CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761279Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	October 25, 2023
Reviewer(s):	Xi Wang, PhD, MPH Division of Epidemiology I
Team Leader:	Benjamin Booth, PhD, MS Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name(s):	Mirikizumab
Application Type/Number:	BLA 761279
Applicant/sponsor:	Eli Lily
TTT:	2022-697

1. BACKGROUND INFORMATION

1.1. Medical Product

Mirikizumab (OMVOH) is an interleukin-23 antagonist (IL-23) indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).[1] FDA issued a complete response letter detailing issues pertaining to the proposed manufacturing of mirikizumab on March 30, 2023.[2,3] On May 24, 2023, the Sponsor resubmitted the application. (b) (4) (b) (4) (b) (4)

Prescribing Information (USPI) for mirikizumab recommends induction dosing by intravenous infusion at 300 mg for at least 30 minutes at Weeks 0, 4, and 8. The maintenance dosing by subcutaneous injection recommended by USPI is at dosing at 200 mg administered by subcutaneous injection (given as two consecutive injections of 100 mg each) at Week 12, and every 4 weeks thereafter.[4]

1.2. Describe the Safety Concern

The Division of Gastroenterology (DG) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based safety signal detection studies among women exposed to mirikizumab during pregnancy.

Safety due to drug exposure during pregnancy is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[5]

UC is an inflammatory bowel disease (IBD) which is an autoimmune condition that often occurs in women of reproductive potential. IBD occurs in 0.5% of the U.S. population and approximately half of those are females. The American College of Obstetricians and Gynecologists (ACOG) recommends the continuation of treatment to optimize disease management and pregnancy outcomes, and therefore exposures, both intended and unintended, to mirikizumab during pregnancy are anticipated. Clinical studies provide insufficient information about the safety of mirikizumab when used during pregnancy. As of March 22, 2022, clinical data are available for the use of mirikizumab in 34 pregnant women and pregnancy outcomes include normal live births (n=7), preterm births (n=1), ongoing cases (n=11), elective abortions (n=6), spontaneous abortions (n=5), and unknown outcomes (n=4). No congenital malformations were reported and the reasons for elective abortion were not specified.[6]

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[1] OMVOH label as of October 3rd, 2023. \\CDSESUB1\evsprod\BLA761279\0069\m1\us\proposed-uspi-clean.docx.
[2] Richards K, Beitz J, BLA Multi-Disciplinary Review and Evaluation, filed under BLA 761279 on March 30, 2023 (DARRTS Reference ID: 5150357).
[3] Beitz J, Complete Response, filed under BLA 761279 on March 30, 2023 (DARRTS Reference ID: 5150402).
[4] See footnote 1.
[5] Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed February 2nd, 2023.
[6] Applicant's Four-Month Update of Safety Information, page 43. \\CDSESUB1\evsprod\BLA761279\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5353-rep-analys-data-more-one-stud\iss\iss-46-120-day-safety-update-report.pdf.

Sponsor proposed labeling for mirikizumab has the following information regarding pregnancy.[7]

8.1 Pregnancy

Risk Summary

Available data from case reports of mirikizumab-mrkz use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although there are no data on mirikizumab-mrkz, monoclonal antibodies can be actively transported across the placenta, and mirikizumab-mrkz may cause immunosuppression in the in utero-exposed infant. An enhanced pre- and post-natal development study conducted in pregnant monkeys at a dose 69 times the maximum recommended human dose (MRHD) revealed no adverse developmental effects to the developing fetus, or harm to infant monkeys from birth through 6 months of age. There are risks of adverse pregnancy outcomes associated with increased disease activity in women with inflammatory bowel disease (see Clinical Considerations).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because mirikizumab-mrkz may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to OMVOH in utero. There are no data regarding infant serum levels of mirikizumab-mrkz at birth and the duration of persistence of mirikizumab-mrkz in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 2 months after birth should be considered because of the half-life of the product.

Data

Animal data

An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys administered mirikizumab-mrkz by intravenous injection during organogenesis to parturition at a dose of 300 mg/kg twice weekly (69 times the MRHD based on exposure comparisons). Mirikizumab-mrkz crossed the placenta in monkeys. No maternal toxicity was noted in this study. No mirikizumab-mrkz-related effects on morphological, functional, or immunological development were observed in infant monkeys from birth through 6 months of age. However, incidences of embryo/fetal loss were higher in the treated groups compared to control (6.7% [1 of 15] in controls vs 26.7% [4 of 15] at 300 mg/kg (69 times the MRHD, based on exposure comparisons)) but were within the range of historical control data. Following delivery, most adult female cynomolgus monkeys and all infants from the mirikizumab-mrkz-treated group had measurable serum

[7] See footnote 1.

concentrations up to 28 days postpartum. In the infant monkeys, mean serum concentrations were approximately 4.8 times the respective mean maternal concentrations.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in pregnant women or women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g. retrospective cohort study using claims or electronic medical record data or a case-control study

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records; the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. The study using claims or electronic medical data may be algorithm-based. If it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.

Analytical tools: The required PMRs target more than one outcome, including major malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births. The required ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully implemented in post marketing surveillance for maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

Two PMRs related to pregnancy outcomes were issued:[8]

1. 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.
2. Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement 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.

[8] See footnote 2.

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	October 25, 2023
Reviewer(s):	Xi Wang, PhD, MPH Division of Epidemiology I
Team Leader:	Benjamin Booth, PhD, MS Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum Assessment for Safety Surveillance of Mirikizumab
Drug Name(s):	Mirikizumab
Application Type/Number:	BLA 761279
Applicant/sponsor:	Eli Lily
TTT #:	2022-697

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Mirikizumab (OMVOH) is an interleukin-23 antagonist (IL-23) indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). FDA issued a complete response letter detailing issues pertaining to the proposed manufacturing of mirikizumab on March 30, 2023.[1] On May 24, 2023, the Sponsor submitted the resubmission. The Sponsor also has ongoing clinical programs seeking approval for mirikizumab for Crohn's disease (CD) and plaque psoriasis (PsO) patients.

Prescribing Information (USPI) for mirikizumab recommends induction dosing by intravenous infusion at 300 mg for at least 30 minutes at Weeks 0, 4, and 8. The maintenance dosing by subcutaneous injection recommended by USPI is at dosing at 200 mg administered by subcutaneous injection (given as two consecutive injections of 100 mg each) at Week 12, and every 4 weeks thereafter.[2]

1.2. Describe the Safety Concern

The Division of Gastroenterology (DG) presented the safety concern of hepatotoxicity in the treatment of UC. There were four studies conducted in the UC program, including AMAC, AMAN, AMBG, and AMAP and one subject was considered as Hy's Law case in the AMBG study.[3]

At DG's request, the Drug-Induced Liver Injury (DILI) Team in the Division of Hepatology and Nutrition (DHN) assessed mirikizumab for hepatotoxicity. The DILI Team completed a case level analysis of 34 subjects with elevations in liver biochemistry.[4] They found that 29 subjects were unlikely to have DILI due to mirikizumab, and 5 subjects were at least possible mirikizumab DILI cases. Among these five possible cases, there was only one Hy's Law case identified which is consistent with DG and the applicant's assessments.

Therefore, the DILI team concluded that "MKZ carries a hepatotoxicity risk that is likely immune-mediated and only one Hy's Law case was identified in approximately 1600 subjects exposed to at least one dose of MKZ. Liver injury is likely to be a concern post-market should MKZ be approved. However, if efficacy and need are significant then we can support approval with proper attention to labeling, monitoring, and post-market research requirements."

The Integrated Review (Section 8.3) for this BLA recommends three measures to mitigate possible DILI risk.[5] First, the label contains following language in the Warning and Precautions section:

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[1] Beitz J, Complete Response, filed under BLA 761279 on March 30, 2023 (DARRTS Reference ID: 5150402)
[2] OMVOH label as of October 3rd, 2023. \\CDSESUB1\evsprod\BLA761279\0069\m1\us\proposed-uspi-clean.docx.
[3] Eli Lily, Summary of Clinical Safety (submitted to BLA 761279 (eTCD 0001) on March 30, 2022, p140).
[4] Lan L, PH Hayashi, M Avigan, and F Anania, Division of Hepatology and Nutrition Consultation, filed under BLA 761279 on Nov 15, 2022 (DARRTS Reference ID: 5080876).
[5] OMVOH label as of October 3rd, 2023. \\CDSESUB1\evsprod\BLA761279\0069\m1\us\proposed-uspi clean.docx

5.4 Hepatotoxicity

A case of drug-induced liver injury (alanine aminotransferase [ALT] 18x the upper limit of normal (ULN), aspartate aminotransferase [AST] 10x ULN, and total bilirubin 2.4x ULN) in conjunction with pruritis was reported in a clinical trial subject following a longer than recommended induction regimen. OMVOH was discontinued. Liver test abnormalities eventually returned to baseline.

Evaluate liver enzymes and bilirubin at baseline and for at least 24 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

Second, a postmarketing study should be required at the time of approval. Third, further evaluation of this safety signal will also occur through an enhanced pharmacovigilance.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

1.4. Statement of Purpose

The purpose of this memo is to evaluate whether the Sentinel Active Risk Identification and Analysis (ARIA) system is sufficient to assess an unexpected risk for serious liver injury from mirikizumab when used in the post-marketing setting to treat adults with UC.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Decisions about sample size should assess DILI as an infrequent event, expected to occur in no more than 1 patient for every 1600 patients treated.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired surveillance population was defined as patients with moderately to severely active UC.

2.2 Is ARIA sufficient to assess the intended population?

Yes, we determined that the Sentinel Distributed Database (SDD) could permit the identification of patients with a medical care encounter linked to a UC diagnosis (ICD-10-CM K51). However, it is not possible to differentiate the severity of UC patients.

3 EXPOSURES

3.1 Treatment Exposure(s)

If approved, exposure to mirikizumab will be adequately captured via National Drug Codes (NDC) codes and/or Healthcare Common Procedure Coding System (HCPCS) codes.

3.2 Comparator Exposure(s)

For a comparator population, we identified UC patients with initiation of therapeutic treatment for moderately to severely active disease. Examples include two JAK inhibitors (tofacitinib and upadacitinib) and ozanimod, three TNFα-inhibitors (adalimumab, golimumab, infliximab), one IL-12/23 inhibitor (ustekinumab), one anti-Integrin agent (vedolizumab), and a recently approved IL-23 inhibitor (risankuzimab).

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify exposure of mirikizumab and comparators after the approval.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcome of interest is mirikizumab-induced liver disease.

4.2 IS ARIA sufficient to assess the outcomes of interest?

No. For pre-market assessment, FDA guidance for industry describes certain laboratory test results, such as alanine transaminase and bilirubin elevation, as the "single clearest predictor" for a drug's potential for severe hepatotoxicity.[6] We determined access to laboratory data (either directly or indirectly through chart review) as a necessary condition for sufficient assessment of DILI risk. However, ARIA currently has limited access to laboratory data in electronic health records (EHRs) and the completeness of lab data in ARIA is uncertain. ARIA does not include medical chart review of patients' records. Validated claims-based algorithms for drug induced hepatoxicity are unavailable in published literature.

5 COVARIATES

5.1 Covariates of Interest

Important baseline covariates include age, sex, medical history (particularly pre-existing liver diseases such as viral and alcoholic hepatitis), and drug-treatments (particularly drugs with DILI potential).

5.2 Is ARIA sufficient to assess the covariates of interest?

Yes. Satisfactory analysis using ARIA might estimate DILI risk in (1) patient groups defined by sex and (2) a patient group without pre-existing liver disease or recent exposure to a non-mirikizumab drug with DILI potential. With this purpose in mind, we assessed variables derived from elements in the: SDD demographic table (i.e., Birth_Date and Sex) as reliable and accurate indicators of patient age and sex; SDD diagnosis table (i.e., ADate, DX, Dx_Codetype, and PDX) as sufficient indicators for the medical history covariates of interest; SDD dispensing table (i.e., RxDate and Rx CodeType) and procedure table (i.e., ADate,PX, and PX_CodeType) as sufficient indicators for the drug treatment covariates of interest.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

[6] Food and Drug Administration Guidance for Industry, July 2009, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, accessed at https://www.fda.gov/media/116737/download on February, 2023, p 4.

6.1 Surveillance or Study Design

We assessed ARIA tools for signal detection and the design of interest will be a cohort study.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes. ARIA Level 2 tools (Covariate Stratification or Propensity Score Analysis) are sufficient for estimating relative risks for the outcome of interest (DILI) during defined periods of time after the initiation of treatment with mirikizumab (drug of interest) or comparator therapeutic.

7 NEXT STEPS

We determine that the Sentinel ARIA is insufficient to evaluate the safety of mirikizumab as it is unable to adequately identify the outcome of interest. The review team recommends a 505(o)(3) PMR fitting the description shown below.[7]

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 mirikizumab, 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 mirikizumab-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.

[7] See footnote 1.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 5, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name, Dosage Form, and Strength:	Omvoh (mirikizumab-mrkz) injection, 300 mg/15 mL vial, 100 mg/mL prefilled pen (b) (4) (b) (4)
Applicant/Sponsor Name:	Eli Lilly
TTT ID #:	2022-702-4
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on October 3, 2023 for Omvoh. The Division of Gastroenterology (DG) requested that we review the revised carton labeling for Omvoh (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to the information request[a] to revise the vial container label route of administration to be consistent with the vial carton labeling. In addition, the Applicant submitted final container label and carton labeling for the autoinjector as well, which we previously reviewed and found acceptable.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Richards, K. Information Request for Omvoh (BLA 761279). Silver Spring (MD): FDA, CDER, OND, DG (US); 2023 OCT 03.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 28, 2023

To: Kelly Richards, Senior Regulatory Health Project Manager
Division of Regulatory Operations for Immunology and Inflammation,
Division of Gastroenterology (DG)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for OMVOH™ (mirikizumab-mrkz) injection, for intravenous or subcutaneous use [resubmission]

BLA: 761279

Background:
In response to DG's consult request dated September 21, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original BLA resubmission for OMVOH™ (mirikizumab-mrkz) injection, for intravenous or subcutaneous use.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI, MG, and IFU is based on the draft labeling emailed to OPDP on September 21, 2023, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the Applicant to the electronic document room on May 24, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 22, 2023
To:	Kelly Richards, RN, MSN, RAC Senior Regulatory Health Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	OMVOH (mirikizumab-mrkz)
Dosage Form and Route:	injection, for intravenous or subcutaneous use
Application Type/Number:	BLA 761279
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On May 24, 2023, Eli Lilly and Company submitted for the Agency's review a Class 2 Resubmission for Biologics License Application (BLA) 761279 for OMVOH (mirikizumab-mrkz) injection, for intravenous or subcutaneous use, in response to the Complete Response Letter issued by the Agency on March 30, 2023. The proposed indication for OMVOH (mirikizumab-mrkz) is for the treatment of adult patients with moderately to severely active ulcerative colitis.

On September 21, 2023, the Division of Gastroenterology (DG) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for OMVOH (mirikizumab-mrkz) injection, for intravenous or subcutaneous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG and IFU for OMVOH (mirikizumab-mrkz).

2 MATERIAL REVIEWED

- Draft OMVOH (mirikizumab-mrkz) MG and IFU received on May 24, 2023 and received by DMPP on September 21, 2023.
- Draft OMVOH (mirikizumab-mrkz) Prescribing Information (PI) received on May 24, 2023, and received by DMPP on September 21, 2023.

3 CONCLUSIONS

We find the Applicant's proposed MG and IFU are acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 12, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name, Dosage Form, and Strength:	Omvoh (mirikizumab-mrkz) injection, 300 mg/15 mL vial, 100 mg/mL prefilled pen (b) (4) (b) (4)
Applicant/Sponsor Name:	Eli Lilly
TTT ID #:	2022-702-3
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on September 8, 2023 for Omvoh. The Division of Gastroenterology (DG) requested that we review the revised carton labeling for Omvoh (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Vee, S. Label and Labeling Review for Omvoh (BLA 761279). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 15. TTT ID No.: 2022-702-2.

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/

SARAH K VEE
09/12/2023 08:57:04 AM

IDALIA E RYCHLIK
09/12/2023 08:40:41 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 15, 2023
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name, Dosage Form, and Strength:	Omvoh (mirikizumab-mrkz) injection, 300 mg/15 mL (20 mg/mL) vial, 100 mg/mL prefilled pen (b) (4) (b) (4)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly
FDA Received Date:	May 24, 2023
TTT ID #:	2022-702-2
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Omvoh (mirikizumab-mrkz) injection, the Division of Gastroenterology (DG) requested that we review the proposed Omvoh prescribing information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

BLA 761279 was originally submitted on March 30, 2022 and received a complete response (CR) on March 30, 2023 due to deficiencies in facilities inspections. Eli Lilly submitted a response to the CR on May 24, 2023. We reviewed the prescribing information, container label, and carton labeling during the previous review cycle (see Appendix B).

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed label and labeling for Omvoh to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We note that we reviewed the proposed prescribing information (PI), container labels, and carton labeling during the previous review cycle (See Appendix B). The Applicant notes that there are no changes to the PI, container labels, and carton labeling for the prefilled (b) (4) pen.

The Applicant states that they revised the vial carton labeling to add *"Dispense enclosed Medication Guide to each patient" on the primary display panel. To make room for this addition, the text "Discard unused portion." was moved to the side panel."*

The proposed carton labeling for the vial may be improved to promote the safe use of the product from a medication error perspective. We provide our recommendations below in Section 5.1 for Eli Lilly.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the carton labeling for Omvoh may be improved to promote the safe use of the product. We provide specific recommendations to the Applicant in Section 5.1 below.

5.1 RECOMMENDATIONS FOR ELI LILLY

We recommend the following be implemented prior to approval of this BLA:

A. Carton Labeling (Vial)
    1. As currently presented the discard statement "Discard Unused Portion" is on the side panel. Including the discard statement in close proximity to the package type helps to increase the intended technique of use. In this instance that is using the vial to achieve a single dose and discarding product remaining in the vial thereafter. Relocate the discard statement "Discard Unused Portion" to the PDP. For example, "Single-dose vial – Discard Unused Portion."
    2. We recommend revising the route of administration from (b) (4) (b) (4) to "For Intravenous Infusion After Dilution" for added clarity. We also recommend removing the statement, (b) (4) as this statement is no longer needed.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Omvoh received on February 24, 2023 from Eli Lilly.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Omvoh</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Nonproprietary Name</td><td>mirikizumab-mrkz</td></tr>
<tr><td>Indication</td><td>for the treatment of moderately to severely active ulcerative colitis in adults</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion and subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>injection</td></tr>
<tr><td>Strength</td><td>300 mg/15 mL (20 mg/mL) vial, 100 mg/mL prefilled pen (b) (4) (b) (4)</td></tr>
<tr><td>Dose and Frequency</td><td><u>Recommended Dosage</u>
• The recommended induction dosage is 300 mg administered by intravenous infusion over at least 30 minutes at Weeks 0, 4, and 8.
• The recommended maintenance dosage is 200 mg administered by subcutaneous injection (given as two consecutive injections of 100 mg each) at Week 12, and every 4 weeks thereafter.</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th></th><th>Strength</th><th>Pack Size</th></tr>
<tr><td>For Intravenous Infusion</td><td></td><td></td></tr>
<tr><td>Single-dose Vial</td><td>300 mg/15 mL (20 mg/mL)</td><td>Carton of 1</td></tr>
<tr><td>For Subcutaneous Use</td><td></td><td></td></tr>
<tr><td>Single-dose Prefilled Pen</td><td>100 mg/mL</td><td>Carton of 2</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>• Store refrigerated at 2°C to 8°C (36°F to 46°F).
• Do not freeze. Do not use OMVOH if it has been frozen.
• Do not shake.
• Keep OMVOH in the original carton to protect from light until the time of use.
• OMVOH is sterile and preservative-free. Discard any unused portion.
• If needed, the prefilled pen may be stored at room temperature up to 30°C (86°F) for up to 2 weeks in the original carton to protect from light. Once OMVOH has been stored at room temperature, do not return to the refrigerator. If these conditions are exceeded, OMVOH must be discarded.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 4, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "mirikizumab". Our search identified two previous reviews[a,b], and we confirmed that our previous recommendations were implemented.

