BLA 761279

BLA APPROVAL

Eli Lilly and Company
Attention: Conrad J. Wong, Ph.D.
Executive Director
Global Regulatory Affairs – North America
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wong:

Please refer to your biologics license application (BLA) dated and received March 30, 2022, submitted under section 351(a) of the Public Health Service Act for Omvoh (mirikizumab-mrkz) injection.

We acknowledge receipt of your resubmission dated May 24, 2023, which constituted a complete response to our March 30, 2023, action letter.

LICENSING

We have approved your BLA for Omvoh (mirikizumab-mrkz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Omvoh under your existing Department of Health and Human Services U.S. License No. 1891. Omvoh is indicated for the treatment of moderately to severely active ulcerative colitis in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture mirikizumab-mrkz drug substance at Eli Lilly Kinsale Limited, Kinsale, County Cork, Ireland (FEI: 3002806888). The final formulated drug product will be manufactured, filled, labeled, and packaged at Eli Lilly and Company, Indianapolis, Indiana (FEI: 1819470). You may label your product with the proprietary name, Omvoh, and market it in 300 mg/15 mL (20 mg/mL) single-dose vials for intravenous infusion and 100 mg/mL single-dose prefilled pens for subcutaneous injection.

DATING PERIOD

The dating period for Omvoh shall be 24 months from the date of manufacture when stored at 2°C to 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 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 Omvoh 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 Omvoh, 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 with minor editorial revisions listed below and reflected in the enclosed labeling.

Prescribing Information
- Removed (b) (4) from page 14

Medication Guide
- Removed (b) (4) from page 3

Instructions for Use-Prefilled Pen
- Removed (b) (4) from page 7

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, Instructions for Use, and Medication Guide). Information on submitting SPL files using eLIST may be found in the 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.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling 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 761279**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Omvoh (mirikizumab-mrkz) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 the potential presence of Omvoh (mirikizumab-mrkz) in human breast milk resulting in effects on the breastfed infant; to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Omvoh (mirikizumab-mrkz) during pregnancy; or to identify an unexpected serious risk of liver injury from the use of Omvoh (mirikizumab-mrkz).

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:

4409-1 Perform a lactation study (milk only) in lactating women who have received Omvoh (mirikizumab-mrkz), regardless of indication, to assess concentrations of mirikizumab-mrkz in breast milk using a validated assay and to assess the effects on the breastfed infant.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2025
Final Report Submission:	12/2026

4409-2 Conduct a prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to mirikizumab-containing products regardless of indication during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2034
Final Report Submission:	12/2035

4409-3 Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement 4409-2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to mirikizumab-containing products regardless of indication during pregnancy compared to an unexposed control population.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Study Completion:	12/2030
Final Report Submission:	12/2031

4409-4 Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active ulcerative colitis who are exposed to Omvoh (mirikizumab-mrkz), relative to other therapies used to treat ulcerative colitis. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the Omvoh (mirikizumab-mrkz)-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	12/2024
Interim Submission:	12/2030
Study Completion:	12/2036
Final Report Submission:	06/2037

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 clinical protocol(s) to your IND 125444 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).**

[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.

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.

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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4409-5 Complete the ongoing phase 2 trial to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical response to Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2024

4409-6 Conduct a one-year trial to evaluate the safety, efficacy, and pharmacokinetics of Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2024
Study Completion: 04/2029

Final Report Submission: 10/2029

4409-7 Conduct a long-term extension trial to evaluate the long-term safety of Omvoh (mirikizumab-mrkz) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in the postmarketing commitment 4409-6. This study can be conducted as part of the postmarketing commitment 4409-6.

The timetable you submitted on October 2, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2024
Study Completion:	04/2034
Final Report Submission:	10/2034

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 125444 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**."

REQUESTED PHARMACOVIGILANCE

We request that for Omvoh (mirikizumab-mrkz) you submit all serious and non-serious domestic and/or foreign cases of hepatotoxicity as 15-day "Alert reports" (described under 21 CFR 600.80(c)(1)) through the 3rd year following initial U.S. approval date.

We request that you provide a separate narrative summary and analysis of hepatotoxicity, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 600.80(c)(2), quarterly during the first 3 years post-approval. Your analysis should include interval and cumulative data relative to the date of approval of Omvoh (mirikizumab-mrkz). Your analysis should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, hepatic enzymes and liver function tests, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

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*.[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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

Biological product deviations, sent by courier or overnight mail, should be addressed to:

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

Your product is a combination product per 21 CFR Part 3. Therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at: https://www.fda.gov/combinationproducts/guidance-regulatory-information/postmarketing-safety-reporting-combinationproducts

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 Kelly Richards, Senior Regulatory Health Project Manager, at (240) 402-4276 or email at kelly.richards@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, M.D.
Acting Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container 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/

NIKOLAY P NIKOLOV
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