U.S. FOOD & DRUG ADMINISTRATION

BLA 761339

BLA APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Paurene Duramad, PhD
Senior Director, Regulatory Affairs
777 Old Saw Mill River Rd.
Tarrytown, NY 10591-6707

Dear Dr. Duramad:

Please refer to your biologics license application (BLA) dated and received December 20, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Veopoz (pozelimab-bbfg), injection.

LICENSING

We have approved your BLA for Veopoz (pozelimab-bbfg) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Veopoz under your existing Department of Health and Human Services U.S. License No. 1760. Veopoz is indicated for the treatment of adult and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture pozelimab-bbfg drug substance at Regeneron Pharmaceuticals, Inc. in Rensselaer, NY. The final formulated drug product will be manufactured and filled at (b) (4) and labeled and packaged at (b) (4) You may label your product with the proprietary name, Veopoz, and market it in 400 mg/2 mL single dose vial, injection.

DATING PERIOD

The dating period for Veopoz shall be 36 months from the date of manufacture when stored at 2 to 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, (b) (4) (b) (4) Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. 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 Veopoz 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 Veopoz, 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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Add page numbers 1-3 for the Medication Guide.
- Revise “years” to “year” in the last sentence in Section 8.4 Pediatric Use.
- Revise “peripheral or facial edema” to “peripheral edema, or facial edema” in the second paragraph in Section 14 Clinical Studies.

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 (Prescribing Information and Medication Guide). 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.

[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.

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 761339**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761339. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

    - the estimated demand in the U.S. for the product, and

    - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for pozelimab-bbfg was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class in the intended population.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

4490-1 Re-evaluate the current anti-drug antibody (ADA) assay with the goal of improving sensitivity in the presence of the trough level of drug expected to be present during sampling. The assay validation assessments will include selectivity, system suitability specifications for negative and positive controls, effects of hemolysis, and a statistical evaluation of distribution and outlier exclusion for cutpoint samples.

The timetable you submitted on August 3, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission: 11/2024

Final Report Submission: 11/2025

4490-2 Re-evaluate clinical samples for anti-pozelimab antibodies (ADA) from clinical Trial R3918-PLE-1878 using the assay described in 4490-1. Evaluate neutralizing capacity of ADA using the assay described in 4490-3 from clinical Trial R3918-PLE-1878 in all confirmed ADA positive samples.

The timetable you submitted on August 3, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2028

4490-3 Develop and validate a sensitive assay to evaluate the neutralizing capacity of anti-pozelimab antibodies (ADA) in confirmed ADA positive patient samples.

The timetable you submitted on August 3, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission: 08/2027

Final Report Submission: 08/2028

4490-4 Conduct a study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and safety of pozelimab in pediatric subjects with CHAPLE disease 1 to 5 years of age. The

study will evaluate a minimum of 5 subjects, including at least 3 subjects less than 3 years of age. Samples will be analyzed for anti-pozelimab antibodies (ADA) using the assays described in PMC 4490-1 and 4490-3. Subjects will be evaluated for a minimum of 12 months.

The timetable you submitted on August 16, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2024

Study Completion: 08/2030

Final Report Submission: 02/2031

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

We remind you of your postmarketing commitments:

4490-5 Conduct a drug product (DP) shipping validation study using the first three commercial shipments of finished DP vials from the pack and label contract manufacturing organization (b) (4) (b) (4) to the third-party distribution center (b) (4) (b) (4) under worst-case conditions. Include at minimum the following testing on DP samples prior to and after shipment: appearance, color, pH, particulate matter, non-reduced and reduced MCE, SE-UPLC, icIEF, potency by bioassay, protein content, volume in container and container closure integrity testing.

The timetable you submitted on July 24, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2024

4490-6 Submit (b) (4) study data and full report.

The timetable you submitted on August 3, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2023

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 142063 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.

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.

[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

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 Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276 or email at kelly.richards@fda.hhs.gov

Sincerely,

See appended electronic signature page}

Nikolay Nikolov, M.D.
Acting Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
    - Prescribing Information
    - Medication Guide
- 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/

NIKOLAY P NIKOLOV
08/18/2023 12:49:41 PM