[a] Vee, S. Label and Labeling Review for mirikizumab-mrkz (BLA 761279). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. TTT ID No.: 2022-630/2022-702.

[b] Vee, S. Label and Labeling Review for mirikizumab-mrkz (BLA 761279). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 OCT 12. TTT ID No.: 2022-630-1/2022-702-1.

APPENDIX F. LABELS AND LABELING

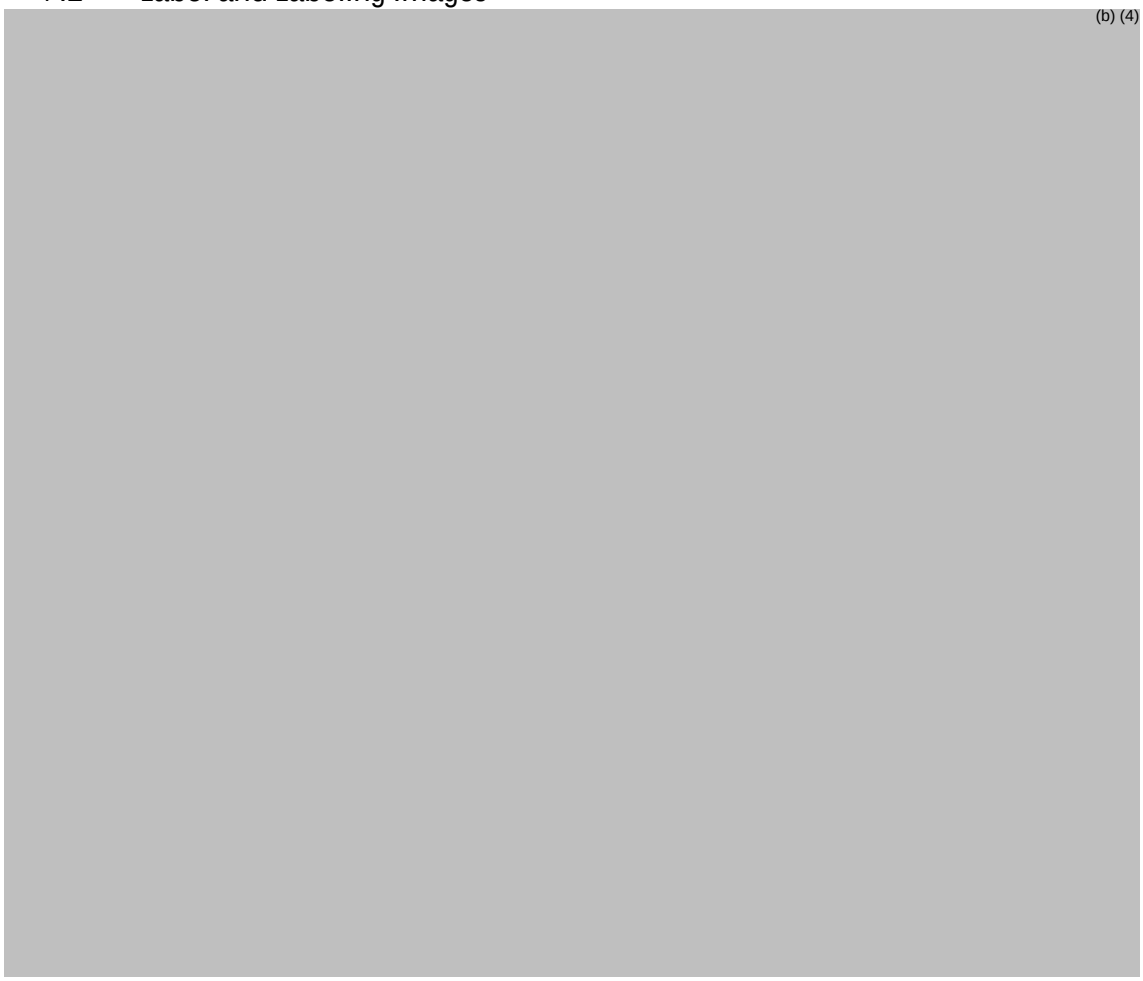
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Omvoh labels and labeling submitted by Eli Lilly.

- Carton labeling received on May 24, 2023
- Prescribing Information (Image not shown) received on March 17, 2023, available from \\CDSESUB1\evsprod\BLA761279\0059\m1\us
- Medication Guide received on March 17, 2023, available from \\CDSESUB1\evsprod\BLA761279\0059\m1\us

F.2 Label and Labeling Images

(b) (4)



[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

SARAH K VEE
08/15/2023 12:33:35 PM

IDALIA E RYCHLIK
08/15/2023 12:41:36 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW	
COA Tracking ID:	C2022145
BLA Number (reference IND):	761279 (125444)
Sponsor:	Eli Lilly and Company
Established Name/Trade Name:	LY3074828 (mirikizumab)
Indication:	Treatment of adult patients with moderately to severely active ulcerative colitis ☐Rare Disease/Orphan Designation ☐Pediatrics
Meeting Type:	BLA Review
Review Division:	Division of Gastroenterology
Clinical Reviewer	Aysegul Gozu
Clinical Team Leader (TL)	Matt Kowalik
Regulatory Project Manager:	Kelly Richards
Reviewer:	Susan Pretko, PharmD, MPH
COA TL:	Onyeka Illoh, OD, MPH
COA Director:	David Reasner, PhD
Instruments reviewed:	☒ Patient-reported outcome (PRO) • Bowel Urgency Numeric Rating Scale • Patient's Global Rating of Change • Patient's Global Rating of Severity

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to BLA 761279 for mirikizumab, proposed for the indication of treatment of adult patients with moderately to severely active ulcerative colitis (UC).

The Applicant proposes the following patient-reported outcome (PRO) measure to support labeling claims:

- Urgency Numeric Rating Scale (NRS): a patient-reported outcome (PRO) measure assessing urgency severity (sudden or immediate need) to have a bowel movement (BM) in the past 24 hours using a 0-10 NRS. A copy of the Urgency NRS is in Appendix 1.

DCOA reviewed the PRO evidence dossier for the Urgency NRS to support a labeling claim.

The review concludes the following:

- The qualitative and quantitative evidence submitted by the Applicant demonstrate that the Urgency NRS is fit-for-purpose[1] to measure urgency (sudden or immediate need) to have a BM for the context of use of this drug development program.
- The meaningful change threshold in Urgency NRS change scores appears to be dependent on baseline urgency severity, where patients with more severe urgency

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)

severity at baseline require a greater amount of improvement to be considered meaningful.

- The treatment difference between the placebo and mirikizumab arms in the phase 3 clinical trials was statistically significant. However, there was a modest separation between treatment arm curves across the range of change scores identified as meaningful (i.e., beginning at a threshold of -3.5 to -4 points; see Section 3.4.6).
- During the BLA review, the Applicant proposed alternative labeling describing the proportion of patients with Urgency NRS weekly average scores of 0 or 1 (b) (4) The qualitative evidence supports that achieving an Urgency NRS score of 0 or 1 would be meaningful to patients.

For future clinical trials with the objective of demonstrating that change in UC symptoms was maintained and/or continued to improve throughout the maintenance treatment period, the analysis should be based on change in symptom scores from maintenance baseline to the end of maintenance treatment, rather than change from induction baseline to the end of the maintenance treatment period.

[Reviewer's Comments: *On March 30, 2023, DG issued a Complete Response for this BLA 761279 due to deficiencies identified by Office of Pharmaceutical Manufacturing Assessment (OPMA) during a pre-license inspection at one of the Applicant's manufacturing facilities. DG anticipates the application will be resubmitted as soon as deficiencies have been satisfactorily resolved.]*

2 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- BLA 761279 is classified as a standard review. The user feel goal date is March 30, 2023.
- The Agency provided comment on the Urgency Numeric Rating Scale (NRS) under the reference IND 125444.
- (b) (4)

Previous COA Reviews:

- C2021351_IND 125444_Pretko (DARRTS Reference ID: 4875007)
- C2018298_IND 125444_Kovacs (DARRTS Reference ID: 4418654)
- C2017346_IND 125444_Kovacs (DARRTS Reference ID: 4368575)
- C2017250_IND 125444_Kovacs (DARRTS Reference ID: 4215706)
- C2017217_IND125444_Kovacs (DARRTS Reference ID: 4161427)

Disease Background:

Ulcerative Colitis (UC) is a chronic, relapsing disease characterized by diffuse mucosal inflammation of the colon. The precise etiology of UC is unknown; however, it is thought to be caused by an inappropriate inflammatory response to the gut contents in genetically predisposed

individuals. Clinical manifestations of active disease include bloody diarrhea (with or without mucus), urgency, tenesmus, abdominal pain, weight loss, fever, and malaise.

Investigational Product:

Mirikizumab (LY3074828) is among the first of a new class of interleukin-23p19 (IL-23p19) inhibitor monoclonal antibody potential treatments for patients with moderately to severely active UC. Mirikizumab was developed with the aim of providing symptomatic relief and reducing colonic inflammation. It is administered via monthly intravenous (IV) infusions during induction treatment when patients are most symptomatic and have the highest UC inflammatory burden. Following induction, monthly self-administered subcutaneous (SC) injections deliver maintenance treatment using a (b) (4) autoinjector (pen).

3 CLINICAL OUTCOME ASSESSMENT REVIEW

3.1 Clinical Trial Population

3.1.1 Study AMAN

Subjects eligible for Study 16T-MC-AMAN included adult subjects aged ≥ 18 and ≤ 80 years with moderately to severely active UC[2] with prior medication failure[3]. A total of 1,162 subjects were included in the modified intent-to-treat (mITT) population.

3.1.2 Study AMBG

Subjects eligible for Study 16T-MC-AMBG included Induction Responders and Induction Non-Responders from Study AMAN. A total of 544 subjects were responders to mirikizumab induction dosing and were re-randomized to receive either placebo or mirikizumab maintenance therapy.

3.2 Clinical Trial Design and Study Endpoints

3.2.1 Study AMAN

Study AMAN was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled 12-week phase 3 study designed to evaluate the safety and efficacy of mirikizumab 300mg IV infusion at Weeks 0, 4, and 8, compared to placebo in inducing clinical remission in patients with moderately to severely active UC.

The primary endpoint was the proportion of patients in clinical remission at Week 12 as assessed by the Modified Mayo score (MMS). Change from baseline in Urgency NRS score at Week 12 was a multiplicity-adjusted secondary endpoint. All of the primary and major secondary endpoints were met. For the Urgency NRS change at Week 12, the results of study AMAN showed a difference between the mirikizumab and placebo treatment groups of -0.95 (p-value: < 0.00001).

[2] Moderately to severely active UC is defined by a modified Mayo score (MMS) of 4 to 9 with an endoscopic subscore (ES) ≥2, with endoscopy performed within 14 days before baseline.
[3] Prior medication failure is defined as patients with an inadequate response to, loss of response to, or intolerance to a) at least 1 of the medications used in conventional treatment (i.e., corticosteroids or immunomodulators AND biologic therapy), or b) biologic therapy for UC.

3.2.2 Study AMBG

Study AMBG was a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-arm study 40-week phase 3 study evaluating the safety and efficacy of mirikizumab 200 mg SC every 4 weeks in maintaining treatment response at Week 40 (Week 52 of continuous study drug treatment).

The primary endpoint was the proportion of patients in clinical remission at Week 40 as assessed by the Modified Mayo score (MMS). Change from induction baseline in Urgency NRS score at Week 40 and the proportion of patients with Urgency NRS = 0 or 1 at Week 40 (among patients with NRS ≥3 at induction baseline), were multiplicity-adjusted secondary endpoints. All of the primary and major secondary endpoints were met. The results of study AMBG showed a difference between the mirikizumab and placebo treatment groups in Urgency NRS change at Week 40 as -1.06 (p-value: < 0.001) and in Urgency responder endpoint as 17.9% (p-value: < 0.001).

***[Reviewer's Comment(s):** For the maintenance hypothesis, the endpoint analysis should test no clinically meaningful within-patient change in Urgency NRS scores from maintenance baseline to week 40, rather than the change from induction baseline to week 40.]*

3.2.3 COA Schedule of COA Assessments

Patient-reported outcome (PRO) data was collected in Studies AMAN and AMBG using an electronic diary (e-Diary) device. The Urgency NRS and Patient Global Rating of Severity (PGRS) were assessed daily through Week 12 in Study AMAN and through Week 40 or early termination visit (ETV) in Study AMBG. In Study AMAN, the Patient Global Rating of Change (PGRC) was assessed at Weeks 4, 8, 12, and ETV and in Study AMBG, the PGRC was assessed from weeks 12-28 in subjects that experienced loss of response and Week 40 and ETV for all other subjects.

Study participants were trained in person by clinical site staff on how to use the e-Diary device at screening Visit 0 of Study AMAN.

***[Reviewer's Comments:** The training material provided to study subjects appears appropriate to support data collected by the Urgency NRS.]*

3.3 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant proposed the following COA-related labeling claims in the draft label (in blue), where study UC-1 is study AMAN and study UC-2 is study AMBG.

Study UC-1

(b) (4)

(b) (4)

Study UC-2

(b) (4)

[Reviewer's comment: *As described in Section 3.4.6., the threshold for meaningful improvement in Urgency NRS scores appears to be between -3.5 and -4.0. The treatment difference between the placebo and mirikizumab arms in the phase 3 clinical trials was statistically significant. However, there was a modest separation between treatment arm curves across the range of change scores identified as meaningful (i.e., beginning at a threshold of -3.5 to -4 points; see Section 3.4.6).*

During BLA review, the Applicant proposed labeling (b) (4) [redacted] *However,* (b) (4) [redacted] *is less likely to be misleading.*

*Bowel urgency is described in labeling for RINVOQ (Skyrizi)[4]. However, bowel urgency was assessed using a different response scale (i.e., Yes/No, in response to the question, "Did you experience bowel urgency in the last 24 hours?" Refer to the COA review for RINVOQ for more detail.[5]**]***

3.4 Clinical Outcome Assessment(s)

3.4.1 Clinical Outcome Assessment Description(s)

3.4.1.1 Urgency NRS

The Urgency NRS is a single-item PRO measure assessing severity of a patient's urgency (sudden or immediate need) to have a bowel movement (BM) in the past 24 hours using an 11-point NRS ranging from 0 ("No urgency") to 10 ("Worst possible urgency"). The Urgency NRS and details on its use in Study AMAN are in **Appendix 1**.

3.4.1.2 PGRS

The PGRS is a single-item PRO measure assessing overall UC symptom severity in the past 24-hours using a 6-point verbal response scale (VRS). The PGRS is in **Appendix 2.1**.

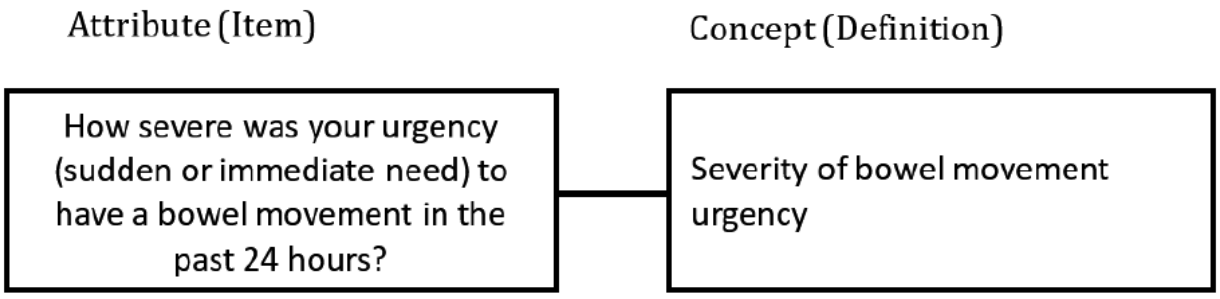
3.4.1.3 PGRC

The PGRC is a single-item PRO measure assessing UC symptoms now compared to how they were before starting the study medicine, using a 7-point VRS. The PGRC is in **Appendix 2.2**.

3.4.2 Conceptual Framework of the Urgency NRS

The conceptual framework of the Urgency NRS is in the figure below.

[4] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211675s003lbl.pdf
[5] C2021397_NDA 211675-s07_Pretko (DARRTS Reference ID: 4949627)



3.4.3 Scoring algorithm

3.4.3.1 Urgency NRS

Daily total scores for the Urgency NRS are calculated as the exact number selected by the respondent on the e-Diary, ranging from 0-10. Weekly scores for the Urgency NRS are subsequently calculated as the mean daily score for a 7-day period.

The weekly Urgency NRS score was recorded as missing if there were fewer than 4 available measurements in the relevant 7 days. To support the missing data rule, the Applicant conducted an interim evaluation in study AMAN based on Spearman correlations between the number of missing Urgency NRS diary days and the average weekly PGRS score, Urgency NRS score, Mayo Stool Frequency subscore, Mayo Rectal Bleeding subscore, and the symptomatic Mayo score and a simulation study.

3.4.3.2 PGRS

PGRS responses are collected daily, and daily scores are graded on a 6-point scale scored as 1) 'none,' 2) 'very mild,'3) 'mild,' 4) 'moderate,' 5) 'severe, and 6) 'very severe.' Weekly PGRS scores are derived as the mean daily score over 7-days, rounded to the nearest integer. If fewer than 4 days are available (i.e., not missing), then the weekly PGRS score is considered missing.

3.4.4 Content Validity for the Urgency NRS

The Applicant conducted the following research activities to inform development and refinement of the Urgency NRS:

- Targeted literature review of published qualitative research studies in patients with mild-severely active UC and evaluation of existing PRO measures.
- Collection of expert input to confirm the concepts of UC that are of greatest clinical relevance to patients (n=2 (1 gastroenterologist and 1 expert in COAs))
- Cross-sectional mixed methods (qualitative and quantitative designs) study consisting of concept elicitation (CE) interviews (n=21), cognitive interviews (n=16), and a 2-week pilot study (n=41) in subjects with mild-severely active UC.
- Hybrid CE/cognitive interviews (n=20 participants with moderate-severely active UC)

Additionally, to better understand the prevalence of bowel movement urgency in patients with UC, the Applicant conducted an ad hoc analysis using real world data from a Study of a Prospective Adult Research Cohort with IBD (SPARC IBD), a multicenter longitudinal study of adult patients

with IBD that collects and links clinical data, PRO data, and serial biosamples throughout the course of the patients' disease.[6]

The top 3 symptoms identified in the CE interviews were frequent BMs, abdominal pain, and urgent/sudden BMs. The Applicant decided to develop a PRO measure assessing urgency given the following:

1. Abdominal pain and frequent BMs are evaluated as part of the MMS
2. Input from 2 clinical experts confirmed urgency symptom severity is an important symptom to measuring UC disease activity

A daily diary format was chosen to minimize the impact of recall bias and to account for the chronic nature and potential day-to-day variation of BM urgency. Given that patients described BM urgency most frequently in terms of the amount of time needed to find a bathroom, the Applicant decided it was most appropriate to assess BM urgency in terms of severity. The 0 to 10-point NRS was selected to provide finer gradation of response options and because it is readily applied cross-culturally and across languages.

