BLA 761328

BLA APPROVAL

AstraZeneca AB
c/o AstraZeneca Pharmaceuticals LP
Attention: Catherine Burke, PhD, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Burke:

Please refer to your biologics license application (BLA) dated September 26, 2022, received September 26, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Beyfortus (nirsevimab-alip), injection, for intramuscular use.

LICENSING

We have approved your BLA for Beyfortus (nirsevimab-alip) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Beyfortus under your existing Department of Health and Human Services U.S. License No. 2059. Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture nirsevimab-alip drug substance at AstraZeneca Pharmaceuticals, LP in Frederick, Maryland (Frederick Manufacturing Center; FEI: 3002617771). The final formulated drug product will be manufactured and filled at (b) (4) then assembled, labeled, and packaged at (b) (4) You may label your product with the proprietary name, Beyfortus, and market it in 50 mg/0.5 mL and 100 mg/mL pre-filled syringe presentations.

DATING PERIOD

The dating period for Beyfortus shall be 18 months from the date of manufacture when stored at 2-8°C. 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 protocol(s) 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 Beyfortus 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 Beyfortus, 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 on the date of this letter, 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 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

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

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 761328**." Approval of this submission by FDA is not required before the labeling is used.

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 Beyfortus (nirsevimab-alip) for the prevention of RSV lower respiratory tract disease.

We note that you have fulfilled the pediatric study requirement for neonates, infants, and children up to 24 months of age.

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 nirsevimab arising from natural variation and/or in response to treatment, and transmission of nirsevimab-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:

4470-1 Provide reports on the prevalence of current and emerging RSV variants, including the frequency of known nirsevimab resistance-associated substitutions, on an annual (AZ-sponsored surveillance studies) or 6-monthly (clinical trials, public sequence databases) basis with the periodic safety report. These study reports should include genotypic data from public sequence databases (i.e., GISAID, NCBI GenBank), and both genotypic and phenotypic data from ongoing clinical studies and surveillance activities, including all new variants and substitutions showing ≥5-fold reduction in susceptibility:

- OUTSMART-RSV and INFORM-RSV studies
- Clinical trials of nirsevimab

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: N/A
Interim Report Submissions:
Annual reports of AstraZeneca-sponsored surveillance studies
Interim Report Submission: 01/2024
Interim Report Submission: 01/2025
Interim Report Submission: 01/2026
Interim Report Submission: 01/2027
Interim Report Submission: 01/2028
Interim Report Submission: 01/2029
6-monthly reports of clinical trials, and public sequence databases
Interim Report Submission: 01/2024
Interim Report Submission: 07/2024
Interim Report Submission: 01/2025
Interim Report Submission: 07/2025
Interim Report Submission: 01/2026
Interim Report Submission: 07/2026
Interim Report Submission: 01/2027
Interim Report Submission: 07/2027
Interim Report Submission: 01/2028
Interim Report Submission: 07/2028
Interim Report Submission: 01/2029
Interim Report Submission: 07/2029
Study Completion: 06/2029
Final Report Submission: 01/2030

4470-2 Based on surveillance studies and a pooled analysis of RSV A and RSV B isolates from nirsevimab-treated subjects (inclusive of all subjects meeting

primary, secondary, or exploratory case definitions), assess phenotypically the individual and concurrent substitutions shown below.

RSV A

Individual substitutions

S62G, K65Q, K65R, E110G, L111I, L119I, K123Q, D200N, V247L, W341R, K419E, N515H

RSV B

Individual substitutions

R42K, K68R, S190N, N200Y, L204S, N208I, K272R, S389P

Concurrent substitutions

- K68N+I206M+Q209R
- I206M+Q209R+K272R
- F15L+A103V+L172Q+S173L
- F15L+A103V+L172Q+S173L+K191R+I206M+Q209R
- F15L+A103V+L172Q+S173L+S190N+K191R+I206M+Q209R+S211N+S389P
- F15L+R42K+A103V+L172Q+S173L+S190N+K191R+I206M+Q209R+ S211N+S389P
- L204S+I206M+Q209R+S211N

