DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761053

BLA APPROVAL

Genentech, Inc.
Attention: Sonali Patel, PharmD
Senior Director, Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Patel:

Please refer to your Biologics License Application (BLA) dated and received on April 28, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ocrevus (ocrelizumab) injection, 30 mg/1 mL.

We acknowledge receipt of your major amendment dated December 16, 2016, which extended the goal date by three months.

LICENSING

We have approved your BLA for Ocrevus (ocrelizumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Ocrevus under your existing Department of Health and Human Services U.S. License No. 1048. Ocrevus is indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ocrelizumab drug substance at Genentech, Inc., in Vacaville, CA. The final formulated product will be manufactured and filled at (b) (4) The drug product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, Ocrevus, and will market it as an injection in a 300 mg/10 mL (30 mg/1mL) single-dose vial.

DATING PERIOD

The dating period for Ocrevus shall be 15 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.

FDA LOT RELEASE

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

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed, agreed-upon carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavyweight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761053**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for ocrelizumab was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of multiple sclerosis and the clinical trial design is similar to that of trials of previously approved drugs for the treatment of relapsing forms of multiple sclerosis.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Primary Progressive Multiple Sclerosis

We are waiving the pediatric study requirement for ages birth up to 17 years because necessary studies are impossible or highly impracticable. This decision is because of the small number of patients in this age group with primary progressive multiple sclerosis.

Relapsing Forms of Multiple Sclerosis

We are waiving the pediatric study requirement for ages birth up to 10 years because necessary studies are impossible or highly impracticable. This decision is because of the small number of patients in this age group with relapsing forms of multiple sclerosis.

In addition, we are deferring submission of your pediatric study for ages 10 up to 17 years because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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)(3)(B) of the FDCA. This required study is listed below.

3194-1 Conduct a two-part study of ocrelizumab in pediatric patients with relapsing multiple sclerosis (RMS) at least 10 years and less than 17 years of age. Part A is an open-label study of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ocrelizumab in pediatric patients. Part A will include two cohorts, one with body weights less than 40 kg and the other with body weights 40 kg or more. The objective of Part A is to determine a dose of ocrelizumab that will result in PK and PD effects that are comparable to those of a 600 mg dose (300 mg given twice 14 days apart) in adult patients with RMS. Safety assessments will continue for at least 2 years after the last dose of

ocrelizumab. Part B is a randomized, double-blind, parallel-group study to evaluate the efficacy and safety of ocrelizumab compared to an appropriate comparator.

Draft Protocol Submission:	02/2019
Final Protocol Submission:	09/2019
Study Completion:	07/2023
Final Report Submission:	01/2024

Submit the protocol(s) associated with this required postmarketing study to your IND 100593, 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 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 (PMRs) UNDER 505(o)

Section 505(o)(3) of the 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 breast cancer and malignancies overall related to the use of Ocrevus (ocrelizumab) or to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Ocrevus (ocrelizumab) during pregnancy.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

3194-2 Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to Ocrevus (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 Ocrevus. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

The timetable you submitted on March 10, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2017
Final Protocol Submission:	11/2017
Study Completion:	11/2029
Final Report Submission:	11/2030

3194-3 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to ocrelizumab during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to ocrelizumab before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on March 10, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2017
Final Protocol Submission:	10/2017
Study Completion:	10/2028
Final Report Submission:	10/2029

3194-4 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3194-3 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to ocrelizumab during pregnancy compared to an unexposed control population.

The timetable you submitted on March 10, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2017
Final Protocol Submission:	10/2017
Study Completion:	03/2023
Final Report Submission:	03/2024

3194-5 An expanded pre-and postnatal development study (including T-cell dependent antibody response [TDAR]) of Ocrevus (ocrelizumab) in nonhuman primate.

The timetable you submitted on March 24, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	05/2017
Final Protocol Submission:	11/2017
Study Completion:	05/2019
Final Report Submission:	12/2019

Submit the protocols associated with these PMRs to your IND 100593, with a cross-reference letter to this BLA. Submit all postmarketing final reports 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 protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance and enhanced pharmacovigilance for pancreatitis, cholecystitis and cholelithiasis, and serious and opportunistic infections, including progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation after exposure to ocrelizumab. Report all confirmed or possible cases to the BLA in an expedited fashion and include comprehensive summaries for these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].

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

We remind you of your postmarketing commitments:

3194-6 Perform a shipping study to confirm validation of the commercial ocrelizumab drug product shipping conditions. The study will be performed using representative shipping routes and drug product that has been stored for an extended period. The study will include testing of pre- and post-shipping samples for product quality (purity by SE-HPLC, reduced and non-reduced CE-SDS, IE-HPLC, sub-visible particles, visible particles, clarity/opalescence, and potency) and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2017

3194-7 Confirm validation of the Antibody-Dependent Cellular Cytotoxicity assay (Method Q12764). The validation study will be performed to demonstrate suitability of the method to be used as a potency assay for drug substance release testing.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2017

3194-8 Confirm validation of the Capillary Electrophoresis Glycan Analysis assay (Method Q12756). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of high-mannose 5 glycan (Man-5) for drug substance release testing.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2017

3194-9 Confirm validation of the (b) (4) assay (Method (b) (4)). The validation study will be performed to demonstrate suitability of the method to be used to assess levels of (b) (4) for drug substance release testing.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2017

3194-10 Confirm validation of the [(b) (4)] assay (Method [(b) (4)]) or develop, validate, and implement an alternative assay to evaluate [(b) (4)] The validation study will be performed to demonstrate suitability of the method for use in detecting [(b) (4)] during drug product storage and to be included in the drug product release specifications. The final validation report and updated specifications, if applicable, will be submitted to the BLA.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2017

3194-11 Manufacture, qualify, and implement new primary and secondary reference standards that are representative of the pivotal clinical study materials. The qualification protocol will be submitted as a PAS, and the final qualification report will be submitted to the BLA.

The timetable you submitted on March 14, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2017
Final Report Submission: 03/2018

3194-12 Perform a leachable study to evaluate the drug product container closure system through the end of shelf-life when stored under the recommended conditions. Testing will be performed at regular intervals and will include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report. The complete data and risk evaluation for potential impact of leachables on product safety and quality will be submitted to the BLA.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2019

3194-13 Confirm that the updates to the ocrelizumab drug substance manufacturing process and controls lead to the manufacturing of drug substance with critical product quality attributes consistent with those of the drug substance used to manufacture pivotal clinical study drug product.

The timetable you submitted on March 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2017
Final Report Submission: 03/2018

Submit chemistry, manufacturing, and controls protocols associated with these PMCs 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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 LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Robert Temple
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
03/28/2017