[Reviewer's Comment: *Based on review of qualitative input from patients with UC, it appears appropriate to assess BM urgency in terms of severity as patients most frequently described their experience with urgency in terms of the amount of time needed to find a bathroom.**]***

Content validity of the Urgency NRS was initially evaluated in semi-structured cognitive interviews (n=16). All participants in the cognitive interviews understood the Urgency NRS as intended and reported the Urgency NRS was relevant to their experience with UC. Additionally, no patients reported issues with the recall period of 'past 24 hours nor difficulty in rating urgency severity using the 11-point NRS, and only 1 participant suggested using a response scale other than the NRS. The majority of subjects (n=12/16) reported that they did not have difficulty remembering to complete the Urgency NRS on a daily basis.

[Reviewer's Comment: *The population in the cognitive interviews were comparable to the population in studies AMAN and AMBG.**]***

Following Agency review of the results of the cognitive interviews, the Agency recommended that the sponsor conduct additional cognitive interviews given that most patients (n=14/16) included in the cognitive interview study had some college or certification program or a higher degree. The sponsor conducted semi-structured hybrid CE/cognitive interviews to confirm that patients with a lower education level understand the concept of urgency and the terminology used in the Urgency NRS as intended.

A total of 20 participants were interviewed (7 of whom reported highest-level of education was a high school diploma or less). All participants reported bowel urgency was part of their experience with UC (n=8 (40%) spontaneously reported, and all other participants reported experiencing bowel urgency when asked directly by the interviewer) and described bowel urgency using similar terminology as participants in the initial CE interviews.

[6] Crohn's & Colitis Foundation. https://www.crohnscolitisfoundation.org/research/current-research-initiatives/sparc-ibd

Participants in the hybrid CE/cognitive interviews were asked about when they had been in remission in relation to bowel urgency. While some participants were able to describe a time in their life since being diagnosed with UC where their bowel urgency went away completely (n=9/20), none used the term "bowel urgency remission" to describe this state.

Of the 7 participants with a high school diploma or less, all reported understanding urgency with BMs and the Urgency NRS response options as intended and endorsed that urgency with BMs was relevant to their experience with UC, that they did not have difficulty responding based on the 'past 24 hours' recall period, and that the 'past 24 hours' recall period was appropriate (only 4/7 participants spontaneously discussed the suitability of the recall period).

Additional input was obtained from the hybrid CE/cognitive issues regarding the Urgency NRS response scale:

- Among all participants, 3 (n=3/20, 15.0%) felt that the 11-point NRS was too broad.
- Mild bowel urgency was described as being able to make it to the bathroom with ease (n=6, 30.0%) and "normal" or "almost normal" (n=6, 30.0%). Others talked about mild urgency meaning less worry (n=4, 20.0%), being able to go places (n=2, 10.0%) and eat any foods (n=2, 10.0%).
    - When placing 'mild' urgency along the 11-point NRS, the majority of participants rated 'mild' along the first third of the scale (i.e., response options up to 3: n=17/20, 85.0%)
- Moderate bowel urgency was described as making sure you are close to the bathroom (n=8, 40.0%) and an increase in BM frequency (n=4, 20.0%); 2 participants described 'moderate' urgency as not having to go to the bathroom very often and being able to delay a bathroom visit for a half hour.
    - When placing 'moderate' urgency along the 11-point NRS, the majority of participants rated 'moderate' between 4 and 6 (n=16/20, 80.0%).
- Severe bowel urgency was described as "uncontrollable" (n=8/20, 40.0%) and placed limits on the ability to leave the house or ability to work (n=8, 40.0%).
    - When placing 'severe' urgency along the 11-point NRS, the majority of participants rated 'severe' as 8-10+ (n=13/20, 65.0%).
    - Seven participants (35.0%) rated 'severe' as 6-8 on the 11-point NRS and described a "worst level" of bowel urgency greater than just 'severe' (e.g., "worst", "super-severe", and "extreme" urgency)

[<u>Reviewer's comment</u>: *The results of the qualitative research demonstrated that bowel urgency is a relevant and important symptom that was spontaneously reported by the majority of participants with moderately-severely active UC. Participants most commonly described urgency severity in terms of the amount of time to find a bathroom to avoid an accident. Based on the qualitative evidence submitted by the Applicant, the Urgency NRS appears to have content validity for the proposed context of use.****]***

3.4.5 Other Measurement Properties

3.4.5.1 2-Week Daily Diary Pilot Study

A 2-week daily diary pilot study with 41 adult patients with UC to assess the measurement properties of the daily diary items in participants with UC, including the Urgency NRS. For each daily diary item, weekly average scores were calculated as the mean item score over each 7-day period (Week 1: Day 1 to Day 7; Week 2: Day 8 to Day 14). Weekly average scores were calculated for participants with at least 4 of 7 days of complete diary data and were considered missing otherwise.

The results of the pilot study for the Urgency NRS are summarized below.

- All participants in Week 1, and 40 participants in Week 2 completed the daily diary for at least 4 of 7 days.
- The mean average Urgency NRS score for Week 1 was 4.47 (SD: 2.46; range: 0-8.33) and for Week 2 was 4.20 (SD: 227; range: 0-7.86).
- No floor nor ceiling effects were observed
- Test-retest reliability was assessed by comparing Week 1 and Week 2 average scores. The Intraclass Correlation Coefficient (ICC) was 0.877 (range: 0.7710 to 0.947).
- Construct validity was assessed using Pearson and Spearman Correlations between the Urgency NRS score and SF and PGRS scores for Week 1. Average Urgency NRS scores were highly correlated (i.e., correlation coefficient > 0.7) with average PGRS score and moderately correlated (correlation coefficient 0.3 to ≤ 0.5) with Average SF scores.

3.4.5.2 Quantitative Assessments in studies AMAN and AMBG

Known-groups validity was evaluated at Baseline for the Urgency NRS using collapsed PGRS scores (PGRS Score ≤ 3 and PGRS Score > 3) and median PGRS Groups at Baseline in Study AMAN. The analysis results showed the Urgency NRS was able to distinguish between known groups defined by collapsed PGRS categories ($p<0.0001$) and by median PGRS ($p<0.0001$)

Responsiveness of Urgency NRS was evaluated using one-way analysis of covariance comparing mean change from Baseline to Week 12 in Study AMAN and to Week 40 in Study AMBG in Urgency NRS score based on Clinical Remission Status, Clinical response status, PGRS scores, uncollapsed PGRS category change, and uncollapsed PGRC categories. For both Study AMAN and AMBG, Urgency NRS scores demonstrated responsiveness based on clinical remission ($p<0.0001$), subjects who met clinical response status ($p<0.0001$), and subjects who reported at least a 2-point improvement (Much better) on the PGIC ($p<0.05$). In Study AMAN, responsiveness was demonstrated for PGIC no change and all improvement categories ($p\leq0.001$), whereas in Study AMBG, responsiveness was demonstrated only for ≥ 2-point improvement in PGRS response categories ($p<0.05$).

[Reviewer's Comments:** The results of these quantitative analyses support the reliability, validity, and responsiveness to change for the Urgency NRS.**]

3.4.6 Interpretation of Meaningful Within-Patient Urgency NRS Score Change

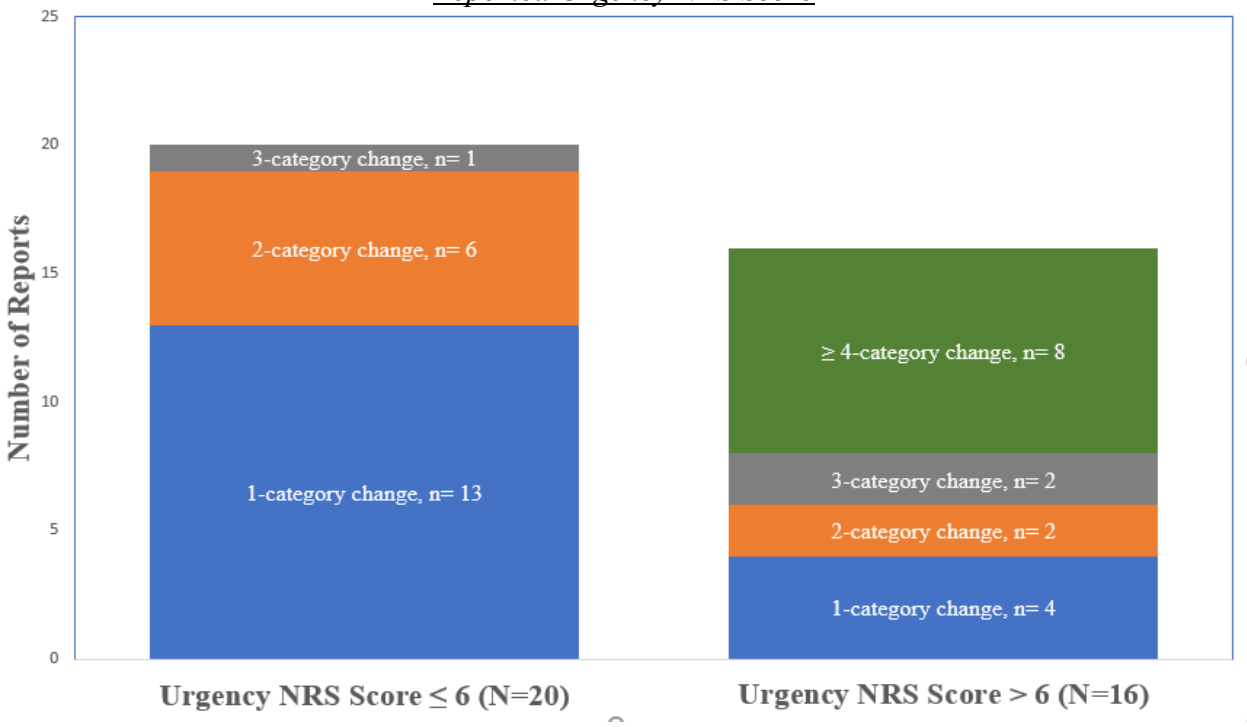
3.4.6.1 Qualitative Evidence

Participants in the cognitive interviews and hybrid CE/cognitive interviews, participants were asked what they perceived to be the minimal amount of improvement on the Urgency NRS to consider that change 'meaningful' (n=16 participants asked in the cognitive interviews; n=20 participants asked in the hybrid CE/cognitive interviews). The Applicant noted that results from the qualitative interviews should be interpreted with caution given the small sample size and that results were based on a hypothetical treatment-related improvement.

In the hybrid CE/cognitive interviews, 9 participants defined meaningful bowel urgency improvement as gone completely, and 9 participants defined improvement in terms of urgency being "reduced", "better", or "normal" but not gone completely.

[Reviewer's Comments: *Figure 1 was developed by the COA reviewer to summarize the qualitative evidence describing amount of change in Urgency NRS scores considered meaningful by subjects with moderately-severely active UC. Information from the cognitive interviews is based on review of the cognitive interview transcripts whereas information from the hybrid CE/cognitive interviews is based on the qualitative summary report (transcripts from the hybrid CE/cognitive interviews were not submitted).*

Figure 1. *Urgency NRS Response Category Change Reflecting Meaningful Improvement, by Reported Urgency NRS Score*



Approximately 56% (n=20) of participants interviewed reported having an Urgency NRS score ≤ 6 and approximately 44% (n=16) of participants interviewed reported having an Urgency NRS score > 6. For participants that reported an Urgency NRS score ≤ 6, the majority reported a 1-

category change as a meaningful improvement (n=13, 65%). However, for participants that reported an Urgency NRS score > 6, only 25% (n=4) reported a 1-category change as a meaningful improvement. Half of participants with more severe urgency reported meaningful improvement as ≥ 4-category change in Urgency NRS scores (n=8) suggesting that patients with more severe urgency need a greater amount of change to consider it a meaningful improvement.

Based on the review of the cognitive interview transcripts, approximately 31% of participants (n=5) reported that change in Urgency NRS score ending in the 3–5-point range would be meaningful (4 participants reported an Urgency NRS score of 4-6 and reported a 1-category improvement would be meaningful; 1 participant reported an Urgency NRS score of 10 and reported moving to a 5 would reflect a meaningful improvement).

Regarding the endpoint based on the weekly average Urgency NRS score of 0 or 1, the largest proportion of participants in the cognitive interviews (n=5/16, approximately 31%) reported they would need to achieve an Urgency NRS score of 1 to consider an ideal treatment a success. Only 1 participant (approximately 6%) reported they would need to achieve an Urgency NRS score of 0.

Amongst hybrid CE/cognitive interview participants (N=20), participants described an improvement in bowel urgency in the past as times when bowel urgency was gone completely, and 9 participants described an improvement in bowel urgency as times when their bowel urgency had "reduced" or "improved".]

3.4.6.2 Quantitative Evidence

The Applicant proposed a threshold of ≥ 3-point improvement to reflect meaningful within patient change in Urgency NRS score, based on triangulation of results from anchor-based (using the PGRS as an anchor) and distribution-based analyses.

[Reviewer's Comments: *Based on internal discussion of the results from the Applicant's anchor-based analysis, subjects with more severe bowel urgency scores at baseline appear to consider meaningful change in bowel urgency using a higher change threshold compared to subjects with less severe bowel urgency scores at baseline. This divergence is supported by the qualitative evidence described in Section 3.4.6.1.*

During the BLA review, the Agency asked the Applicant to conduct subgroup analyses on subjects with an MMS ≥ 5 for the change from baseline in Urgency NRS scores at Week 12 (AMAN) and Week 40 (AMBG). The results of these analyses are in Appendix 3. Based on these data, the Applicant updated the proposed range of thresholds for clinically meaningful within-patient change on the Urgency NRS to be from -3.2 to -4.9 points. Refer to the BLA 761279 Multi-Disciplinary Review and Evaluation (Unireview) for more detail (DARRTS Reference ID: 5150357).

Based on COA review of the anchor-based analyses, the range of thresholds identified as meaningful appears to be between -3.5 and -4 points.

The PGRS is not an ideal anchor scale to interpret Urgency NRS scores given that it asks patients to rate their overall UC symptoms rather than asking specifically about the bowel urgency concept. However, based on the correlation observed between the Urgency NRS and PGRS in the daily diary pilot study (see Section 3.4.5.1.), and clear separation of curves in the eCDF plots in Appendix 3, the PGRS appears to function as an appropriate anchor scale for the proposed purpose.

The PGRC may be appropriate for secondary analyses supporting interpretation of meaningful change in Urgency NRS scores, although it is noted that the results of the PGRC may be subject to recall bias.

During BLA review, a concern was raised that subjects with more BMs in the day have more opportunity to experience urgency and thus "Urgency severity" may capture both Urgency severity and frequency. This is supported by real-world data from the Study of a Prospective Adult Research Cohort with IBD (SPARC-IBD), a prospective, multicenter, longitudinal study of adult patients with IBD, as shown in Table 8[7]*.*

Table 8. Associations of Urgency and Clinical Outcomes within 7 Days of Enrollment

	No Urgency[a] (N=207)	Mild[a] (N=164)	Moderate[a] (N=74)	Moderately Severe or Severe[a] (N=69)	Total
Average daily bowel movement					
n	207	164	74	65	510
Mean (SD)	2.8 (2.02)	3.8 (3.71)	5.2 (3.06)	7.6 (4.69)	4.1 (3.56)
Median	2.0	3.0	5.0	6.0	3.0
Min, Max	0, 10	1, 40	1, 16	1, 20	0, 40

Additionally, in the CE interviews, 20 participants provided information on symptoms that occur with "severe bowel urgency" and frequent BMs was reported as the most common co-occurring symptom (n=18/20, 90.0%), followed by abdominal pain (n=13/20, 65%), blood in stool (n=9/20, 45%), and fatigue (n=6/20, 30%). However, average SF was only moderately correlated with average Urgency NRS score as described in Section 3.4.5.1. Future research should further explore the relationship between bowel urgency severity and BM frequency.]

[7] IND 125444 SN 108 (103) received July 11, 2019 containing a COA Evidence Dossier for the Urgency NRS.

6. APPENDICES

Appendix 1. Additional Information for the Urgency NRS

Appendix 1.1. Copy of the Urgency NRS

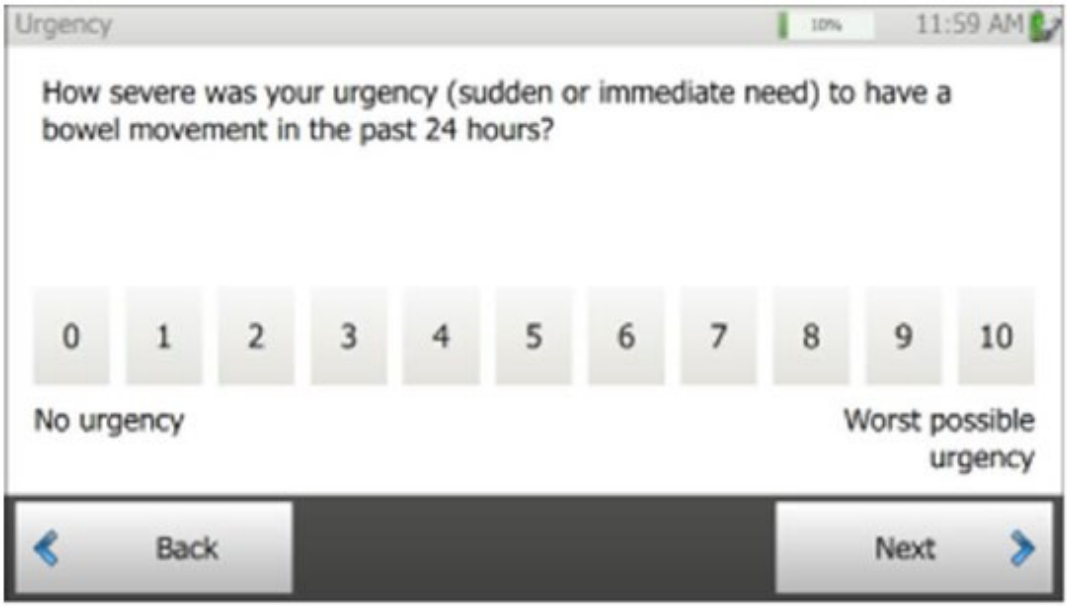


Figure 5.1. Screenshot of urgency numeric rating scale.

