DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761063

BLA APPROVAL

Eli Lilly and Company
Attention: Conrad J. Wong, Ph.D
Advisor, Regulatory Affairs - North America
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wong:

Please refer to your Biologics License Application (BLA) dated and received September 27, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Emgality (galcanezumab-gnlm) injection, 120 mg/mL.

LICENSING

We have approved your BLA for Emgality (galcanezumab-gnlm) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Emgality under your existing Department of Health and Human Services U.S. License No. 1891. Emgality is indicated for the preventive treatment of migraine in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture galcanezumab-gnlm at your facility, ImClone Systems LLC, in Branchburg, New Jersey. The final formulated product will be manufactured, filled, labeled, and packaged at Eli Lilly and Company in Indianapolis, Indiana. You may label your product with the proprietary name, Emgality, and market it in a single-dose prefilled syringe delivering 1 mL of 120 mg/mL galcanezumab-gnlm, and a prefilled pen delivering 1 mL of 120 mg/mL galcanezumab-gnlm.

DATING PERIOD

The dating period for Emgality 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 no more than (b) (4) °C.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Emgality 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 Emgality, 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 AND 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 CFR 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 Prescribing Information, 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 CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on May 3, 2018, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761063**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for galcanezumab-gnlm was not referred to an FDA advisory committee because outside expertise was not necessary; evidence of the efficacy of galcanezumab-gnlm 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 study requirement for episodic migraine in patients 0 to 5 years of age. In children 0 to 5 years of age, clinical studies for the preventive treatment of episodic migraine would be highly impracticable because very few children of this age can be definitively diagnosed with episodic migraine and even fewer would be candidates for preventive therapy.

We are waiving the pediatric study requirement for chronic migraine in patients 0 to 11 years of age. In children 0 to 11 years of age, clinical studies for the preventive treatment of chronic migraine would be highly impracticable because few children of this age can be definitively diagnosed with chronic migraine and even fewer would be candidates for preventive therapy.

We are deferring submission of your pediatric studies in episodic migraine, for children and adolescents 6 to 17 years of age, and for chronic migraine, for adolescents 12 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:

3498-1 Deferred pediatric randomized, double-blind, placebo-controlled study under PREA to assess the pharmacokinetics (Part A), and efficacy and safety (Part B) for the preventive treatment of episodic migraine in children and adolescents ages 6 through 17 years. Part A includes an option to enroll in an open-label safety extension phase (9 months), followed by a post treatment phase (4 months). Part B includes a double-blind treatment phase (3 months) and an open-label safety extension phase (9 months), followed by a post treatment phase (4 months). This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission:	02/2019
Study completion:	02/2024
Final report submission:	03/2024

3498-2 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 (3 months) and an open-label safety extension phase (9 months), followed by a post treatment phase (4 months). This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission:	02/2019
Study completion:	02/2024
Final report submission:	03/2024

Submit the protocol(s) to your IND, 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 Emgality 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:

3498-3 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 Emgality during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Emgality 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 24, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	11/2019
Annual Interim Report Submissions:	11/2020
	11/2021
	11/2022
	11/2023
	11/2024
	11/2025
	11/2026
	11/2027
	11/2028
	11/2029
	11/2030
	11/2031
Study Completion:	11/2032
Final Report Submission:	11/2033

3498-4 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3498-3 (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, preterm births, and small-for-gestational-age births in women exposed to Emgality during pregnancy compared to an unexposed control population.

The timetable you submitted on September 24, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	11/2019
Annual Interim Report Submissions:	11/2020
	11/2021
	11/2022
	11/2023
	11/2024
	11/2025
Study Completion:	12/2026
Final Report Submission:	12/2027

Submit clinical protocol(s) to your IND 111295, 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 cases of anaphylaxis or suspected anaphylaxis after exposure to Emgality. 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 Emgality 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 Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) 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).

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 4207
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 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 E. Andrew Papanastasiou, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
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
09/27/2018