DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761083

BLA APPROVAL

Genentech, Inc.
Attention: Robyn Harrington
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Harrington:

Please refer to your Biologics License Application (BLA) dated June 23, 2017, received June 23, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for HEMLIBRA® (emicizumab-kxwh) injection, 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/mL.

LICENSING

We have approved your BLA for HEMLIBRA® (emicizumab-kxwh) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, HEMLIBRA under your existing Department of Health and Human Services U.S. License No. 1048. HEMLIBRA is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture emicizumab-kxwh drug substance at Chugai Pharma Manufacturing Co., Ltd. in Kita-ku, Tokyo, Japan. The final formulated product will be manufactured and filled at Chugai Pharma Manufacturing Co., Ltd. in Utsunomiya City, Tochigi, Japan, and labeled and packaged at F. Hoffmann-La Roche Ltd. in Kaiseraugst, Switzerland. You may label your product with the proprietary name, HEMLIBRA, and will market it in 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/mL single-dose vials.

DATING PERIOD

The dating period for HEMLIBRA shall be 24 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 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 HEMLIBRA 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 HEMLIBRA (emicizumab-kxwh), 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 carton and immediate container labels submitted on October 31, 2017, 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, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761083**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for HEMLIBRA was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of emicizumab-kxwh for the intended population.

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 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:

PMC 3299-1 Conduct an assessment of binding anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

The timetable you submitted on November 13, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2019

PMC 3299-2 Conduct an assessment of neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting neutralizing APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The neutralizing APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

The timetable you submitted on November 13, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

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

We remind you of your postmarketing commitments:

PMC 3299-3 Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation, and titer assay validation reports and assay standard operating procedures.

The timetable you submitted on November 3, 2017, states that you will develop and validate the assay according to the following schedule:

Final Report Submission: 01/2019

PMC 3299-4 Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay standard operating procedure.

The timetable you submitted on November 3, 2017, states that you will develop and validate the assay according to the following schedule:

Final Report Submission: 12/2019

PMC 3299-5 Re-evaluate the action limit and acceptance criterion for (b) (4) testing by validated (b) (4) method after data from (b) (4) drug substance batches are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results, action limit and acceptance criterion, and any proposed changes to the approved limit or criterion.

The timetable you submitted on November 6, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2018

PMC 3299-6 Re-evaluate the drug substance stability acceptance criteria for stability samples held at the (b) (4) °C condition after data from (b) (4) drug substance lots stored at (b) (4) °C for (b) (4) months are available. The final report should include the corresponding data, the analysis, and statistical plan used to evaluate the results and acceptance criteria and any proposed changes to the approved criteria.

The timetable you submitted on November 6, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2019

Submit clinical protocols to your IND 122954 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. 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.

For a period of 5 years, submit all cases of thrombotic microangiopathy and thromboembolic events reported with HEMLIBRA (emicizumab-kxwh) as 15-day Alert reports (as described under 21 CFR 600.80(c)(1)), and provide detailed analyses of events of thrombotic microangiopathy and thromboembolic events reported from clinical study and post-marketing reports in your periodic safety report. These analyses should show cumulative data relative to the date of approval of HEMLIBRA (emicizumab-kxwh) as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of thrombotic microangiopathy and thromboembolic events reported with HEMLIBRA (emicizumab-kxwh) should also be provided in the periodic safety report.

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 Laura Wall, Regulatory Project Manager, at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Office Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

RICHARD PAZDUR
11/16/2017