Appendix 1.2. Details on use of the Urgency NRS in Study AMAN

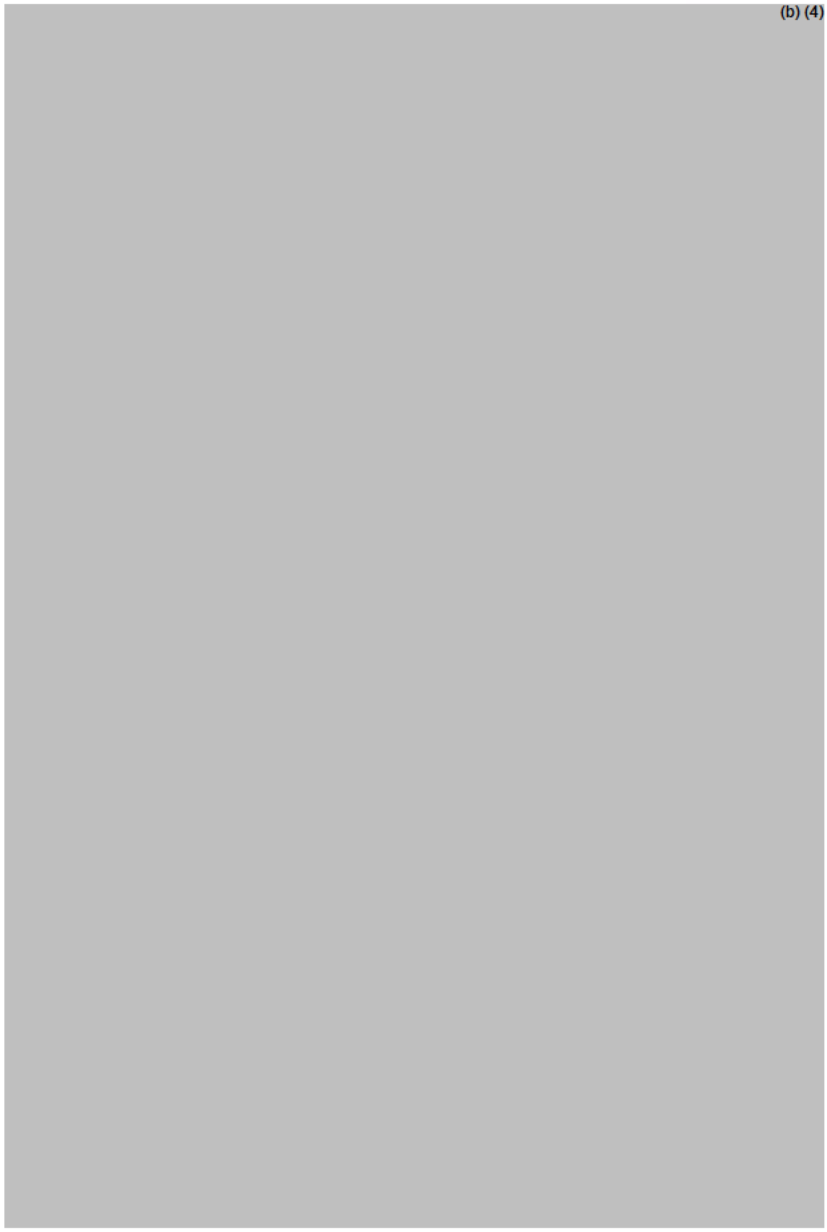
The Urgency NRS was completed daily via electronic data capture on a provisioned hand-held mobile TrialMax Touch™ device (e-Diary). During Study AMAN, the Urgency NRS was collected daily from screening (Visit 0; ≤28 days from Visit 1) through Week 12 (Visit 5) or ETV.

The Urgency NRS is 1 of 8 items collected in the daily e-Diary. The item is fourth in the order of collection, following the completion of the severity of rectal bleeding (RB) item, stool frequency (SF) count, and a nocturnal stool count item. The Applicant states that the Urgency NRS can be completed within 1 minute by clinical study participants.

Appendix 2. Copies of the PGRS and PGRC

Appendix 2.1. Copy of the PGRS

(b) (4)

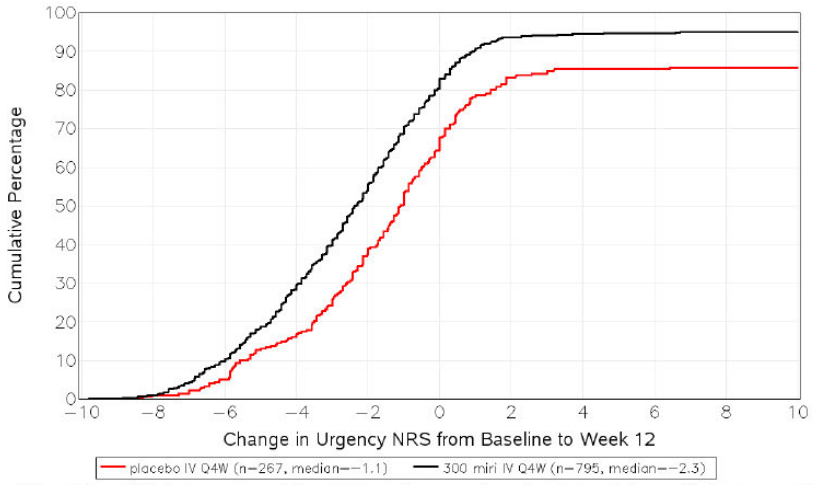


Appendix 2.2. Copy of the PGRC

(b) (4)

Appendix 3. Evidence to support interpretation of urgency NRS scores

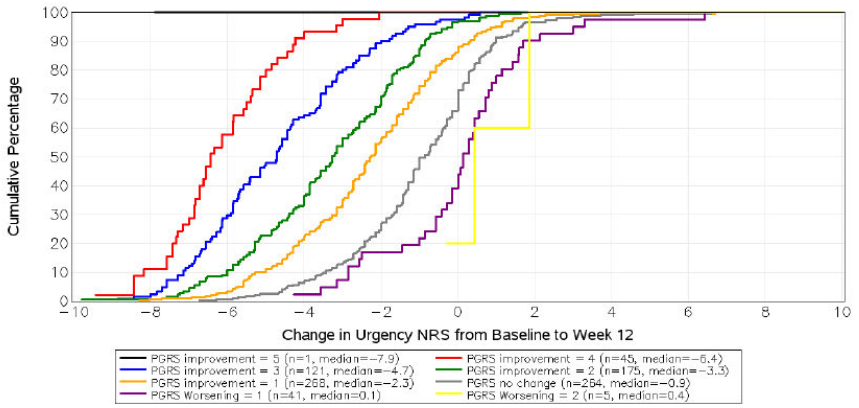
Change from Baseline to Week 12



Abbreviations: IV = intravenous; miri = mirikizumab; n= number of participants in specified category; NRS = Numeric Rating Scale; Q4W = once every 4 weeks.

Figure 4.5. **Empirical cumulative distribution plot of change from baseline to Week 12 on Weekly Urgency NRS score by treatment, Study AMAN.**

Empirical Cumulative Distribution Plot of Change from Baseline to Week 12 on Weekly Urgency NRS Score by Uncollapsed Change from Baseline to Week 12 in Day 7 PGRS in 7-Day Period
Modified Intent-to-Treat Population - Patients with Baseline MMS >=5
I6T MC AMAN - Induction Period



Abbreviations: n = number of patients with non-missing values; MMS = Modified Mayo Score; NRS = Numeric Rating Scale; PGRS = Patient's Global Rating of Severity.

Note: Weekly Urgency NRS was calculated by averaging data from available daily diary entries of Urgency NRS for a 7-day period. If fewer than
4 diary entries were available in a 7-
day period, the weekly Urgency NRS and the worst PGRS were considered missing. Daily PGRS scores were considered missing if the patient did not respond for PGRS on that day. All analyses are as observed.

Dataset: /lillyce/prd/ly3074828/i6t mc aman/final/data/analysis/restricted/adsl addd4.sas7bdat
Program: /lillyce/prd/ly3074828/i6t mc aman/final/programs/tfl/gho/f urg chg pgrs cdf pdf mitt mms5.sas
Output: /lillyce/prd/ly3074828/i6t_mc_aman/final/output/restricted/tfl/gho/f_urg_chg_pgrs_cdf_pdf_mitt_mms5.rtf

Table 5.7. **Change in the Weekly Average Urgency NRS Score (Unrounded) from Baseline to Week 12 by Change from Baseline in PGRS**
Modified Intent-to-Treat Population – Patients with Baseline MMS ≥5
I6T-MC-AMAN – Induction Period

PGRS Calculation: [Worst PGRS in 7 Day Period]

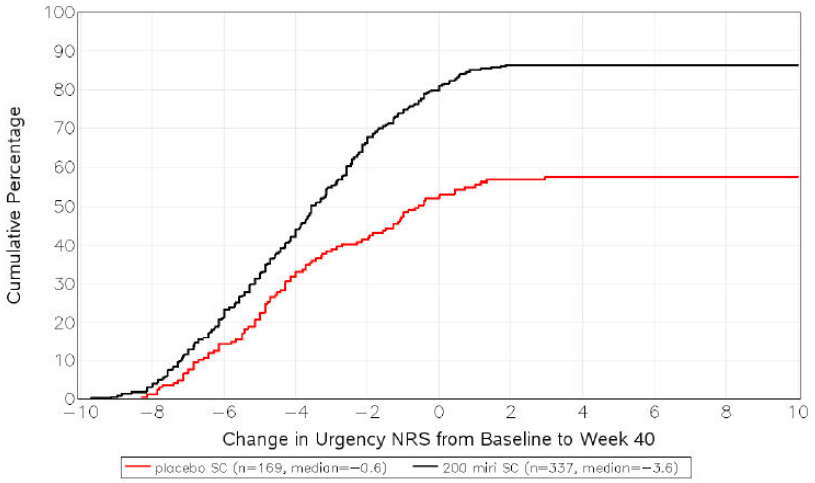
Change from Baseline in PGRS	N (%)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Improved 5 Categories	2(0.2)	-7.57	-7.57	-7.21	-6.86	-6.86
Improved 4 Categories	47(4.8)	-7.83	-7.17	-6.57	-5.00	-4.00
Improved 3 Categories	93(9.5)	-7.14	-6.00	-5.14	-4.14	-2.29
Improved 2 Categories	212(21.6)	-6.33	-5.24	-3.57	-2.14	-0.86
Improved 1 Category	326(33.2)	-4.57	-3.33	-2.14	-1.00	0.00
No Change	267(27.2)	-3.25	-2.00	-0.71	0.29	1.14
Worsened 1 Category	33(3.4)	-0.86	0.14	0.54	1.57	3.20
Worsened 2 Categories	3(0.3)	-0.57	-0.57	1.86	4.82	4.82
Worsened 3 Categories	0					
Worsened 4 Categories	0					
Worsened 5 Categories	0					
Overall	983(100.0)	-5.88	-4.29	-2.29	-0.71	0.43

N = number of patients with non-missing values; NRS = Numeric Rating Scale; PGRS = Patient's Global Rating of Severity.

Weekly Urgency NRS was calculated by averaging data from available daily diary entries of Urgency NRS for a 7-day period.

The PGRS parameter was calculated several different ways: (1) the worst PGRS in a 7-day window, and (2) each day in the 7-day window. Each page represents a different way of calculating the PGRS parameter.

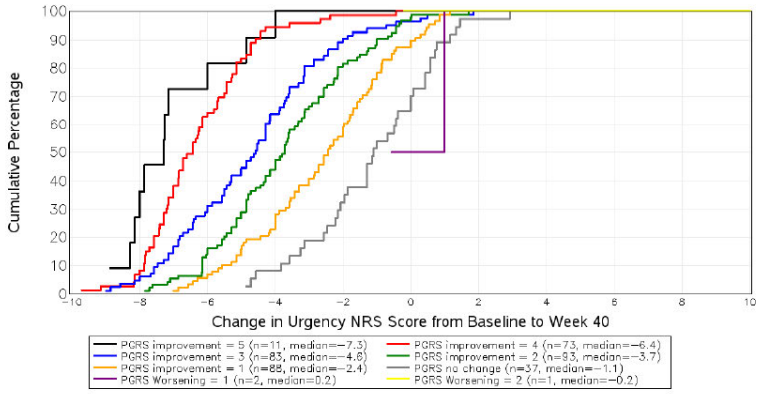
Change from Baseline to Week 40



Abbreviations: miri = mirikizumab; n= number of participants in specified category; NRS = Numeric Rating Scale; SC = subcutaneous.

Figure 4.6. **Empirical cumulative distribution plot of change from baseline to Week 40 on Weekly Urgency NRS score by treatment, Study AMBG.**

Empirical Cumulative Distribution Plot of Change from Baseline to Week 40 on Weekly Urgency NRS Score by Uncollapsed Change from Baseline to Week 40 in Worst PGRS in 7-Day Period
Modified Intent-to-Treat Population - Mirikizumab Induction Responder - Patients with Baseline MMS >=5
I6T-MC-AMBG - Randomized Withdrawal Maintenance Period



Abbreviations: n = number of patients with non-missing values; MMS = Modified Mayo Score; NRS = Numeric Rating Scale; PGRS = Patient's Global Rating of Severity.

Note: Weekly Urgency NRS was calculated by averaging data from available daily diary entries of Urgency NRS for a 7-day period. If fewer than 4 diary entries were available in a 7-day period, the weekly Urgency NRS and the worst PGRS were considered missing. Daily PGRS scores were considered missing if the patient did not respond for PGRS on that day. All analyses are as observed.

Dataset: /lillyce/prd/ly3074828/i6t mc ambg/intrm1/data/analysis/restricted/adsl addd4.sas7bdat
Program: /lillyce/prd/ly3074828/i6t mc ambg/intrm1/programs/tfl/psychometric/f urg chg pgrs cdf pdf mitt mms5.sas
Output: /lillyce/prd/ly3074828/i6t_mc_ambg/intrm1/output/restricted/tfl/psychometric/f_urg_chg_pgrs_cdf_pdf_mitt_mms5.rtf

Table 5.8. **Change in the Weekly Average Urgency NRS Score (Unrounded) from Baseline to Week 40 by Change from Baseline in PGRS**
Modified Intent-to-Treat Population – Mirikizumab Induction Responders with Baseline MMS ≥5
I6T-MC-AMBG – Randomized Withdrawal Maintenance Period

PGRS Calculation: [Worst PGRS in 7 Day Period]

Change from Baseline in PGRS	N	(%)	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Improved 5 Categories	11	(2.8)	-8.29	-8.14	-7.29	-6.00	-4.86
Improved 4 Categories	73	(18.8)	-7.86	-7.29	-6.43	-5.43	-4.57
Improved 3 Categories	83	(21.4)	-7.46	-6.43	-4.57	-3.17	-2.00
Improved 2 Categories	93	(24.0)	-6.14	-5.14	-3.71	-2.29	-1.00
Improved 1 Category	88	(22.7)	-5.57	-4.00	-2.43	-1.14	0.14
No Change	37	(9.5)	-3.83	-2.23	-1.10	0.43	1.17
Worsened 1 Category	2	(0.5)	-0.57	-0.57	0.21	1.00	1.00
Worsened 2 Categories	1	(0.3)	-0.21	-0.21	-0.21	-0.21	-0.21
Worsened 3 Categories	0						
Worsened 4 Categories	0						
Worsened 5 Categories	0						
Overall	388	(100)	-7.29	-6.00	-4.14	-2.14	-0.43

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/

SUSAN M PRETKO
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DAVID S REASNER
04/15/2023 09:02:42 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 15, 2023

TO: Jessica Lee, MD
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Division Director
DNDSI/OSIS

SUBJECT: Routine inspection of four clinical sites involved with study 16T-MC-AMBW submitted in support of BLA 761279 (Mirikizumab).

1. Inspection Summary

OSIS arranged an inspection of the clinical portion of study I6T-MC-AMBW (BLA 761279, Mirikizumab) conducted at 1) Labcorp Clinical Research Unit (CRU), Inc., Madison, WI; 2) Covance CRU, Inc., Dallas, TX; 3) Labcorp CRU, Inc., Daytona Beach, FL; and 4) Bio-Kinetic Clinical Applications, LLC., Springfield, MO.

At the inspection close-out, Form FDA 483 and three discussion items were issued at Labcorp CRU, Inc., Madison, WI. In addition, one item was discussed at Covance CRU, Inc., Dallas, TX. The remaining two audited clinical sites received no objectionable conditions or discussion items.

After reviewing the inspectional findings and inspection-related documents, I conclude that the clinical data from study I6T-MC-AMBW generated at the following three clinical sites are reliable.

1. Labcorp CRU, Inc., Madison, WI.
2. Labcorp CRU, Inc., Daytona Beach, FL.
3. Bio-Kinetic Clinical Applications, LLC., Springfield, MO.

In contrast, clinical data from Covance CRU, Inc. Dallas, TX are reliable; however, additional clinical review is needed for subjects (b) (6) (b) (6) because some of their laboratory reports were not initialed/signed as reviewed by the clinical investigator during the study, and there is concern with potential unreported safety issues with the subjects. The laboratory reports are available as attachments in this review (see **Attachment-9**). Comparison of laboratory reports collected during the inspection with submitted data listings of these ten subjects, I found that some of the subjects (Subject (b) (6)) had abnormal clinical laboratory values. Therefore, the Division of Gastroenterology should review the clinical laboratory reports from these subjects to determine if their reported safety assessments are accurate.

2. Inspected Study:

BLA 761279

Study Number: I6T-MC-AMBW
Study Title: "A bioequivalence study of injections of Mirikizumab solution using an investigational 1 mL pre-filled syringe and an investigational 1 mL autoinjector in healthy participants."
Study Conduct Dates: November 12, 2020 to May 17, 2021.

3. Inspectional Findings

Site Number: 002
Clinical Investigator: Nicholas Siebers, MD (FEI # 3023090676)
Clinical Site: Labcorp CRU Inc. (FEI # 1046818)
Address:3402 Kinsman Blvd., Madison, WI 53704

ORA investigators Denise L. Burosh and Dina A. Tallman (OBIMO/DBIMOII) inspected Labcorp CRU, Inc., Madison, WI from October 3 to 7, 2022.

The previous inspection of Labcorp CRU, Inc. (Fka, Covance Clinical Research Unit Inc.) was conducted from April 2 to 6, 2018. At the conclusion of the inspection, no Form FDA 483 was issued; however, the following three items were discussed:

1. Unauthorized personnel had entry access to pharmacy.
2. Missed reporting of an adverse event.
3. Minor documentation errors in the subject records.

During the current inspection, Investigators Burosh and Tallman verified only the corrective action for the unauthorized entry access to pharmacy.

The current inspection included auditing the following items:

-Institutional review board approvals.
-Correspondence with sponsor and IRB.
-Screening and informed consent process.
-Informed consent forms (ICF).
-Employee training.
-Protocol adherence.
-Adverse event reporting.
-Randomization schedule confirmation.
-Test article accountability, dispensing, and storage.
-Dose preparation and administration.
-Equipment calibration.
-Pharmacokinetic sample collection, processing, storage, and shipment.
-Verification of source data with clinical study report.

At the conclusion of the inspection, Investigators Burosh and Tallman observed one objectionable condition and issued Form FDA 483 to the clinical site. In addition, three-items were discussed with the site's management. The Form FDA 483 observation (**Attachment-1**), the site's response dated October 27, 2022 (**Attachment-2**), and my evaluation are presented below.