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: N/A
Interim Report Submissions:
Annual reports of AstraZeneca-sponsored surveillance studies
Interim Report Submission: 01/2024
Interim Report Submission: 01/2025
6-monthly reports of clinical trials, and public sequence databases
Interim Report Submission: 01/2024
Interim Report Submission: 07/2024
Interim Report Submission: 01/2025
Interim Report Submission: 07/2025
Study Completion: 10/2025
Final Report Submission: 12/2025

The timetable you submitted on June 29, 2023, states that you will notify the Agency within 2 months of receipt of new phenotypic data for individual or concurrent 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.[3]

[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.

Submit clinical protocol(s) to your IND 118524 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 commitments:

4470-3 Conduct a long-term follow-up study (Study D5290N00001: HARMONIE study extension for the UK cohort) to evaluate antibody dependent enhancement of RSV disease after nirsevimab administration to neonates and infants prior to or during their first RSV season. The assessment for antibody dependent enhancement of RSV disease should include RSV lower respiratory tract infection (LRTI) hospitalization events. The follow-up period should continue through Day 511 post-dosing.

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2023
Trial Completion (for HARMONIE extension):	04/2025
Final Report Submission (for HARMONIE extension):	10/2025

4470-4 Conduct an observational, U.S.-based long-term follow-up study of infants

eligible to receive nirsevimab in their first year of life to assess the impact of RSV disease through Day 511 post dosing. This study should include assessment of MA RSV LRTI and RSV hospitalization. The study may be conducted using existing databases for the 2023 and 2024 RSV seasons.

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2025
Interim Report Submission:	08/2026
Study Completion:	03/2028
Final Report Submission:	03/2029

4470-5 Submit the interim and the final study reports and datasets for the ongoing HARMONIE trial, "A Phase IIIb Randomized Open-label Study of Nirsevimab (Versus no Intervention) in Preventing Hospitalizations Due to Respiratory Syncytial Virus in Infants."

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	N/A
Interim Report Submission:	10/2023
Trial Completion:	03/2024
Final Report Submission:	07/2024

4470-6 Submit the final study report and datasets for Trial D5290C00004, a phase 3 randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of nirsevimab for the prevention of medically attended RSV respiratory tract infection (MA RSV LRTI) in preterm and term infants.

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	N/A
Trial Completion:	03/2023
Final Report Submission:	10/2023

4470-7 Submit the final study report and datasets for Trial D5290C00005, a double-blind, active-controlled trial to evaluate the safety, efficacy, and pharmacokinetic of nirsevimab for the prevention of medically attended RSV respiratory tract infection (MA RSV LRTI) in high-risk infants and children.

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	N/A
Trial Completion:	03/2023
Final Report Submission:	10/2023

4470-8 Submit the final study report and datasets for Trial D5290C00008, "A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age."

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	N/A
Trial Completion:	04/2023
Final Report Submission:	10/2023

4470-9 Submit the final study report and datasets for the CHIMES trial (D5290C00006; NCT05110261), "A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Nirsevimab, a Monoclonal Antibody With Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm and Term Infants in China."

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	N/A
Trial Completion:	12/2025
Final Report Submission:	08/2026

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4470-10 Provide data from real world shipping studies covering all transportation configurations, temperatures, modes, and routes of commercial transportation to evaluate product quality of the final drug product in the commercial container closure system pre- and post-shipment.

The timetable you submitted on July 7, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2023
Study Completion:	06/2024
Final Report Submission:	12/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 118524 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*.[4]

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 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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.

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

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

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

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 Saebyeol Jang, PhD, RAC-US, Senior Regulatory Project Manager, at (240) 402-9953.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
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/

JOHN J FARLEY
07/17/2023 11:17:06 AM