BLA 761432

CORRECTED BLA APPROVAL

Merck Sharp & Dohme LLC
Attention: Sandra L. Wood, PhD
Senior Director, Global Regulatory Affairs
351 North Sumneytown Pike
P. O. Box 1000
Mailstop: UG2CD68
North Wales, PA 19454

Dear Dr. Wood:

Please refer to your biologics license application (BLA) received October 10, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Enflonsia (clesrovimab-cfor) injection for intramuscular use.

We also refer to our approval letter dated June 9, 2025 which contained the following errors:

- In HIGHLIGHTS OF PRESCRIBING INFORMATION, ADVERSE REACTIONS, injection-site erythema percentage (3.7%) is incorrect and has been corrected to match the percentage in Table 1, (3.8%).
- In the Full Prescribing Information: Contents, section: 2.1 heading "Recommened" Dosage, the word Recommended is misspelled.

This corrected action letter incorporates the correction of the errors. The effective action date will remain June 9, 2025, the date of the original approval letter.

LICENSING

We have approved your BLA for Enflonsia (clesrovimab-cfor) effective June 9, 2025. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Enflonsia under your existing Department of Health and Human Services U.S. License No. 0002. Enflonsia is indicated for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture clesrovimab-cfor drug substance at (b) (4) The final formulated drug product will be manufactured and filled at (b) (4)

(b) (4), then assembled, labeled, and packaged at Merck Sharp & Dohme LLC, Wilson, North Carolina. You may label your product with the proprietary name, Enflonsia, and market it in 105 mg/0.7mL (150 mg/mL) solution in a single-dose prefilled syringe.

DATING PERIOD

The dating period for Enflonsia shall be 30 months from the date of manufacture when stored at 2°C to 8°C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Enflonsia to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Enflonsia, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective June 9, 2025 for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). Information on submitting SPL files using eLIST may be found

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761432**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Enflonsia (clesrovimab-cfor) was not referred to an FDA advisory committee because this drug is not the first in its class, the Application did not raise significant safety or efficacy issues, and there were no controversial issues that would necessitate an advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We are waiving the pediatric study requirement for children older than 24 months of age for this application because the necessary studies are impossible or highly impracticable. Children older than 24 months of age have a lower incidence of medically attended RSV lower respiratory tract disease, with fewer hospitalizations and less severe disease, and thus are unlikely to benefit from use of Enflonsia (clesrovimab-cfor) for the prevention of RSV lower respiratory tract disease.

We are deferring submission of your pediatric study for ages >12 to ≤24 months of age for this application because the product is ready for approval for use in pediatric patients ≤12 months of age and the trial in children older than 12 months to 24 months of age is currently ongoing.

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

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4841-1 Conduct a study in children up to 24 months of age with underlying conditions who are at increased risk for respiratory syncytial virus (RSV) disease.

The timetable you submitted on May 30, 2025, states that you will conduct this study according to the following schedule:

Study Completion:	01/2026
Final Report Submission:	08/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 130097, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 0 to ≤12 months of age (including infants ≤12 months of age with underlying conditions that increase the risk for RSV disease) with this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of RSV variants with reduced susceptibility to clesrovimab arising from

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

natural variation and/or in response to treatment, and transmission of clesrovimab resistant RSV variants.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4841-2 Conduct a surveillance study of current and emerging respiratory syncytial virus (RSV) variants from global locations, with F protein sequencing and identification of clesrovimab binding site substitutions and their frequency. These surveillance activities should include active collection and characterization of RSV samples from global regions (i.e., North America [US/Canada], Europe, rest of the world) and will target at least 100 samples from each region when fully operational, as well as periodic analysis of sequences from public databases (i.e., GISAID, NCBI, GenBank). The surveillance study should also determine the cell culture neutralization activity of clesrovimab against those RSV clesrovimab binding epitope variants carrying substitutions (VAF >10%) and with unknown impact on clesrovimab susceptibility that are capable of growing in cell culture. Phenotypic characterization will include RSV variants whose prevalence is ≥5% within an RSV season (or over two consecutive years in public databases) and/or ≥3-fold increase above 1% from the previous season across all sequenced samples and from all sites within a global region. RSV variants of interest for phenotypic testing will include those carrying substitutions of unknown impact on clesrovimab susceptibility, detected in Site IV, adjacent to the clesrovimab binding epitope (within ≤5 Å distance), or outside Site IV at highly conserved positions (≥99% in GenBank).

The timetable you submitted on June 3, 2025, states that you will conduct this study according to the following schedule:

Strain Surveillance Study	
Draft Protocol Submission:	12/2025
Final Protocol Submission:	07/2026
Interim Report Submission:	07/2028
Interim Report Submission:	07/2029
Interim Report Submission:	07/2030
Interim Report Submission:	07/2031
Interim Report Submission:	07/2032
Interim Report Submission:	07/2033
Final Report Submission:	07/2034

Public Sequence Database Analysis

Interim Report Submission:	07/2025
Interim Report Submission:	07/2026
Interim Report Submission:	07/2027
Interim Report Submission:	07/2028
Interim Report Submission:	07/2029
Interim Report Submission:	07/2030
Interim Report Submission:	07/2031
Interim Report Submission:	07/2032
Interim Report Submission:	07/2033
Final Report Submission:	07/2034

Submit interim reports on an annual basis, and conduct public sequence database analysis for as long as strain surveillance is ongoing. In addition, after confirmation of the results, the Agency should be notified within 2 months of receipt of new phenotypic data for variants or individual substitutions showing ≥5-fold reduction in susceptibility, and no later than15 days for substitutions showing ≥100-fold reduction in susceptibility.

4841-3 Conduct a study to assess F protein substitutions in cell culture neutralization assays, in the background subtype in which they were identified based on non-clinical, surveillance, and clinical studies of clesrovimab. The list of substitutions is provided below:

RSV A: N380S, N426H, N428D, R429H, S436F, V447M, Y457H, K465R, S466N, K470R

Also: test S443T if RSV B S443L shows reduced susceptibility to clesrovimab, and test K445R if RSV B K445N shows reduced susceptibility.

RSV B: I402V, K433R, F435S, V442M, S443L, K445N, G446V, V452E

Also: test V447I if RSV A V447M shows reduced susceptibility to clesrovimab.

The timetable you submitted on May 30, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	12/2025
Final Protocol Submission	07/2026
Interim Report Submission	07/2027
Interim Report Submission	07/2028
Final Report Submission	07/2029

The timetable you submitted on May 30, 2025, states that you will notify the Agency within 2 months of receipt of new, confirmed, phenotypic data for variants or individual

substitutions showing ≥5-fold reduction in susceptibility, and no later than 15 days for substitutions showing ≥100-fold reduction in susceptibility.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 130097 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) , REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4841-4 Conduct a study to assess the cell culture neutralization of clesrovimab against RSV with substitutions that confer >100-fold reduction in susceptibility to nirsevimab, as reported in the BEYFORTUS™ USPI:

RSV A: N67I+N208Y

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

RSV B: K68N+N201S, K68N+N208S, L203I, N208D

The timetable you submitted on May 30, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2027

Submit clinical protocols to your IND 130097 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Nina Mani, Senior Regulatory Project Manager, at 240-402-0333 or Nina.Mani@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Director (Acting)
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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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