3.1 FDA 483 Observation

3.1.1. Observation 1:

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, you failed to follow Section 8.3.7.2 and 10.8.3 of the protocol, SOP#PH-SOP-022, and sponsor agreement requirements for product complaints during conduct of bioequivalence study number 844-2497 (Protocol # I6T-MC-AMBW, IND #125444, BLA 761279) which required reporting of (b) (4) defects or deficiencies identified during the study to the sponsor. During the study you identified (b) (4) (b) (4) and did not report the defect to the sponsor on the "Product Complaint Form."

Site's Response: The site acknowledged the finding and stated (b) (4)

(b) (4) (b) (4) The pharmacist did not report to the sponsor during the clinical trial; however, a product complaint was filed with the sponsor following the observation by the ORA Investigators.

To prevent similar occurrence in the future, the site updated the SOP-0490 v2.0 titled "Recall and Product Complaint Procedures" with effective from December 5, 2022.

OSIS Evaluation: The finding is a protocol violation and does not affect the reliability of study data. Protocol Section 8.3.7.2. (Prompt Reporting of Product Complaints to Sponsor) (**Attachment-3**) states that product complaint will be reported to the sponsor within 24 hours after the clinical investigator is aware of the product complaint. However, the site did not report the finding to the sponsor (Eli Lilly) until ORA investigators discussed it on October 4, 2022 (**Attachment-4**). Because the site (b) (4) did not use in the study, there is no impact on the reliability of data from the audited study, even though it's a protocol violation.

The site's proposed corrective actions are adequate to prevent similar findings in future studies.

3.1.2. Discussion Item #1:

An incorrect storage date printed on the storage box label was identified during the verification of retention samples for the study.

Site's Response: The site acknowledged the finding and stated that the error occurred due to not updating the date in the label template before printing labels.

OSIS Evaluation: The finding is not a regulatory requirement for BLAs submitted under 351(a) or a protocol requirement for the study. In addition, the finding did not affect the reliability of study data. The information collected during the inspection indicates that the retention sample storage boxes were labeled

with incorrect retention date [redacted] instead of 03-Nov-2020 (**Attachment-5**). The correct date (03-Nov-2020) of retention samples is evident from the "Clinical Trial Material Inventory Log" (**Attachment-6**) that was also collected during the inspection. Therefore, the labeling error does not affect the identity of study product and does not affect study data. In addition, the finding is not a regulatory requirement or protocol violation.

3.1.3. Discussion Item #2:

Staff at the clinical site placed initials rather than signature on the Informed consent document under "Signature of Person Conducting the Informed Consent Discussion and Verification of Literacy."

Site's Response: The site stated that per their standard operating procedures (SOPs), the staff signed the copy of the informed consent document maintained in the subject folder and initialed the take home copy of informed consent document that was provided to study subjects.

OSIS Evaluation: The finding is a protocol violation and does not affect the reliability of study data. Both protocol section 10.1.2 (Informed Consent Process) and site's SOP require that staff sign the ICF when obtaining informed consent (**Attachment-7**). However, the establishment inspection report (EIR) contains insufficient information to ascertain the number of informed consent documents that were initialed instead of signed. An e-mail received from Investigator Burosh indicates that the finding impacted only one subject (Subject [redacted] **Attachment-8**).

It's worth noting that all reviewed informed consent documents were signed by subjects including Subject [redacted] before study initiation. Therefore, the finding has no impact on the audited study data even though it is a protocol violation and SOP deviation.

3.1.4. Discussion Item #3:

During dosing observation of study [redacted] **[a different study]** [redacted]

Site's Response: The site did not comment on the finding during the inspection.

OSIS Evaluation: The finding does not affect the reliability of data from audited study because the finding was associated with a different study (b) (4) (b) (4) (b) (4) Therefore, this finding has no impact on the audited study data.

Site Number: 003
Clinical Investigator: Jeanelle L. Kam, MD (FEI # 3023092874)
Clinical Site: Covance CRU, Inc. (FEI # 3007024261)
Address:1341 West Mockingbird Lane, Suite 200E, 700E, and 800E Dallas, TX 75247

ORA investigators Travis M. Beard and Habacuc V. Barrera (OBIMO/DBIMOII) inspected Covance CRU, Inc., Dallas, TX from November 15 to 18, 2022.

The previous inspection of Covance CRU, Inc. was conducted from June 3 to 7, 2019. At the conclusion of the inspection, Form FDA 483 was issued for not maintaining the blinding codes during the study.

During the current inspection, Investigators Beard and Barrera verified corrective actions for the above observation with updated standard operating procedures including retention of the blinding codes.

The current inspection included auditing the following items:

-Case report forms (CRFs).
-Informed consent process.
-Protocol deviations.
-Institutional review board approvals.
-Test article accountability and storage.
-Randomization.
-Adverse events.

At the conclusion of the inspection, Investigators Beard and Barrera did not observe any objectionable conditions; however, they discussed one item with site's management at close-out. The discussion item, the site's response during the inspection, and my evaluation are presented below.

3.2.1. Discussion Item #1:

Clinical laboratory reports of some visits were not documented as reviewed by the clinical investigator during the study for the following subjects.

Subject [redacted] Visit 15; Subject [redacted] Visit 15; Subject [redacted] Visit 6; Subject [redacted] Visit 15; Subject [redacted] Visit 15; Subject [redacted] Visits 1, 2, and 6; Subject [redacted] Visit 1; Subject [redacted] Visits 1 and 15; Subject [redacted] Visits 1 and 2; and Subject [redacted] Visit 1.

Site's Response: The site stated that the clinical laboratory reports were reviewed, and no clinically significant results were noted by the clinical investigator. In addition, the site initiated an internal investigation to determine the issue further.

OSIS Evaluation: The finding is a protocol violation that could affect the reliability of reported safety data for Subjects [redacted]
Per study protocol, the clinical investigator must review the laboratory reports, document the review, record any clinically relevant changes occurring during the study in the "adverse events" section of the eCRF, and file the laboratory reports with source documents. Evidence collected during the inspection indicates that clinical laboratory reports of ten subjects (**Attachment-9**) were not documented as reviewed by the clinical investigator during the study. The finding raises doubt about whether the laboratory reports of these subjects were reviewed, and whether their safety was assessed during study conduct.

Investigators Beard and Barrera reviewed fax copies of laboratory reports received during [redacted]ection on November 15, 2022 from pathol[redacted] laboratory [redacted] Only one of the reports for subject [redacted] collected during the inspection was reviewed by someone who annotated "not clinically significant" next to abnormal laboratory values. However, the report was not signed, and it is not clear who reviewed the clinical laboratory report.

Despite the finding, all clinical laboratory results including those mentioned in the finding were correctly reported to the Agency. Laboratory results are found in the data listing titled "LB." I compared exhibits (**Attachment-9**) collected during the inspection with submitted data listings of these ten subjects and found that some of the subjects (Subject [redacted] and [redacted]) had abnormal clinical laboratory values. Therefore,

the Division of Gastroenterology should review the clinical laboratory reports from these subjects to determine if their reported safety assessments are accurate.

Site Number: 001
Clinical Investigator: Hugh A. Coleman, DO (FEI # 3013925315)
Clinical Site: Labcorp CRU, Inc. (FEI # 3004834650)
Address: 1900 Mason Avenue, Suite 140, Daytona Beach, FL 32117

ORA investigator Scott B. Laufenberg (OBIMO/OPS) inspected Labcorp CRU, Inc., Daytona Beach, FL from November 14 to 18, 2022.

The previous inspection of Labcorp CRU, Inc., Daytona Beach, FL (Fka, Covance CRU, Inc.) was conducted from October 23 to 27, 2017. At the conclusion of the inspection, No Form FDA 483 was issued; however, one-item was discussed related to randomization of study subjects and not conducting the study per the investigational plan.

During the current inspection, Investigator Laufenberg did not find any issues with randomization procedures for the audited study.

The current inspection included auditing the following items:

-Clinical trial performance.
-Protocol adherence.
-Subject record review including case histories.
-Informed consent process and consent documents.
-Ethics review committee approvals and correspondence.
-Screening and inclusion/exclusion criteria assessment.
-Adherence to the randomization schedule.
-Laboratory reports.
-Investigational product accountability, dispensation, dosing, and storage.
-Adverse event documentation and reporting.
-Pharmacokinetic sample collection, processing, and storage.
-Concomitant medications.
-Verification of clinical data submitted to the Agency.

At the conclusion of the inspection, Investigator Laufenberg did not observe any objectionable conditions, and did not issue Form FDA 483 to the clinical site or had any discussion items.

Site Number: 004
Clinical Investigator: Donald W. Burkindine, DO (FEI # 3023092892)
Clinical Site: Bio-Kinetic Clinical Applications, LLC. (FEI # 1000511105)
Address:1820 West Mt. Vernon Street, Springfield, MO 65802

ORA investigator Karen M. Montgomery (OBIMO/DBIMOII) inspected Bio-Kinetic Clinical Applications, LLC, Springfield, MO from November 7 to 9, 2022.

The previous on-site clinical inspection of Bio-Kinetic Clinical Applications, LLC, Springfield, MO was conducted from July 8 to 10, 2019. At the conclusion of the inspection, no Form FDA 483 was issued.

The current inspection included auditing the following items:

-Subject records.
-Case report forms
-Protocol deviations
-Protocol adherence.
-Ethics review board approvals
-Adverse event reporting.
-Test article accountability.
-Randomization adherence.
-Informed consent process
-Dosing.
-Concomitant medications.
-Pharmacokinetic sample collection, processing, storage, and shipment.
-Training logs.
-Correspondence.

At the conclusion of the inspection, Investigator Montgomery did not observe any objectionable conditions, and did not issue Form FDA 483 to the clinical site or had any discussion items.

CC:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza/Pham
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou

ORA/OMPTO/OBIMO/OPS/Bell/Laufenberg
ORA/OMPTO/OBIMO/DBIMOII/Walker/Burosh/Tallman
ORA/OMPTO/OBIMO/DBIMOII/Hines/Beard/Barrera
ORA/OMPTO/OBIMO/DBIMOII/Myskowski/Montgomery

Draft: GM 03/08/2023; 03/09/2023; 3/13/2023; 3/15/2023
Edits: RCA 03/9/2023, 3/13/2023, 3/14/2023; AD 03/14/2023

OSIS File #: 9487

eNSpect Assignment ID: 199631
eNSpect Op ID #s:
225380 (Covance Clinical Research Unit, Inc., Daytona Beach, Fl)
225421 (Covance Clinical Research Unit, Inc., Madison, WI)
225398 (Covance Clinical Research Unit, Inc., Dallas, TX)
225399 (Bio-Kinetic Clinical Applications, LLC., Springfield, MO)

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/

GAJENDIRAN MAHADEVAN
03/15/2023 05:04:52 PM

RUBEN C AYALA
03/15/2023 05:11:49 PM

ARINDAM DASGUPTA
03/15/2023 09:44:30 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	1/27/2023		
To:	Kelly Richards, Clinical Analyst		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	DROII
From	Papatya Kaner OPEQ/OHT3/DHT3C/THT3C3		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Subject	BLA 761279, Omvoh (mirikizumab) ICC 2200307 ICCR 837779		
Recommendation	**Filing Recommendation Date: 5/29/2022** ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☑ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 8/30/2022 ☐ CDRH did not provide a Mid-Cycle Recommendation ☑ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 1/27/2023 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Papatya Kaner -S Digitally signed by Papatya Kaner -S Date: 2023.01.26 11:24:46 -05'00'		Alan M. Stevens -S3

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1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761279
Sponsor	Eli Lilly and Company
Drug/Biologic	Omvoh (mirikizumab)
Indications for Use	Moderate to severe ulcerative colitis
Device Constituent	(b) (4) autoinjector
Related Files	

Review Team		
Lead Device Reviewer		
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	1/27/2023
Interim Due Dates	**Meeting/Due Date**
Filing	5/29/2022
74-Day Letter	6/12/2022
Mid-Cycle	8/30/2022
Primary Review	1/27/2023
Internal Meeting(s)	2/15/2023
Sponsor Meeting(s)	N/A

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2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems			X	

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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TABLE OF CONTENTS

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3. PURPOSE/BACKGROUND

3.1. Scope

Eli Lilly and Company is requesting approval of Omvoh (mirikizumab). The device constituent of the combination product is [redacted] (b) (4) an autoinjector.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

DG requests that a CDRH reviewer be assigned to review the biologic/device combination product submitted with the BLA.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device Description
- Labeling
- Design Controls
- Risk Analysis
- Design Verification

This review will not cover the following review areas:

- Clinical Validation
- Human Factors Validation
- Facilities & Quality Systems

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Omvoh (mirikizumab) in a [redacted] (b) (4) autoinjector	Moderate to severe ulcerative colitis
[redacted] (b) (4) autoinjector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
Supporting Doc #1 (Sequence #0001)	3.2.P Drug Product 3.2.R Regional Information
Supporting Doc #35 (Sequence #0035)	1.14 Labeling
Supporting Doc #7 (Sequence #0009)	1.11 Information Not Covered Under Modules 2 to 5

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4. DEVICE DESCRIPTION

4.1. Device Description

(b) (4)

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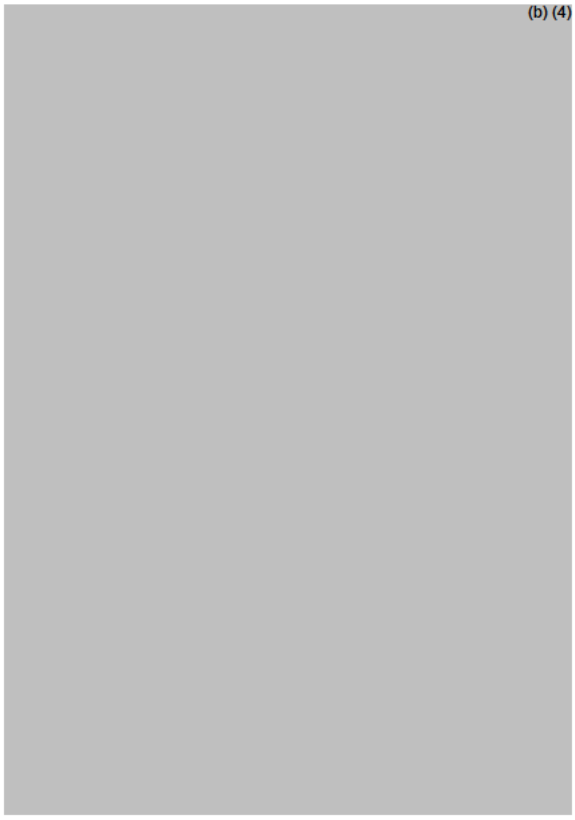

Figure 3.2.R.2-1 **Mirikizumab** (b) (4)

Autoinjector Device Description:
This section describes the mirikizumab autoinjector combination product that has a device constituent part with the same functionality as the approved autoinjectors. The intended use, indications for use, clinical performance requirements, operation steps and human factors considerations are provided here. Section 3.2.R.9.2 provides information shared by all versions of the autoinjector, i.e., development of the autoinjector, autoinjector mode of action, additional design considerations (visual inspection of biological product, depth of injection, graduation marks and fill lines, safety features), materials, drug and device compatibility, drug stability, and shelf-life, expiration dating and stability testing.

Intended Use:
The autoinjector is intended to automatically insert the needle to a predetermined depth below the skin surface and inject the drug product from the enclosed syringe.

Indication for Use:
The autoinjector is a prefilled, single-use, injection device that enables patients, caregivers, or healthcare professionals to administer a fixed-dose of mirikizumab via subcutaneous (SC) injection. Mirikizumab is indicated for the treatment ulcerative colitis.

Autoinjector Clinical Performance Requirements:
The design requirements for the mirikizumab autoinjector were based on the requirements identified for the approved autoinjectors. The functions of the autoinjector essential to clinical performance are to automatically insert the needle to a specified depth and perform the injection with the required dose accuracy. Table 3.2.R.2-1 lists the requirements that are essential to the clinical performance of the device and provides references to where the autoinjector design verification results are found.

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Table 3.2.R.2-1 Autoinjector Clinical Performance Requirement and Verification Results

Name	Performance Requirements	Verification Results	Shipping	Stability	Batch Release
Dose Accuracy	(b) (4)	Table 3.2.R.4.1-2 Table 3.2.R.4.1-4	Table 3.2.P.2.4.1.5-10 Table 3.2.P.3.5.3.8-1 Table 3.2.P.3.5.3.8-2	Table 3.2.P.8.3.1.8-2 Table 3.2.P.8.3.1.8-3	Table 3.2.P.5.4.4-1
Injection Time		Table 3.2.R.4.2-1	Table 3.2.P.2.4.1.5-11 Table 3.2.P.3.5.3.8-1 Table 3.2.P.3.5.3.8-2	Table 3.2.P.8.3.1.8-2 Table 3.2.P.8.3.1.8-3	Table 3.2.P.5.4.4-1
Button Activation Force		Table 3.2.R.9.4-5	Table 3.2.P.2.4.1.5-12 Table 3.2.P.3.5.3.8-1 Table 3.2.P.3.5.3.8-2	Table 3.2.P.8.3.1.8-2 Table 3.2.P.8.3.1.8-3	Table 3.2.P.5.4.4-1*
Extended Needle Length		Table 3.2.R.4.1-3	Table 3.2.P.2.4.1.5-13 Table 3.2.P.3.5.3.8-1 Table 3.2.P.3.5.3.8-2	N/A**	N/A**

* (b) (4)

**

Autoinjector Operation:

The mirikizumab autoinjector is shown in Figure 3.2.R.2-1. The internal mechanism of the autoinjectors used in clinical studies is the same as the commercial version; however, the injection button and base cap colors and printing on the lock ring and base cap are different. The color and ink differences do not change the dose injection technique, the drug flow path, or alter how the user operates the autoinjector.

(b) (4)

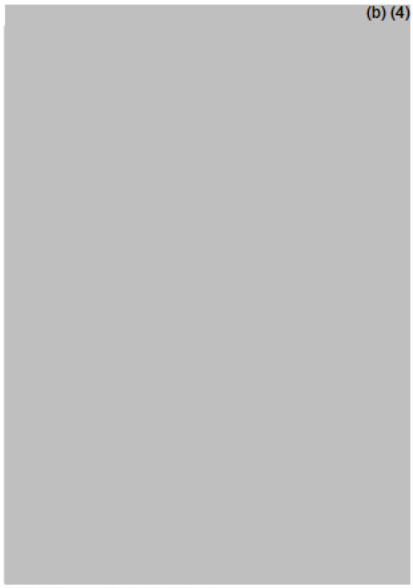

Figure 3.2.R.2-1 **Mirikizumab Autoinjector**

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4.2. Steps for Using the Device

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Steps for Using the Autoinjector:

1. Remove the base cap and discard.
2. Position the autoinjector for injection and unlock.
3. Press the injection button to start the injection and hold the device until the injection is complete.

