DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761089

BLA APPROVAL

Teva Pharmaceuticals USA, Inc.
c/o Teva Pharmaceutical Products R&D
Attention: Khalid Yousif
41 Moores Rd, P.O. Box 4011
Frazer, PA 19355

Dear Dr. Yousif:

Please refer to your Biologic License Application (BLA) dated and received October 16, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ajovy (fremanezumab-vfrm) injection, 150 mg/mL.

We acknowledge receipt of your major amendment dated May 14, 2018, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2016 to Teva Pharmaceuticals USA, Inc., North Wales, PA, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Ajovy (fremanezumab-vfrm). Ajovy is indicated for the preventive treatment of migraine in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture fremanezumab-vfrm at your facility, Celltrion, Inc., in Yeonsu-gu, Incheon, South Korea. The final formulated product will be manufactured and filled at (b) (4)
You may label your product with the proprietary name, Ajovy, and market it in a single-use prefilled syringe delivering 1.5 mL of 150 mg/mL fremanezumab-vfrm.

DATING PERIOD

The dating period for Ajovy 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 Ajovy 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 Ajovy (fremanezumab-vfrm), 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, patient package insert, and instructions for use). 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 label submitted August 22, 2018, and immediate container label submitted on July 5, 2018, as soon as they are available, but no more than 30 days after they are printed. We note your agreement in the August 22, 2018, submission to use an expiration date format of the following for the carton and container: MMMYYYY. 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 761089**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for fremanezumab-vfrm was not referred to an FDA advisory committee because outside expertise was not necessary; evidence of the efficacy of fremanezumab-vfrm was deemed acceptable and non-controversial, and its safety profile was deemed acceptable.

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 studies requirement for children 0 to 5 years of age. In children 0 to 5 years of age, clinical studies for the preventive treatment of migraine would be highly impracticable because very few children of this age can be definitively diagnosed with migraine and even fewer would be candidates for preventive therapy.

We are deferring submission of your pediatric studies for children 6 to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies 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 these postmarketing studies must be reported annually, according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

3485-1 A juvenile animal toxicology study in one species.

Final Report Submission: 04/2018 (submitted)

3485-2 An open-label pharmacokinetic, safety, and tolerability study in pediatric migraine patients ages 6 through 11 years, with an optional open-label safety extension phase (40 weeks).

Final protocol submission: 05/2018 (submitted)
Study completion: 09/2019
Final report submission: 12/2022

3485-3 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of episodic migraine in children and adolescents ages 6 through 17 years. This study includes a double-blind treatment phase (12 weeks) and an open-label safety extension phase (40 weeks). This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission: 03/2019
Study completion: 03/2022
Final report submission: 12/2022

3485-4 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of chronic migraine in adolescents ages 12 through 17 years. This study includes a double-blind treatment phase (12 weeks) and an open-label safety extension phase (40 weeks). This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission: 03/2019
Study completion: 03/2023
Final report submission: 12/2023

Submit the protocol(s) to your IND 106,533, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a biologics license application (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 identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Ajovy (fremanezumab-vfrm) 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 studies:

3485-5 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Ajovy during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Ajovy before or during pregnancy and the other consisting of women without migraine. 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 September 6, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	12/2019
Annual Interim Report Submissions:	06/2021
	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
Study Completion:	12/2027
Final Report Submission:	12/2028

3485-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3485-5 (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 Ajovy during pregnancy compared to an unexposed control population.

The timetable you submitted on September 6, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	12/2019
Annual Interim Report Submissions:	06/2021
	06/2022
	06/2023
	06/2024
	06/2025
	06/2026
	06/2027
Study Completion:	12/2027
Final Report Submission:	12/2028

Submit clinical protocol(s) to your IND 106,533, 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 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 for liver toxicity, myocardial infarction, stroke, and retinal detachment after exposure to Ajovy. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age and gender. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of fremanezumab-vfrm therapy, concomitant therapies, treatment given for the event, and outcome. Include a comparison to background rates expected in a migraine population of the same age and gender.

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 Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of 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/

ELLIS F UNGER
09/14/2018