U.S. FOOD & DRUG ADMINISTRATION

BLA 761169

BLA APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Janie Parrino, MD
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Parrino:

Please refer to your biologics license application (BLA) dated and received on February 25, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for INMAZEB (atoltivimab, maftivimab, and odesivimab-ebgn) injection, for intravenous use.

LICENSING

We have approved your BLA for INMAZEB (atoltivimab, maftivimab, and odesivimab-ebgn) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, INMAZEB under your existing Department of Health and Human Services U.S. License No. 1760. INMAZEB is indicated for the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Zaire ebolavirus* infection.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture atoltivimab, maftivimab, and odesivimab drug substances at Regeneron Pharmaceuticals Inc. in Rensselaer, NY. The final formulated drug product will be manufactured and filled at (b) (4) (b) (4) and labeled and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, INMAZEB, and market it as 241.7 mg of atoltivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL in single dose vials for intravenous injection.

DATING PERIOD

The dating period for INMAZEB shall be 30 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 substances 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 INMAZEB 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 INMAZEB, or in the manufacturing facilities, will require the submission of information to your biologics license application 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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). 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*.[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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*

[1] 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.

Specifications. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761169**." Approval of this submission by FDA is not required before the labeling is used.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

Your request for a tropical disease priority review voucher is denied. This application is not eligible for a tropical disease priority review voucher because it does not contain "one or more new clinical investigations (other than a bioavailability study) that are essential to approval of the application and conducted or sponsored by the sponsor of the application" as required by section 524(a)(4)(A)(iii) of the FD&C Act.

In your request, you identified two studies that you claim should qualify you to meet this requirement for a tropical disease PRV. We reviewed the information you provided and concluded that study R3470-3471-3479-HV-1528 is not a new clinical investigation (other than a bioavailability study) essential to approval of this application. Additionally, we concluded that you did not conduct or sponsor the PALM trial. Therefore, BLA 761196 is not eligible for a tropical disease PRV.

MATERIAL THREAT MEDICAL COUNTERMEASURE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a material threat medical countermeasure priority review voucher (PRV), as provided under section 565A of the FDCA. This PRV has been assigned a tracking number, PRV BLA 761169. All correspondences related to this PRV should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license 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. This PRV may be transferred by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher. The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application.

FDA has published a draft guidance, *Material Threat Medical Countermeasure Priority Review Vouchers,* at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm592548.pdf.

This guidance, when finalized, will represent the current thinking of the FDA on this topic.

ADVISORY COMMITTEE

Your application for INMAZEB was not referred to an FDA advisory committee because:

(1) the clinical trial design is acceptable;

(2) the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class in the intended population; and

(3) the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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 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 serious risk of emergence of Ebola virus resistance to INMAZEB and the development of cross-resistance between individual monoclonal antibodies in the combination.

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:

3936-1 Conduct a phenotypic study to determine the impact on binding and antiviral activity against REGN-EB3, atoltivimab (REGN3470), odesivimab (REGN3471), and maftivimab (REGN3479) using lentivirus-based particles pseudotyped with *Zaire ebolavirus* (EBOV) glycoprotein (GP) containing these substitutions to determine shifts in susceptibility: I274M, W275L, G528R, I544T, H549R, N563T, and E564A.

The timetable you submitted on August 3, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 02/2021
Final Report Submission: 05/2021

3936-2 Conduct a study to characterize genotypically/phenotypically known atoltivimab (REGN3470), odesivimab (REGN3471), and maftivimab (REGN3479) resistant variants and those identified through VSV-based chimeric virus cell culture escape studies with respect to binding, neutralization, and ADCC assays with the individual mAbs (REGN3470, REGN3471, REGN3479) and the REGN-EB3 mAb combination (INMAZEB). Specifically assess cross-resistance between atoltivimab (REGN3470) and odesivimab (REGN3471) resistant variants using an ADCC assay.

The timetable you submitted on September 18, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 09/2022
Final Report Submission: 03/2023

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 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:

[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.

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 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 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:

3936-3 Submit a final report with complete, unblinded safety data for all subjects who were enrolled after interim results of the initial phase of the PALM trial and were treated with atoltivimab, maftivimab, and odesivimab-ebgn (REGN-EB3) for *Zaire ebolavirus* infection during the PALM Extension Phase.

The timetable you submitted on August 3, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2022

3936-4 Conduct a study to define the precise epitopes of atoltivimab (REGN3470), odesivimab (REGN3471), and maftivimab (REGN3479).

The timetable you submitted on August 3, 2020, states that you will conduct this study according to the following schedule:

Study Completion: 12/2020
Final Report Submission: 04/2021

3936-5 Perform complete resistance analysis of sequences derived from subjects treated with REGN-EB3 in the PALM trial, if access to the data becomes available.

The timetable you submitted on August 26, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2022

3936-6 Collaborate with US public health agencies, other public health agencies, and local health authorities, as appropriate to design and conduct a trial to evaluate the efficacy, safety and pharmacokinetics of a higher dose of INMAZEB (atoltivimab, maftivimab, and odesivimab-ebgn) vs. INMAZEB 150 mg/kg in *Zaire ebolavirus*-infected adult and pediatric patients with cycle threshold (CT) values for nucleoprotein targets of less than or equal to 22 to determine if a change in dosing regimen is needed in these patients.

The timetable you submitted on October 7, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2022

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

We remind you of your postmarketing commitments:

3936-7 Re-evaluate and update REGN-EB3 drug substance (DS) and drug product lot release and stability specifications based on lots manufactured by the (b) (4) DS processes. The corresponding data, the analysis, and updated specifications will be submitted with the PAS for the registration of the (b) (4) commercial manufacturing process.

The timetable you submitted on August 3, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2021

3936-8 Conduct a real-world Transport Qualification study that includes a product quality assessment using REGN-EB3 drug product. The real-world Transport Qualification study results will be submitted in a final report to the BLA.

The timetable you submitted on August 3, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2021

3936-9 Re-evaluate and optimize the manufacture, qualification and stability controls used to ensure the performance of Ebola Virus-Like Particles (VLPs) in the pseudovirus neutralization assays. The re-evaluation, development study results and the final control strategy for Ebola VLPs will be provided in the final report to the BLA.

The timetable you submitted on August 28, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

3936-10 Provide microbial hold time data in a microbial challenge study to support the total in-use time (storage and infusion time) of diluted INMAZEB in 5% Dextrose Injection beyond 4-hours at ambient temperature. The study should be conducted for twice the worst-case in-use time and bracketing the drug product concentrations that would be administered to patients. The study should also be representative of the in-use conditions; for example, neonates may be kept at temperatures above 20-25°C during infusion and the higher temperatures should be simulated in the study supporting in-use conditions

The timetable you submitted on September 18, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2021

We note that this final report must be submitted as a prior approval supplement to your approved BLA.

Submit clinical protocols to your IND 125507 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 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 for licensed biological products (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 for licensed biological products (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:

[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

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 molecular entities and 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, call Alicia Moruf, PharmD, MPH, RAC-US, Regulatory Project Manager, at 301-796-3953.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Office Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- 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
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