Autoinjector Materials:

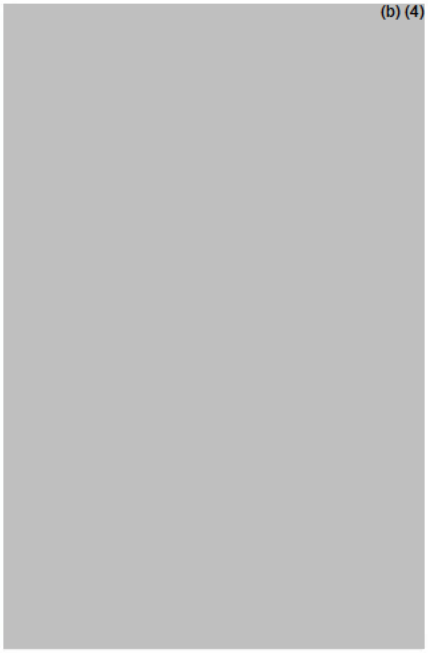

Figure 3.2.R.5-1 Mirikizumab Autoinjector Contact Parts

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Table 3.2.R.9.2-1 Material Identification

	Component	Material
External Patient Contact Components of the Autoinjector	Injection button	(b) (4)
	Lock ring (body upper)	
	Device body under label (body lower)	
	Clear base (baseplate)	
	Base cap	
	(b) (4	
Internal Components		

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Device description is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☑ **Finalize Filing Review Section**	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☑ N/A **Site(s) needing inspection:**
Reviewer Comments CDRH lead reviewer was not consulted for facilities inspection.

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Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A	
74-Day Letter Deficiencies: ☐ Yes ☐ No ☐ N/A	

	Date Sent: 5/20/2022	**Date/Sequence Received:** 5/24/2022
Information Request #1	(b) (4)	
Sponsor Response		

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	(b) (4)
Reviewer Comments	Sponsor addressed all the questions with detailed information, responses are acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		

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Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
General labeling review is deferred to CDER.

6.2. Device Specific Labeling Review

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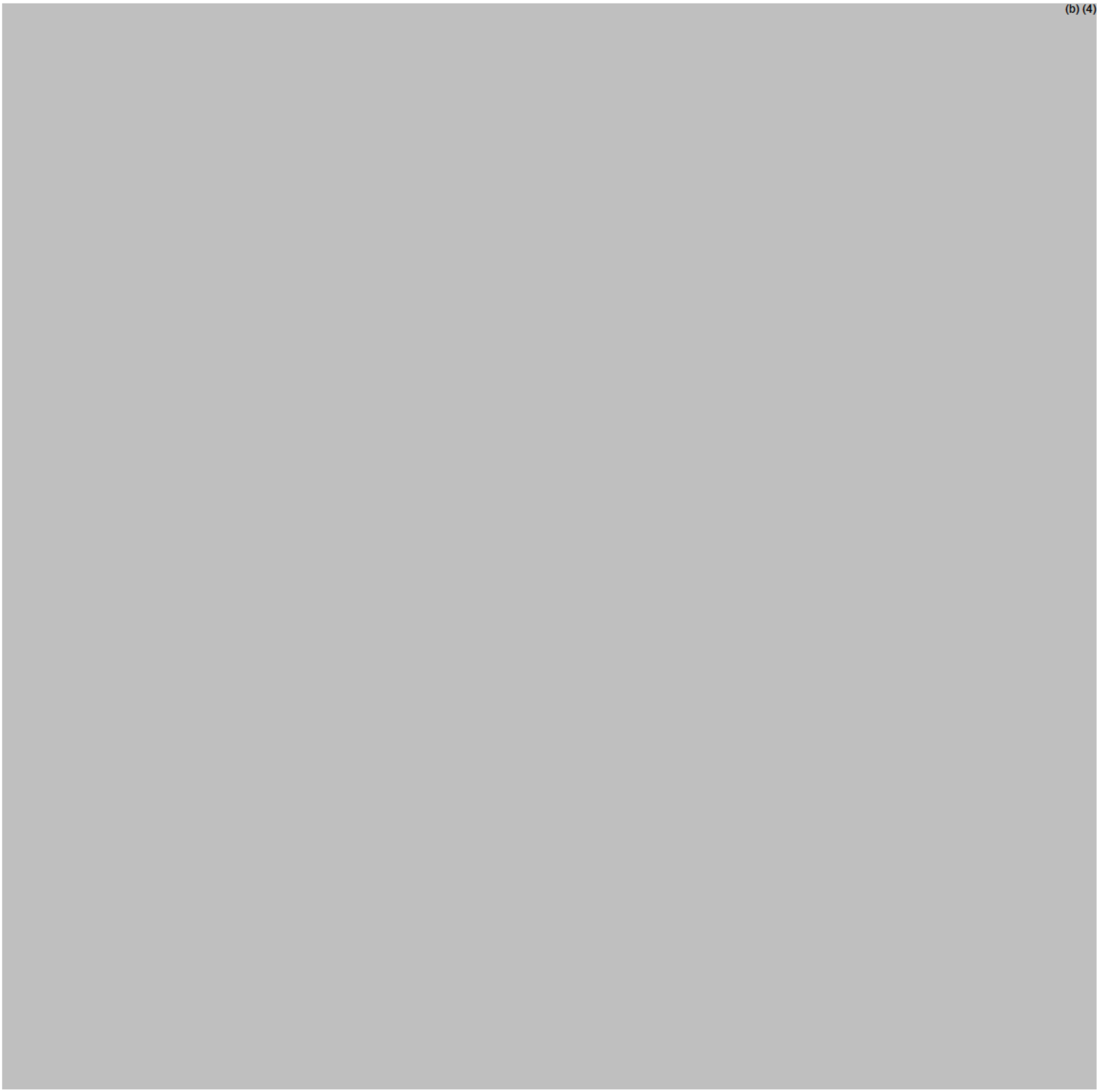

Reviewer Comments
Labeling contains relevant information and is acceptable.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
- ☐ Insert Consultant Name ; The full memo is located in Appendix B.
- ☐ The Lead Reviewer

,

Below is a summary of the review & recommendation:

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Clinical labeling review is deferred to CDER.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product			
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)			
Mitigations are adequate to reduce risk to health			
Version history demonstrates risk management throughout design / development activities			
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)			
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing			
To-be-marketed device was used in the pivotal clinical trial			
Bioequivalence Study utilized to-be-marketed device			
Verification methods relevant to specific use conditions as described in design documents and labeling			
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			
Traceability demonstrated for specifications to performance data			

Reviewer Comments

7.2. Design Inputs and Outputs

Essential Performance Requirements

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7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	**Y**
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	**N**
IEC 60601-1-2:2014	**N/A**

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Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	**Y**
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	**N/A**
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	**N/A**
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	**Y**
Applying Human Factors and Usability Engineering to Medical Devices	**Y**

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014 *Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems*	**Y**	**Y**
ISO 11608-5:2012 *Needle-based injection systems for medical use — Requirements and test methods — Part 5: Automated functions* and complies with the dose accuracy	**Y**	**Y**

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Design control deficiencies were resolved during filing, please see Section 5.1 above for the filing deficiencies and Sponsor responses.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

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8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Risk analysis deficiencies were resolved during filing, please see Section 5.1 above for the filing deficiencies and Sponsor responses. The approach used for risk analysis for (b) (4) autoinjector (b) (4) follows ISO 14971:2019, this is acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

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9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

(b) (4)

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9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☑ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☑ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments One design verification deficiency was resolved during filing, please see Section 5.1 above for the filing deficiency (Information Request #1) and Sponsor responses. One stability deficiency was resolved during late cycle; please see below Information Request #2 sent on 1/13/2023. Sponsor response to this deficiency was received on 1/19/2023.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
Information Request #2	**1/13/2023**	**1/19/2023**
Sponsor Response		

(b) (4)

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	(b) (4)
Reviewer Comments	Sponsor's response was received under Sequence 52 on 1/19/2023; they addressed all the questions with detailed information, responses are acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Design Verification Review Section**

9.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☑

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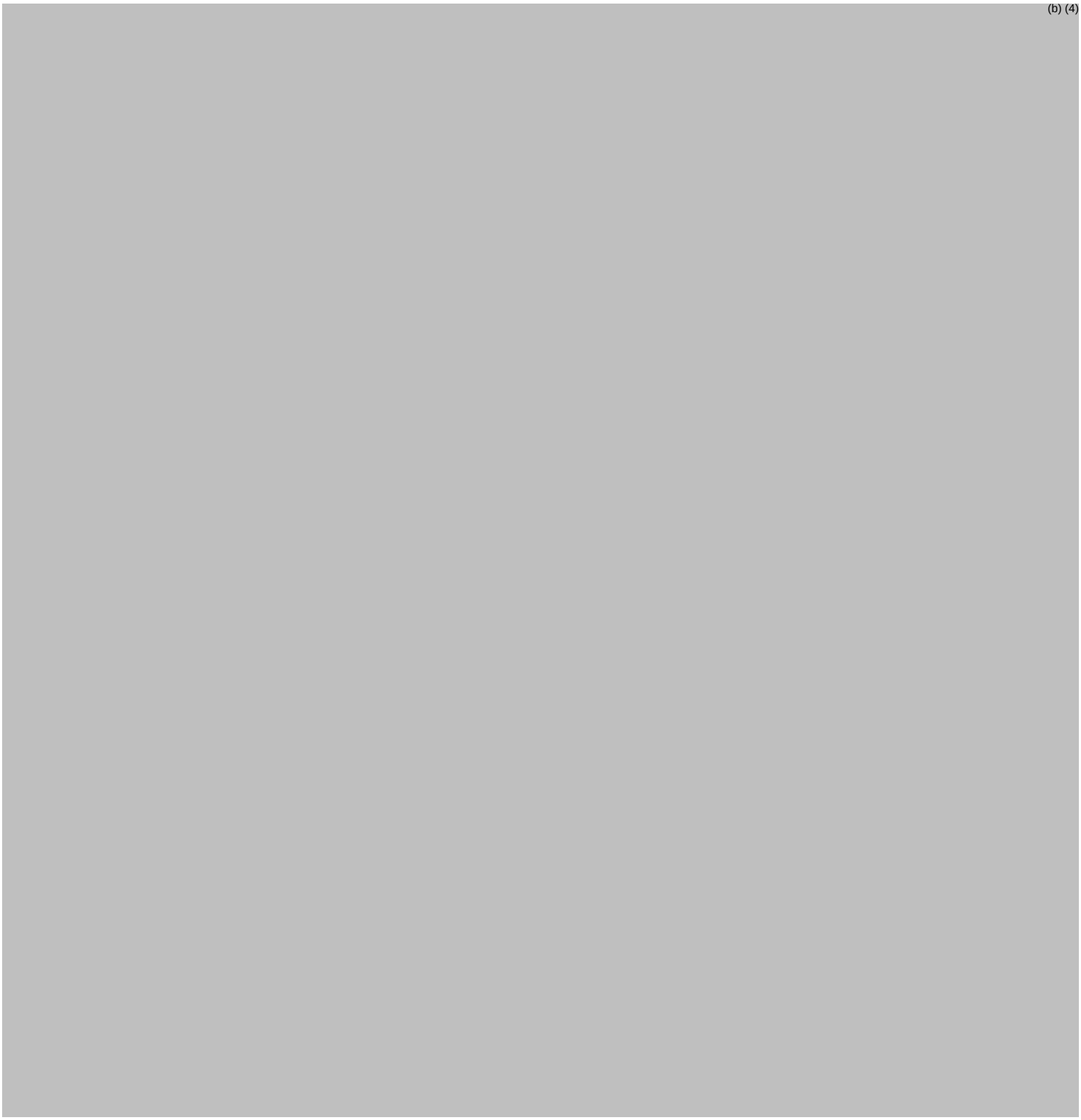
12.3. Control Strategy Review

Table 3.2.R.8.5-1 summarizes the Lilly PDS detailed procedures that demonstrate compliance with 21 CFR 820.30.

(b) (4)



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(b) (4)

[redacted]

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☑ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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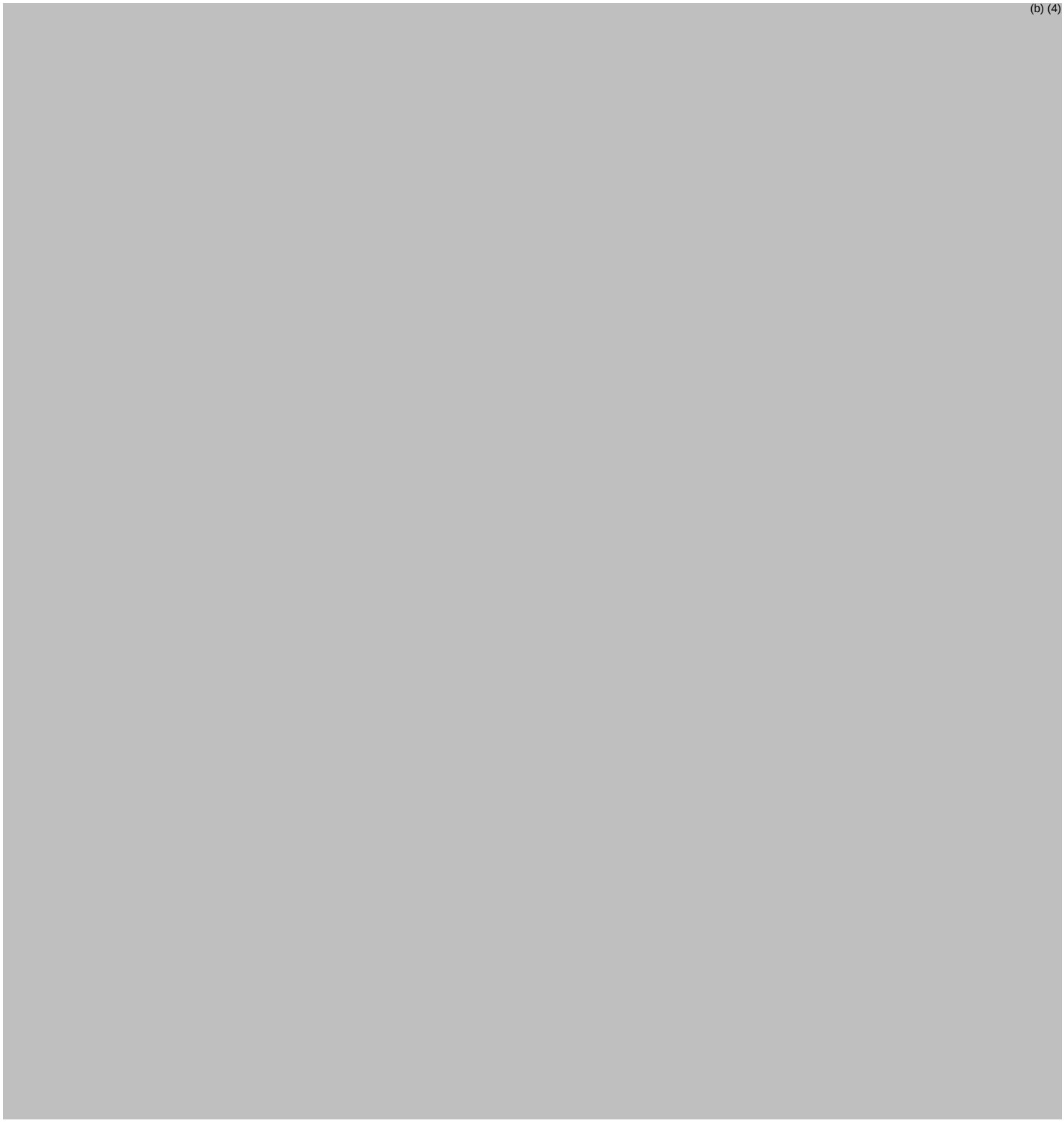
13.APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

(b) (4)



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14.APPENDIX B (CONSULTANT MEMOS)

14.1. Human Factors Review Memo – Insert Consultant Name

14.2. Clinical Review Memo – Insert Consultant Name

14.3. Insert Discipline Review Memo – Insert Consultant Name

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/s/

KELLY D RICHARDS
02/15/2023 10:19:52 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatrics and Maternal Health Review

Date: 12/14/2022 **Date consulted:** 4/8/2022

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health (DPMH)

To: Kelly Richards, RN, MSN, Senior Regulatory Project Manager (RPM)
Division of Gastroenterology (DG)

Drug: Omvoh (mirikizumab)

BLA: 761279

Applicant: Eli Lilly and Company

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of adult patients with moderately to severely active ulcerative colitis

Materials Reviewed:

- BLA 761279 submitted on March 30, 2022.
- DPMH consult review of BLA 761262, Carrie Ceresa, PharmD, MPH, dated 1/28/22. DARRTS Reference ID: 4929145.[1]

[1] The Skyrizi BLA review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below. Rather the cross-reference is included to avoid duplicating background information.

Consult Question: "DG requests DPMH review of submitted labeling and assistance with developing postmarketing commitments outside of PREA."

INTRODUCTION

On March 30, 2022, Eli Lilly and Company submitted an original BLA (761279) for Omvoh (mirikizumab) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). On April 8, 2021, the Division of Gastroenterology (DG) consulted the Division of Pediatrics and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

BACKGROUND

Drug Characteristics (based on currently proposed labeling)

- *Mechanism of action:* humanized immunoglobulin G4 (IgG4) variant monoclonal antibody that is directed against the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. IL-23 is an important driver of mucosal inflammation in UC and affects the differentiation, expansion, and survival of T cell subsets, and innate immune cell subsets, which represent sources of pro-inflammatory cytokines.
- *Dosage and administration:*
  - *Induction dosage:* 300 mg intravenous (IV) at Week 0, Week 4, and Week 8.
  - *Maintenance dosage:* 200 mg subcutaneous (SC) every 4 weeks
- *Molecular weight:* 147,000 Daltons
- *Bioavailability:* 44%
- *Half-life:* 9.3 days

Identified safety concerns (based on currently proposed labeling)

- *Contraindications:* none
- *Warnings and Precautions:* hypersensitivity reactions, infections, hepatic enzyme elevations, immunizations
- *Adverse reactions:* injection site reactions, upper respiratory tract infections, headache, rash

Condition: Ulcerative Colitis and Pregnancy

- Ulcerative Colitis (UC) is an inflammatory bowel disease (IBD) which is an autoimmune condition that often occurs in women of reproductive potential. During pregnancy it is important to optimize disease management and pregnancy outcomes by the continuation of treatment.[2] IBD includes Crohn's disease (CD) and ulcerative colitis (UC). Approximately 0.5% of the United States population (1.6 million people) have IBD and approximately half of those are females.[3]
- The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine make the following recommendations:

[2] The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine. ACOG Committee Opinion. Number 776. Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Immune Modulating Therapies in Pregnancy and Lactation. Vol. 133, No. 4, April 2019.

[3] Mahadevan U, C Robinson, N Bernasko et al. Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group. Gastroenterology 2019; 156:1508-1524.

