BLA 761371

BLA APPROVAL

Genentech, Inc.
Attention: Isa Samuels
Senior Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Isa Samuels:

Please refer to your biologics license application (BLA) dated November 10, 2023, received November 13, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) injection.

LICENSING

We have approved your BLA for Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ocrevus Zunovo under your existing Department of Health and Human Services U.S. License No. 1048. Ocrevus Zunovo is indicated for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, and primary progressive multiple sclerosis (PPMS), in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ocrelizumab drug substance at Genentech Inc., Vacaville, CA, and (b) (4) Hyaluronidase drug substance will be manufactured at (b) (4). The final formulated drug product will be manufactured, filled, and primary packaged at (b) (4). The final formulated drug product will be labelled and secondary packaged at (b) (4) You may label your product with the proprietary name, Ocrevus Zunovo, and market it in a 920 mg ocrelizumab and 23,000 units hyaluronidase per 23 mL injection in a single-dose vial.

DATING PERIOD

The dating period for Ocrevus Zunovo shall be 24 months from the date of manufacture when stored at 2-8°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 ocrelizumab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4). The dating period for your hyaluronidase drug substance shall be (b) (4) months from the date of manufacture (b) (4) (b) (4).

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Ocrevus Zunovo 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 Ocrevus Zunovo, 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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 Medication Guide). Information on submitting SPL files using eLIST may be found in the

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

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 labeling that is identical to the carton labeling submitted on September 3, 2024, and the container label that is identical to the container label submitted on August 19, 2024, 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 761371**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for ocrelizumab and hyaluronidase-ocsq was not referred to an FDA advisory committee because this drug is not the first in its class, the clinical trial design was acceptable, and evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class or 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.

We are waiving the pediatric study requirement for treatment of pediatric patients with primary progressive MS and pediatric secondary progressive MS for this application because necessary studies are impossible or highly impracticable. This decision is because of the small number of patients in this age group with primary and secondary progressive MS.

We are waiving the pediatric study requirement for ages 0 to less than 10 years for patients with pediatric relapsing-remitting MS because necessary studies are impossible

[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.

or highly impracticable. This decision is because of the small number of patients in this age group with relapsing forms of multiple sclerosis.

We are deferring submission of your pediatric studies for ages 10 to less than 18 years for patients with pediatric relapsing-remitting MS for this application because the pediatric studies required for intravenously-administered ocrelizumab have not been completed.

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

4689-1 Conduct an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ocrelizumab and hyaluronidase in pediatric patients with relapsing multiple sclerosis (RMS) at least 10 years and less than 17 years of age, weighing 40 kg or less. The objective of this study is to determine a dose of ocrelizumab and hyaluronidase that will result in PK and PD effects that are comparable to those of the dose administered to adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of ocrelizumab and hyaluronidase.

Draft Protocol Submission:	06/2027
Final Protocol Submission:	12/2027
Study Completion:	10/2031
Final Report Submission:	04/2032

4689-2 Conduct a pediatric assessment, with extrapolation to ocrelizumab and hyaluronidase, of the findings from Studies WN42086 (a randomized, double-blind, parallel-group study in pediatric patients ages 10 through 17 years to evaluate the safety and efficacy of Ocrevus [intravenous ocrelizumab] compared to an appropriate control for the treatment of RMS) and WA39085 (an open-label study of the safety, tolerability, PK, and PD of ocrelizumab in pediatric patients), which are studies intended to fulfill PMR 3194-14 for Ocrevus (ocrelizumab).

Draft Protocol Submission:	06/2027
Final Protocol Submission:	12/2027
Study Completion:	10/2031
Final Report Submission:	04/2032

If the results of Studies WN42086 and WA39085 do not support this extrapolation, separate studies to evaluate the efficacy and safety of ocrelizumab and hyaluronidase-ocsq should be conducted.

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 100593, with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies 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 these studies. 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.

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 known serious risk of injection-related reactions or to assess a signal of a serious risk of breast cancer and malignancies overall.

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 these serious risks.

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

4689-3 Conduct an observational, single-arm safety study to assess the risk of injection-related reactions in patients treated with subcutaneously-administered ocrelizumab. The study should evaluate the incidence, clinical features, and severity of injection-related reactions to enable a detailed characterization of local and systemic injection-related reactions that can occur with subcutaneously-administered ocrelizumab. The study should involve monitoring subjects for at least 2 years following subcutaneously-administered ocrelizumab treatment initiation.

[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.

The timetable you submitted on August 14, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2025
Final Protocol Submission:	02/2026
Study Completion:	02/2030
Final Report Submission:	02/2031

4689-4 Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

The timetable you submitted on August 21, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2025
Final Protocol Submission:	02/2026
Study Completion:	11/2029
Final Report Submission:	11/2030

For potential fulfillment of PMR 4689-4, patients treated with ocrelizumab and hyaluronidase can be enrolled in the ongoing Study BA39731, intended to fulfill PMR 3194-2 for Ocrevus (ocrelizumab).

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 100593 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute

[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.

clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4689-5 Perform real-time Ocrevus Zunovo drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals at regular intervals through the end of shelf-life. The final results of this study and the toxicology risk evaluation for the levels of leachate detected in the drug product will be provided in the final study report to the BLA.

The timetable you submitted on August 16, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2025

Submit clinical protocols to your IND 100593 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 314.81(b)(3)(i)]. 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.

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

[5] 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

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 Elaine Gettelman, Regulatory Project Manager, by phone at (240) 402-6425 or by email at elaine.gettelman@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD, MA
Director (Acting)
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

PAUL R LEE
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