.58	-0.44, -0.13

For comparison, two entry inhibitors approved for heavily treatment-experienced patients, maraviroc and ibalizumab, demonstrated mean changes (from baseline through Day 7 following 10 days of monotherapy) in HIV-1 RNA of $\geq 1.6 \log_{10}$ and $0.6 \log_{10}$, respectively. For ibalizumab, 83% achieved $\geq 0.5 \log_{10}$ decrease versus 3% with placebo. Of note, maraviroc is active only with CCR5-tropic infections, which are less common in treatment-experienced patients. GS-6207 is likely to show an improvement over existing therapies, because all subjects were susceptible to this new class regardless of treatment history.

b. Include any additional relevant information. Consider the following in your response:

- **Clinical efficacy:** From the clinical review perspective, this submission lacks clinical efficacy data in the intended patient population (heavily treatment-experienced patients with evidence of multi-drug resistance); however, GS-6207 represents the first investigational agent in a new class of capsid inhibitors. Although the data was not in the target population, the Sponsor provided preliminary clinical data that showed approximately $2 \log_{10}$ decrease in HIV-1 RNA (viral load) at 10 days, which was statistically significant and consistent among all individuals at relatively low doses. Because the HTE population will likely be susceptible to this new class, similar activity is anticipated.
- **In vitro data:** Activity of GS-6207 was demonstrated on isolates from patients with PI resistance (darunavir and atazanavir). Of note, the isolates used were contained clones of the gag-protease region from patients with wildtype INSTI and NRTI genotypes. Antiviral activity of GS-6207 against PI-resistant isolates harboring resistance substitutions at protease cleavage sites is pending.

Phenotypic susceptibility was demonstrated in treatment-naïve & heavily treatment-experienced isolates with a 5-day assay using recombinant isolates including the HIV-1 gag-PR sequence.

In vitro activity of GS-6207 was tested against viruses with common resistance mutations to NRTI, NNRTI, PI, and INSTI. No meaningful fold shift was observed in EC50 for GS-6207 in comparison to the wild-type control strain. Susceptibility measured for wild-type was similar to TN (mean 200 pM versus 192 pM, respectively)

The following resistance mutations were selected in vitro: L56I, M66I, Q67H, K70N, N74D/S, and T107N. T107N, a low-level resistance mutation, was detected in only 1 (< 1%) of TN patient samples. Q67H was identified in < 20 (< 0.2%) from published dataset of capsid sequences.

- **Clinical safety:** To date, 132 subjects have received GS-6207 (92 have received an SC formulation and 18 have received a PO formulation). There have been no deaths, drug-related serious adverse events or Grade 3-4 adverse events reported. The most commonly reported adverse events were: injection site erythema (38%), injection site pain (35%), and injection site nodules (23%).

In Study GS-US-200-4072, no Grade 2, 3, or 4 treatment emergent adverse events were reported. Injection site: pain (5, 62.5%), erythema (4, 50%), and induration (4, 50%) were the most common events. One subject experienced an asymptomatic Grade 3 lipase elevation, which was not attributed to the study drug as lipase elevations are occasionally observed in people living with HIV.

12. Division's recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

The Division endorses granting Breakthrough Designation for the following reasons:

1. GS-6207 targets a serious condition. There is a need for new ARVs that confer potent and durable antiviral activity against viral strains that are resistant to multiple existing ARV options. This need is most acute for HTE subjects who

have limited remaining treatment options. Lack of virologic control leads to further immune destruction and an increased risk of mortality caused by opportunistic infections.

2. GS-6207 is a first-in-class selective inhibitor of HIV-1 capsid function and inhibits HIV at multiple points in the viral lifecycle, including interfering with capsid-mediated nuclear uptake of pre-integration complexes, and impairing virion production and proper capsid core formation. Virus produced in the presence of GS-6207 display aberrantly shaped capsids. These malformed virus particles can still infect new target cells but cannot replicate as they are unable to support reverse transcription without a properly formed capsid core. As an antiretroviral agent with a new mechanism of action and no overlapping resistance with any approved agents, GS-6207 has the potential to meet the high unmet medical need in HTE patients with limited treatment options

3. GS-6207 is being developed as a subcutaneous injection for HTE subjects and may provide a more convenient dosing option to which patients can adhere.

4. The available POC data demonstrates potent anti-viral activity at a variety of doses. Preliminary clinical data from a POC trial in treatment-naïve patients showed approximately 2 log decrease in HIV-1 RNA (viral load) after 10 days of treatment with GS-6207. Although the Sponsor has not demonstrated clinical data in the targeted population (either patients with prior ART experience or heavily-treatment experienced), the supportive in vitro data suggest a high likelihood of potential effectiveness regardless of prior treatment experience.

5. No significant safety signals were detected in the Phase 1 trials to date.

DENY:

Provide brief summary of rationale for denial:

[If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:]

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):
 - (b) (4); therefore, the Sponsor will need to finalize the choice of SC formulation/concentration and optimize long-term stability.
 - The next step for the sponsor following completion of the Phase 1b trial would be a randomized placebo-controlled trial comparing GS-6207, at several dose levels as functional monotherapy to placebo in HIV-infected patients with drug resistance to multiple drugs/drug classes or who are failing their current regimen.
- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES
NO

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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/

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