    - "Many commonly prescribed drugs can be used safely during pregnancy without risk of teratogenicity or pregnancy complications, whereas a few are strictly contraindicated."[2]
    - "Decision making regarding patient plans should be individualized and shared and should include consideration of pregnancy and maternal risks associated with untreated disease."[2]
    - "In general, immunomodulating drugs that are not contraindicated in pregnancy are compatible with breastfeeding. Health care providers are encouraged to use LactMed to find the most up-to-date information for counseling."[2]
- Concerns related to IBD during pregnancy include impact on maternal and fetal outcomes. One of these concerns includes disease flareup which complicates 30 to 35% of pregnancies. According to the *American Gastroenterological Association IBD Parenthood Project Working Group*, a meta-analysis of 14 studies found a higher risk of active disease during pregnancy in patients who had active disease during conception compared to those in remission at conception.[3,4] These results are consistent with a multicenter European cohort study demonstrating that 14% of patients in remission at conception relapsed during pregnancy; however, 26% of patients with active disease at conception remained with active disease until delivery.[5] Increased rates of preterm birth are associated with active disease. Likewise, in a Danish cohort study on the impact of CD on birth outcomes, preterm birth risk was 2-times higher in women with low to moderate-high disease activity during pregnancy compared to those without active disease.[6]
    - In addition, active perianal disease, which presents as anorectal fistula/abscess, rectovaginal fistula, anal fissure or anal stenosis, holds a 10-fold increased risk of 4th degree laceration when active disease is present in pregnant patients with CD.[7]
- Treatment guidelines for IBD during pregnancy and lactation from the American Gastroenterological Association IBD Parenthood Project 2019 Working Group can be viewed in Appendix A.[3]

REVIEW

PREGNANCY

Nonclinical Experience

An enhanced pre- and postnatal development study conducted in cynomolgus monkeys administered mirikizumab by intravenous injection during organogenesis to parturition at a dose of 300 mg/kg twice weekly (69 times the maximum recommended human dose [MRHD] based on exposure comparisons). Mirikizumab crossed the placenta in monkeys. No maternal toxicity was noted in this study. No mirikizumab-related effects on morphological, functional or immunological development were observed in infant monkeys from birth through 6 months of

[4] Abhyankar A, Ham M, Moss AC. Meta-analysis: the impact of disease activity at conception on disease activity during pregnancy in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;38:460– 466.
[5] Bortoli A, Pedersen N, Duricova D, et al, Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003– 2006. Aliment Pharmacol Ther 2011;34:724–734.
[6] Norgard B, Hundborg HH, Jacobsen BA, et al. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007;102:1947–1954.
[7] Hatch Q, Champagne BJ, Maykel JA, et al. Crohn's disease and pregnancy: the impact of perianal disease on delivery methods and complications. Dis Colon Rectum 2014;57:174–178.

age. However, incidences of embryo/fetal loss were higher in the treated groups compared to control (6.7% [1 of 15] in controls vs 26.7% [4 of 15] at 300 mg/kg (69 times the MRHD, based on exposure comparisons) but were within the range of historical control data. Following delivery, most adult female cynomolgus monkeys and all infants from the mirikizumab-treated group had measurable serum concentrations up to 28 days postpartum. In the infants, mean serum concentrations were approximately 4.7 times the respective mean maternal concentrations.

For additional details, refer to the Nonclinical Review by Blessy George, PhD.

Clinical Trials

Pregnant women were excluded from clinical trials during the development program for mirikizumab. At the time of the 120-day Safety Update, the applicant noted a total of 34 pregnancies have occurred in female participants during any mirikizumab study participation as of March 22, 2022. Pregnancy outcomes include: normal livebirth (n=7), preterm birth (n=1), ongoing (n=11), elective abortion (n=6), spontaneous abortion (n=5), and unknown (n=4). No congenital anomalies were reported and the reasons for elective abortion were not specified.

Review of Literature

Applicant's Review of Literature

The applicant did not perform a literature search related to mirikizumab use and pregnancy.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[8], TERIS[9], Reprotox[10], and Briggs[11] to find relevant articles related to the use of mirikizumab during pregnancy. Search terms included "mirikizumab" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant articles were identified.

LACTATION

Nonclinical Experience

No animal lactation studies were performed with mirikizumab.

Clinical Trials

Lactating women were excluded from clinical trials during the development program for mirikizumab. At the time of the 120-day Safety Update, the applicant stated no lactation exposure cases have been reported during the clinical development program.

Review of Literature

Applicant's Review of Literature

The applicant did not perform a literature searched related to mirikizumab use and lactation.

[8] Truven Health Analytics information, http://www micromedexsolutions.com/Accessed 9/1/22.
[9] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 9/1/22.
[10] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 9/1/22.
[11] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[8], TERIS[9], Reprotox[10], and Briggs[11], *Medications and Mothers' Milk[12]*, and LactMed[13] to find relevant articles related to the use of mirikizumab during lactation. Search terms included "mirikizumab" AND "breastfeeding" or "lactation." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of mirikizumab. No organ weight or histopathology effects were observed in the male or female reproductive tract in sexually mature cynomolgus monkeys that received subcutaneous mirikizumab once weekly for 26 weeks, at a dose of 100 mg/kg (at least 7 times the MRHD of mirikizumab based on exposure comparisons).

For additional details, refer to the Nonclinical Review by Blessy George, PhD.

Review of Literature
Applicant's Review of Literature
The applicant did not perform a literature search related to mirikizumab use and fertility.

DPMH Review of Literature
This Reviewer performed a search in PubMed, Embase, Reprotox[10] to find relevant articles related to the use of mirikizumab and effects on fertility. Search terms included "mirikizumab" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS
Pregnancy
Pregnant women were excluded from clinical trials with mirikizumab during the clinical development program. At the time of the 120-day Safety Update, a total of 34 pregnancy exposure cases were reported with outcomes including: normal livebirth n=7, preterm birth n=1, ongoing n=11, elective abortion n=6, spontaneous abortion n=5, and unknown n=4. Overall, these limited available human data are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, DPMH recommends subsection 8.1 of Omvoh labeling include a Risk Summary statement to summarize the limited available human pregnancy exposure data and the lack of reproductive toxicity findings in animal studies at exposures up to 69 times the maximum recommended human dose.

There are no available pregnancy pharmacokinetic (PK) data for mirikizumab to inform evidence-based dosing recommendations during pregnancy. Although the impact of pregnancy

[12] Hale, Thomas (2020) Medications and Mothers' Milk online. Accessed 9/1/22.
[13] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 9/1/21.

physiology on PK of biologics is understudied, there are published literature that support the need for pregnancy PK data collection and indicate serum concentrations of monoclonal antibodies may be decreased, similar, or increased compared to non-pregnant adults.[14] There are also no available human data regarding the amount of mirikizumab placental transfer, mirikizumab levels at birth in infants exposed in utero, or the duration of persistence of mirikizumab in infant serum after delivery. Considering mirikizumab is an IgG4 monoclonal antibody, placental transfer is presumed based on published literature for other monoclonal antibodies.[15] Published literature for other monoclonal antibodies indicate the amount of placental transfer varies widely and the half-life observed in adults may not be predictive of the half-life or the duration of pharmacodynamic effects in the in utero exposed infant.[15] Available animal data also indicate mirikizumab crossed the placenta in monkeys and was detected in all infant monkeys up to 28 days after birth, with mean serum concentrations approximately 4.7 times the respective mean maternal concentrations.

Given the lack of available human PK and placental transfer data specific to mirikizumab use in pregnancy, DPMH recommends including language in subsection 8.1 similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Pregnancy labeling should include information under Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the in utero exposed infant, and the risks and benefits that should be considered prior to administration of live vaccines. The labeling should include a statement that a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown. In discussion with the DG Clinical Pharmacology Team, DPMH agrees that live vaccines should be delayed for a minimum of at least 2 months (half-life of 9.3 days x 5-6) after birth. Pregnancy labeling should also include a Clinical Consideration regarding disease-associated maternal and embryo/fetal risk noting published data suggest that the risk of adverse pregnancy outcomes in women with IBD is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Mirikizumab is indicated for a condition that would be expected to be seen in females of reproductive potential (including during pregnancy), and current data are insufficient to inform women regarding mirikizumab use during pregnancy. Therefore, DPMH recommends a postmarketing requirement (PMR) for the applicant to conduct a pregnancy exposure registry and a complementary study of a different design (such as a claims database study). Refer to the FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies, published May 2019. DPMH also recommends including language regarding the planned postapproval pregnancy exposure registry in subsection 8.1 and section 17 of labeling along with the applicant's pharmacovigilance contact information. After the pregnancy registry study protocol has been finalized, the applicant should submit a prior approval supplement (PAS) to update PLLR labeling with the established pregnancy registry contact information.

[14] Wiersma TK, et al. The Effect of Pregnancy and Inflammatory Bowel Disease on the Pharmacokinetics of Drugs Related to Inflammatory Bowel Disease-A Systematic Literature Review. Pharmaceutics 2022, 14, 1241.
[15] Soh MC, et al. The Use of Biologics for Autoimmune Rheumatic Diseases in Fertility and Pregnancy. Obstetric Medicine 2020, Vol. 13 (1) 5-13.

DPMH had several meetings with the DG Review Team to discuss recommendations for issuing a PMR for the applicant to conduct a pregnancy PK and placental transfer study at approval to evaluate the clinical pharmacokinetics of mirikizumab in maternal plasma during pregnancy and at delivery, in cord blood at the time of delivery, and post-delivery in plasma of infants exposed to mirikizumab in utero. The DG Review Team agreed this is an important topic and, if properly conducted in an adequate number of pregnant patients and infants, it would provide useful information. However, since requesting this type of study for the mirikizumab program will impact other future IBD and chronic inflammatory programs that are shared across multiple divisions, it will be prudent to have broader discussion before such a PMR or postmarketing commitment (PMC) is issued specifically for this application.[16]

Lactation

Lactating women were excluded from clinical trials with mirikizumab. At the time of the 120-day Safety Update, no lactation exposure cases were reported. There are no available data on the presence of mirikizumab in human milk, the effects on the breastfed infant, or the effects on milk production. The molecular weight for mirikizumab is 147,000 Daltons, and according to breastfeeding experts, the amount in human milk, if any, is expected to be low. Considering mirikizumab is an IgG4 monoclonal antibody, DPMH recommends including language in subsection 8.2 of Omvoh labeling similar to the Agency's approach to PLLR labeling for other monoclonal antibodies. Lactation labeling should include information under Risk Summary that "maternal IgG and monoclonal antibodies are known to be present in human milk" as well as the "the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to mirikizumab are unknown." The following risk/benefit statement should also be included: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Omvoh and any potential adverse effects on the breastfed infant from Omvoh or from the underlying maternal condition."

Mirikizumab is indicated for a condition that would be expected to be seen in females of reproductive potential (including during lactation), and there are no available data to inform women regarding mirikizumab use during lactation. Therefore, DPMH recommends issuing a PMR for the applicant to conduct a clinical lactation study with mirikizumab to inform labeling. Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 2019.

Females and Males of Reproductive Potential

There are no available human data on the effects of mirikizumab on male or female fertility. Animal fertility studies do not indicate any adverse effects. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, DPMH recommends omitting subsection 8.3 from labeling for Omvoh.

[16] DPMH Personal Communication with Jessica Lee, MD, DG Division Director dated 11/30/22.

PMR RECOMMENDATIONS

DPMH recommends the following:

1) The applicant should be required to 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.
2) The applicant should be required to evaluate the clinical pharmacokinetics of mirikizumab in maternal plasma during pregnancy and at delivery, in cord blood at the time of delivery, and post-delivery in plasma of infants exposed to mirikizumab in utero. These assessments may be conducted as a sub-study of the pregnancy registry.
3) The applicant should be required to conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfill postmarketing requirement study 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.
4) The applicant should be required to perform a lactation trial (milk-only) in lactating women who have received mirikizumab regardless of indication to assess concentrations of mirikizumab in breast milk using a validated assay and to assess the effects on the breastfed infant. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

Reviewer's Comment
As noted above under the Discussion section, the DG Review Team has determined a PMR will not be issued for a pregnancy PK and placental transfer study as recommended by DPMH.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Omvoh (mirikizumab) Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Omvoh during pregnancy. Pregnant women exposed to Omvoh and health care providers are encouraged to call Eli Lilly and Company at (XXX)-XXX-XXXX.

Risk Summary

Available data from case reports of mirikizumab use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Although there are no data on mirikizumab, monoclonal antibodies can be actively transported across the placenta, and mirikizumab may cause immunosuppression in the in utero-exposed infant. There are risks of adverse pregnancy outcomes associated with increased disease activity in women with inflammatory bowel disease *(see Clinical Considerations).* An enhanced pre- and postnatal development study conducted in pregnant monkeys at a dose 69 times the maximum recommended human dose (MRHD) revealed no adverse developmental effects to the developing fetus, or harm to infant monkeys from birth through 6 months of age *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Because mirikizumab may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to Omvoh in utero. There are no data regarding infant serum levels of mirikizumab at birth and the duration of persistence of mirikizumab in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 2 months after birth should be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys administered mirikizumab by intravenous injection during organogenesis to parturition at a dose of 300 mg/kg twice weekly (69 times the MRHD based on exposure comparison). Mirikizumab crossed the placenta in monkeys. No maternal toxicity was noted in this study. No mirikizumab-related effects on morphological, functional or immunological development were observed in infant monkeys from birth through 6 months of age. However, incidences of embryo/fetal loss were higher in the treated groups compared to control (6.7% [1 of 15] in controls vs 26.7% [4 of 15] at 300 mg/kg (69 times the MRHD, based on exposure comparisons) but were within the range of historical control data. Following delivery, most adult female cynomolgus monkeys and all infants from the mirikizumab-treated group had measurable serum concentrations up to 28

days postpartum. In the infants, mean serum concentrations were approximately 4.7 times the respective mean maternal concentrations.

8.2 Lactation

Risk Summary

There are no data on the presence of mirikizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous maternal IgG and monoclonal antibodies are transferred in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to mirikizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Omvoh and any potential adverse effects on the breastfed infant from Omvoh or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise patients who are exposed to Omvoh during pregnancy to contact Eli Lilly and Company at XXX-XXXXXXX *[see Use in Specific Populations (8.1)]*.

APPENDIX A-IBD treatment in pregnancy guidelines from the 2019 American Gastroenterological Association IBD Parenthood Project Working Group[3]

Medication	Maintenance dosing recommendation	Breastfeeding considerations
Aminosalicylates	Maintain prepregnancy dosing	
Mesalamine	All preparations are now phthalate-free	Compatible with breastfeeding No preparation preference Monitor infant for diarrhea
Sulfasalazine	Consider 2-mg folate supplement in pregnancy Azulfidine EN contains phthalate	Compatible with breastfeeding Mesalamine preferred
Immunomodulators	Dosing may be altered due to increased renal clearance with pregnancy. Therapeutic drug monitoring recommended	Routine infant monitoring not necessary
Cyclosporine (calcineurin inhibitor)	Limited data in pregnancy suggest associations with hypertension, gestational diabetes, preterm birth, low birthweight/SGA. Used as a salvage therapy.	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Methotrexate	Contraindicated in pregnancy. Stop 3 months before conception.	Limited human data. Not advised.
Thiopurines (azathioprine, 6-mercaptopurine)	Continue as monotherapy In appropriate patients, consider cessation of thiopurine as combination therapy, given possible association with increased infant infections. Use with caution in combination with allopurinol, which carries potential embryo toxic effects	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Small molecules		
Tofacitinib	Limited human data. Consider other options, particularly in first trimester	Limited human data. Not advised.
Biologics	Maintain prepregnancy dosing Continue dosing throughout all 3 trimesters If possible, plan final dose according to drug half-life to minimize transfer	Compatible with breastfeeding Encourage participation in pregnancy registries if not already done during pregnancy.
Adalimumab	Plan final pregnancy injection 2–3 wk before EDC and resume postpartum[a] (1–2 wk if weekly dosing)	
Certolizumab pegol	May continue scheduled dosing throughout pregnancy.	
Golimumab	Plan final pregnancy injection 4–6 wk before EDC and resume postpartum[a]	
Infliximab	Plan final pregnancy infusion 6–10 wk before EDC and resume postpartum[a] (If every-4-wk dosing, then 4–5 wk before EDC) Base dosing on prepregnancy weight during pregnancy and immediate postpartum	
Natalizumab	Plan final pregnancy infusion 4–6 wk before EDC and resume postpartum[a]	
Ustekinumab[b]/ Vedolizumab[b]	Plan final pregnancy dose 6–10 wk before EDC and resume postpartum[a] (If every-4-week dosing, then 4–5 wk before EDC)	
Corticosteroids	Reserved for active flares in pregnancy. Not recommended for planned maintenance therapy during pregnancy.	Compatible with breastfeeding Subtherapeutic infant exposure expected, even with flare dosing Avoiding feeding 1–2 h post-dose (non-enteric coated forms) can further minimize exposure but is not necessary
Antibiotics	Reserved for perianal disease and pouchitis and not recommended for planned maintenance therapy (amoxicillin/metronidazole preferred over ciprofloxacin)	Amoxicillin/clavulanic acid compatible with breastfeeding Ciprofloxacin preferred over metronidazole

EDC, estimated date of confinement; SGA, small for gestational age.
[a]48 hours post-delivery
[b]Limited pregnancy data

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/s/

KRISTIE W BAISDEN
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TAMARA N JOHNSON
12/15/2022 09:20:58 AM

LYNNE P YAO
12/19/2022 03:24:16 PM

HUMAN FACTORS RESULTS AND COMPARATIVE ANALYSES REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 19, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name, Dosage Form, and Strength:	Omvoh[a] (mirikizumab-xxxx)[b] injection 100 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly & Company
FDA Received Date:	March 30, 2022
OSE RCM #:	2022-632
DMEPA 1 Safety Evaluator:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director of Human Factors:	Jason Flint, MBA, PMP

[a] The proposed proprietary name, Omvoh, was found conditionally acceptable under the BLA.

[b] The proposed nonproprietary name has not yet been conditionally accepted. We therefore refer to the proposed product as "mirikizumab-xxxx" throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

This review evaluates a human factors (HF) validation study results report submitted under BLA 761279 for Omvoh (mirikizumab-xxxx) injection with proposed prefilled pen (PFP) device constituent parts that are intended for the treatment of adult patients with moderately to several active ulcerative colitis. Additionally, Eli Lilly submitted a comparative analyses (b) (4)

(b) (4)

1.1 PRODUCT DESCRIPTION

Prefilled Pen

The proposed PFP is a single use, disposable needle-based injection device containing a 100 mg dose of mirikizumab-xxxx. The user interface includes two autoinjectors with a deliverable volume of 1 mL, device labels, the carton with quick reference for injection (QRI), and instructions for use (IFU). See Figure 1 below.

Figure 1: Proposed AI

(b) (4)

(b) (4)

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMANFACTORS DEVELOPMENT PROGRAM

The Sponsor submitted a Type B End of Phase (EOP) 2 meeting request under IND (b) (4) on October 6, 2017, and we provided comments regarding their HF development program that were communicated as preliminary meeting comments on January 5, 2018[c]. In response to these comments, the Sponsor submitted a use-related risk analysis (URRA) and comparative analyses for the proposed (b) (4) PFP (b) (4) on May 31, 2019 under IND (b) (4) On July 11, 2019, we provided our identified issues and determined the Sponsor would need to submit HF validation study for the proposed product[d]. On October 15, 2019, the Sponsor submitted responses to our URRA review comments. We provided responses to the Sponsor's October 15, 2019 submission on November 7, 2019[e]. On September 30, 2020, the Sponsor submitted their HF validation study protocol for our review. On December 3, 2020, we communicated our recommendations for their HF validation study protocol[f].

On March 30, 2022 the Sponsor submitted their Biologic Licensing Application (BLA) for mirikizumab. The submission included HF validation study results report for the proposed PFP presentation; however, we noted the submission (b) (4) (b) (4) Therefore, we sent an Information Request (IR) on May 24, 2022 (b) (4) . On May 26, 2022, the Sponsor submitted a response to the IR, which included an updated comparative analyses (b) (4) (b) (4) The HF validation study results report for the PFP presentation along with the comparative analyses (b) (4) (b) (4) is the focus of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

[c] Attinello, C. Type B EOP 2 Preliminary Meeting Comments for mirikizumab. Silver Spring (MD): FDA, CDER, OND, DDDP (US); 2018 JAN 05. IND (b) (4)

[d] Schlick J. URRA review for mirikizumab (IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 July 11. RCM No.: 2019-1172.

[e] Schlick J. Review of URRA Response for mirikizumab (IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 07. RCM No.: 2019-1172-1.

[f] Barlow, M. HF Validation Study Protocol Review for mirikizumab (IND (b) (4) and IND 125444). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 03. RCM No.: 2020-2064.

[g] Dunson, A. Information Request for mirikizumab (BLA 761279). Silver Spring (MD): FDA, CDER, OSE (US); 2022 May 26.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study & Comparative Analyses	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Sponsor Response to Agency Information Request (IR)	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the study design of the HF validation study and the subsequent supplemental study, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product. Additionally, the sections below also provide our evaluation of the comparative analyses (b) (4)

3.1 SUMMARY OF HF VALIDATION STUDY DESIGN

Table 2 presents a summary of the HF validation study design. Table 3 presents a summary of the HF supplemental study.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• Injection-experienced patient participants with ulcerative colitis (or Crohn's disease or psoriasis included as proxies) [n=15] • Injection-naïve patient participants with ulcerative colitis (or Crohn's disease included as proxies) [n=15] • Injection-experienced caregivers of patients with ulcerative colitis (or a chronic condition) [n=15] • Injection-naïve caregivers of patients with ulcerative colitis (or a chronic condition) [n=15] • Healthcare provides (HCPs) who administer injections to patients with ulcerative colities (or a chronic condition) at least once per month [n=15]
Training	The participants did not receive training.
Test Environment	The test room was representative of the intended use environment with respect to lighting, sound levels, and temperature/ humidity. Test sessions were conducted in a testing room configured to allow participants to sit at a table with a session moderator while being monitored through a 1-way mirror from an adjacent observation room by sponsor and/or other study personnel. The test sessions were also observed remotely by sponsor and/or other study personnel.

	(b) (4) [redacted]
Sequence of Study	• Scenario 1: Differentiation • Scenario 2: Simulated Injection • Root Cause Analysis for Simulated Injection Scenario • Scenario 3: Knowledge Tasks • Root Cause Analysis for Knowledge Tasks Scenario

Table 3. Study Methodology for Human Factors (HF) Supplemental Study	
Study Design Elements	Details
Participants	• 8 injection-naïve and 8 injection-experienced patients (targeted UC patients, also included patients with Crohn's disease, irritable bowel syndrome (IBS), diverticulitis, and hiatal hernia as proxies • 7 injection-naïve and 8 injection-experienced caregivers of patient with ulcerative colitis (or a chronic condition).
Training	The participants did not receive training.
Test Environment	The test room was representative of the intended use environment with respect to lighting, sound levels, and temperature/humidity. Test sessions were conducted in a testing room configured to allow participants to sit at a table with a session moderator while being monitored through a 1-way mirror from an adjacent observation room by sponsor and/or other study personnel. The test sessions were also observed remotely by sponsor and/or other study personnel. (b) (4) [redacted]

Sequence of Study	• Scenario 1: Simulated Injection • Root Cause Analysis for Simulated Injection Scenario • Scenario 2: Knowledge Tasks • Root Cause Analysis for Knowledge Tasks Scenario

3.2 COMPARATIVE ANALYSES (b) (4)

(b) (4)

(b) (4)

4 RESULTS AND ANALYSIS

Tables 4, 5, and 6 describe the study results for the HF validation study and HF supplemental study, the Applicant's analysis of the results, and DMEPA 1's analysis and recommendations.

Table 4. HF Validation Simulated Use Results					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Choose Injection Site [C]	Use Errors (n=2; 1 injection-naïve patient; 1 injection-naïve caregiver)	-P22 injected in the wrong injection site. During the first injection, the participant appeared to look at the QRI and placed the pad on their right lower arm by the wrist. The moderator asked where they would inject if they were at home, and P22 reported the thigh or abdomen while reading the QRI, asking if they needed to be that specific. -C26 injected in the exact same spot for the second injection.	-P22 said they chose their arm because they felt compelled to attach the injection pad first thing before reading the instructions. They expected their arm/wrist to be less painful. They added that their eyes were drawn to Step 1 in the QRI and they skipped the injection site information. -C26 said they chose the same spot because they did not see the information about not injecting into the exact same spot twice in the QRI. They said they focused on QRI Steps 1-3. C26 stated that they were less concerned with doing something wrong, because they were not administering the injection to a real	The occurrence rate of choosing the incorrect injection site observed in the validation study was 2 out of 142 total attempts (75 for injection 1, 67 for injection 2). Lilly's risk management process identified that the observed use problems could lead to the following hazards: intramuscular, intravenous, intradermal injections, or repeated injection site trauma. These hazards could lead to minor pain or discomfort (severity 2), minor immune response/injection site reaction (severity 2), possible development of antibodies (severity 2), or higher than expected bioavailability (severity 2). Selecting an improper or exact same injection site is a use error common to all medication delivery devices and the mitigations implemented to reduce its	Based on the use-related risk analysis (URRA), we note the potential harm associated with these use issues include pain/discomfort due to an intramuscular injection or due to an injection at the same site, along with potential for antibody development or higher expected bioavailability due to intradermal or intravenous injection. We acknowledge the current mitigation strategies in place including dedicated figures and statements in the IFU and the Quick Reference for Injection (QRI) on the inner carton lid. Furthermore, we note the participants were able to identify the correct information. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			person and were more focused on attaching the injection pad to the manikin correctly.	occurrence are appropriate. The QRI and IFU have dedicated sections for injection site instructions. Both appropriately describe through graphics and text the proper selection of the acceptable injection sites. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Remove Base Cap [C]	Use Errors (n=2; 1 injection-naïve patient; 1 injection-experienced caregiver)	-P13 removed the base cap during injection 1 then injected with the base cap on during injection 2. -C03 partially twisted the base cap but did not fully remove it during injection 1. He administered injection 1 into the based cap. C03 successfully removed the base cap for injection 2.	-P13 said she forgot to remove the base cap during the second injection as she was concentrating less on what to do during the second injection. P13 confirmed that she knew that she should remove the base cap before injecting. She successfully removed the base cap during the first injection. -C03 explained that he felt resistance from the base cap and the	In the validation study, the occurrence rate of not removing the base cap was 2 out of 142 total attempts (75 for injection 1, 67 for injection 2). Lilly's risk management process identified no dose delivered as a potential hazard of not removing the base cap. This hazard could lead to a delay in treatment/reduced therapeutic benefit (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the	Based on the URRA, we note the potential harm associated with these use issues include a delay in treatment or negative impact on efficacy due to no dose delivered. We acknowledge the current mitigation strategies in place including a dedicated step incorporating instructions and a figure displaying removal of the base cap in the IFU and QRI. Furthermore, we note one participant was able to self-correct for the second injection. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			resistance told him "To stop turning," adding that he was concerned about potentially breaking the device. He noted he had expected the needle to come through the gray base cap due to similarity with his current pen, Ozempic. C03 had assumed that twisting it would make the needle come out, and he realized the base cap was supposed to come off when reading the QRI statement not to recap the device.	mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The QRI and IFU instruct to remove the gray base cap by twisting, and both show a redundant directional arrow to indicate the direction to twist. The pen includes sequential numbering on various parts of the pen, starting with '1' on the gray base cap. The gray base cap also includes a directional arrow to indicate the direction to twist, consistent with the illustrated instructions. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Place Device against Injection Site [C]	Use Errors (n=2; 1 injection-naive patient; 1 injection-experienced caregiver)	-P13 read the steps in the IFU and placed the device upside-down on the injection pad. After they unlocked the device, the moderator asked the participant to	-P13 explained that they expected the narrow end of the injection device to contain the needle, and	In the validation study, the occurrence rate of placing the device upside down on the injection site was 2 out of 140 total attempts (74 for	Based on the URRA, we note the potential harm associated with these use issues include an injection site reaction due to wrong injection site, delay in

		set the device on the table. The participant looked at the IFU again and subsequently oriented the device correctly to complete the first injection. -C28 referenced the QRI, placed their thumb over the needle opening in the clear base and moved the device toward the injection pad on the table. The moderator paused the participant and asked them to attach the injection pad to the manikin, reminding them that there was a needle and to be careful. C28 attached the injection pad to the manikin, read the QRI again, and oriented the device correctly to administer the first injection.	they thought the larger end gave them a better grasp. They further explained that during the pause they looked at the IFU and noticed the image in Step 2, stating that they noticed the fingers on the blue button. -C28 explained that they thought the needle was going to come out of the injection button side of the pen, because they expected it to pop out when they unlocked the pen. C28 also explained that they did not initially see information in the QRI about how to orient the device. They said they were nervous during the session due to "all the cameras and stuff." They confirmed that the information in the QRI "made sense" to them.	injection 1, 66 for injection 2). Lilly's risk management process identified that the observed use problems could lead to the following hazards: an injection into the wrong injection site (thumb or palm), no dose (to patient), and unintended dose to someone other than the patient. These hazards could lead to the following harms: a minor immune response or injection site reaction (severity 2), delay in treatment/reduced therapeutic benefit (severity 3), or immune response to someone other than the patient (no adverse events expected) (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The IFU parts diagram states which end contains the needle and the	treatment or negative impact on efficacy due to no dose, or possible development of antibodies due to injection into unintended user. We acknowledge the current mitigation strategies in place including dedicated statements and figures displaying the correct orientation in the IFU and QRI. However, we note these participants would have injected into their thumb/wrong injection site. Therefore, we recommend the user interface be revised to address these use issues. See section 5.3 for our recommendation.

				location of the clear base. The QRI and IFU consistently shows the device with the needle end/clear base oriented downwards or towards the skin. The QRI and IFU instruct to place the clear base flat and firmly against the skin. Illustrated instructions include labels showing 'needle' when removing the base cap and 'clear base' when placing the device against the stomach. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Unlock Device [C]	Use Difficulty (n=1; 1 injection-experienced caregiver)	-C10 referenced the QRI and IFU and unlocked both devices. They followed the IFU while performing subsequent steps and relocked the device before placing it against the injection pad. They attempted to press the injection button for a few minutes, eventually re-unlocking the device and completing the first injection successfully.	-C10 explained that they unlocked the pens early to be efficient. C10 further explained that they had forgotten that they had done the steps in the QRI out of order in unlocking the pens immediately after removing the base caps. When they had relocked the devices, they	In the validation study, the occurrence rate of not unlocking the device was 1 out of 142 total attempts (75 for injection 1, 67 for injection 2). Lilly's risk management process identified the following as potential hazards of not unlocking the device: high forces on the button or no dose. These	Based on the URRA, we note the potential harm associated with this use issue include pain/discomfort due to excessive manipulation force, delay in treatment or negative impact on efficacy due to no dose. We acknowledge the current mitigation strategies in place including a dedicated step with

			thought they were instead unlocking them. They realized they had relocked the device when the button would not depress to administer the injection. C10 confirmed that they saw and understood the (un)lock symbols.	hazards could lead to minor pain or discomfort (severity 2) or delay in treatment/reduced therapeutic benefit (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The QRI and IFU instruct how to unlock the device using the lock ring, and both show lock/unlock symbols and directional arrows to indicate the direction to twist. The force required to unlock the device is appropriate for intended users. The pen includes sequential numbering on various parts of the pen, with '2' on the lock ring. The lock ring displays lock and unlock symbols and directional arrows, consistent with the illustrated instructions. After analyzing the root causes, controls, and the	statements and figures depicting the correct use. Furthermore, we note the participant was able to self-correct. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

				severity of harm, Lilly determined the residual use-related risk level has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Hold at Injection Site until Injection is Complete [C]	Use Errors (n=3; 2 injection-experienced caregivers, 1 HCP)	-C01, C28, H15 removed the device from the injection site before the second click.	-Both C01 and C28 stated that they had previous experience with EpiPens and/or syringes, and C01 lifted the device early because they thought there would be only one click and expected the injection would be instantaneous like EpiPen. C28 admitted that they assumed they held the device for enough time without counting out 10 seconds. They did not look for the hold time for the device due to knowing how to use an EpiPen. C01 additionally explained that during the first injection, they had not seen the information in Step 3 of the QRI to wait for the second click or to hold	In the validation study, the occurrence rate of not holding the device until the injection was complete was 3 out of 140 total attempts (74 for injection 1, 66 for injection 2). Lilly's risk management process identified that the observed use problems could lead to the following hazards: underdose, intradermal injection, unintended needle movement, or needle breaking during the injection. These hazards could lead to reduced therapeutic benefit (severity 3), minor pain or discomfort (severity 2), or infection that may require antibiotics (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are	Based on the URRA, we note the potential harm associated with these use issues include negative impact of efficacy due to an underdose (missed dose or partial dose). We acknowledge the current mitigation strategies in place including a dedicated step with instructions and figures presenting the correct use in the IFU and QRI. Additionally, we note two of the participants were able to self-correct during the second injection. The other participant did not attempt a second injection. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			for 10 seconds. They added that they had been focused on the QRI information that two devices constituted one dose and supposed that they had missed the injection time information for that reason. C28 additionally explained that they did not see the information in the QRI about holding the device for 10 seconds, because they were focused on the text in Steps 1-3 and the bolded labels at the top right of the QRI. Further, they said they did not read the circle showing 10 seconds in Step 3 due to believing that this circle with arrows would depict how to unlock the device. -H15 said that they were accustomed to giving injections that require pushing a plunger rather than pressing an auto-injection button and	appropriate. The pen provides auditory feedback indicating when the injection starts (first click) and when the injection is complete (second click). The QRI and IFU instruct to hold the clear base flat and firmly against the skin during the injection, and to press and hold the blue button for 10 seconds or until a second loud click is heard. The pen provides visual feedback through the clear base, where the user can watch the gray plunger travel as the dose is administered. The IFU also states that a complete injection can be confirmed by ensuring the gray plunger is visible in the clear base. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	

			expected this product would administer the dose as quickly as their typical injections. They said they would not expect the double-click sound for an injection. H15 also explained that they did not read Step 3 in the QRI, initially believing that this step contained information they already knew. They confirmed that they understood the information when they read it during follow up.		
Discard Device [C]	Use Errors (n=15; 1 injection-experienced patient, 2 injection-naïve patients; 1 injection-experienced caregiver; 4 injection-naive caregivers) Use Difficulty (n=2; 1 injection-naive patient) Close Calls (n=2; 1 injection-naïve caregiver)	<u>Use Errors</u> -P14, P20, C07, C14, C29, and C30 threw away (or indicated they would do so) into the household trash. -P06 noted they would recycle them because they are plastic. -C15 looked at the QRI and disposed of the devices in the regular trash can. They then looked at the IFU, pulled the devices out of the trash can, placed the devices back into the carton. <u>Use Difficulties</u> -P22 initially noted they would wrap the used devices in a plastic bag and dispose of them in the household trash. They then	<u>Use Errors</u> -P14, C07, and C29 noted that they did not notice the sharps container in the study room. C07 had expected to hand the devices back to the moderator once they had finished the injections. P14 noted that they normally dispose of their sharps in the trash at home because of the need to get a new sharps container when the current one becomes full.	In the validation study, the occurrence rate of disposing of the device incorrectly was 15 out of 141 total attempts (75 for injection 1, 66 for injection 2). Lilly's risk management process identified the following as potential hazards of disposing of the device incorrectly: a used needle stick to another person or a broken syringe. These hazards could lead to major infection requiring medical intervention (severity 4) or minor pain or discomfort as a result of cuts	Based on the URRA, we note the potential harm associated with these use issues include transfer of infectious agent, infection, and pain/discomfort due to used needle stick to another person and broken glass. We acknowledge the current mitigation strategies in place including dedicated instructions and a figure in the IFU along with a dedicated statement in the QRI. However, even with the mitigation strategies, several participants had use issues. Therefore, we agree with the Sponsor's assessment, proposed additional mitigation

		looked back through the QRI and stated they should put them in sharps. <u>Close Calls</u> -C09 placed the devices back in the carton after the injections. C09 initially did not understand that another step was needed. They stated they would "throw away" the used devices and correctly placed them in the sharps container.	C07 noted they would dispose of the devices at the pharmacy if they were picking up a prescription weekly but would dispose of used devices in the household trash if going to the pharmacy only once a month. C07 noted that they recognized the sharps container as something used in a healthcare facility or pharmacy. P20, C07, C14, and C30 said they did not see the disposal information in the QRI and/or IFU. P20, C07, and C30 had focused on QRI Steps 1-3 and on any boldface information and noted they had stopped reading after the information about administering the injections. C14 found the disposal information in the QRI during the knowledge assessment but commented that the text is small.	from broken glass (severity 2). Inappropriate device disposal is a use error common to all medication delivery devices and the mitigations implemented to reduce its occurrence are appropriate. The primary mitigation to reduce used needle sticks after injection is the needle retraction feature. Once all the medication has been fully delivered from the device into the skin, the needle will automatically retract from the skin and up into the clear base. The needle orifice of the pen's clear base is minimized to restrict user access both before and after use. The QRI and IFU instruct to put the used pen in a sharps container. The IFU also follows the FDA guidance2 by detailing through graphics and text disposal procedures and options for a sharps container in a dedicated section for Disposing of (b) (4) Pen. For the participants who either did not dispose of the device correctly or experienced difficulties during simulated	implementation, and proposal to conduct a supplemental HF validation study to evaluate the proposed mitigation.

			C29 stated that they do not know what a sharps container is and believed that the IFU graphic depicted a red trash can. They followed the information that said to dispose of the pens in heavy-duty plastic by using the trash can instead. When asked, P20, C07, C14, C29, and C30 demonstrated that they understood the disposal information in the labeling. P06 also said they first assumed that recycling the device was appropriate because it was plastic. The participant then explained that they did not see it the disposal information in the QRI because they had skipped to the "IMPORTANT" line highlighted in blue. They said they first noticed the relevant information in the IFU (and interpreted it correctly) during the	use, they were asked Question E: "What do these materials say about how to dispose the device after use?" All participants who were asked Question E located and comprehended how to properly discard the devices within the IFU. Of the eight (8) disposal use errors during simulated injection, six (6) participants had a contributing root cause of insufficient prominence/text size of information in the QRI or IFU. Lilly determined that edits to QRI step 3 may make disposal information more salient and thereby reduce this use-related risk. One (1) QRI modification was made to mitigate use problems associated with task 9, Discard device: In order to focus users' attention on the disposal information and on other, more salient presentations of the dosing information, the (b) (4) was removed from Step 3.The modified user interface was evaluated in the	

			knowledge assessment but had not unfolded the IFU during the injections. C15 explained that they had disposed of these devices as they would other home-use products like light bulbs. They noted that they saw the disposal information in the IFU after placing the devices in the trash can and was not sure why they then placed them back into the carton rather than into the sharps container. C15 understood the IFU disposal information. They speculated that they had been following their habit of putting used household devices back into their boxes for disposal. <u>Use Difficulties</u> -P22 explained that they did not realize they would need to dispose of the used devices in a particular	supplemental validation study.	

			manner as they had not previously administered injections. They noted that they knew to dispose of the devices in the sharps container after reading the QRI and understood the IFU disposal information. <u>Close Calls</u> -C09 explained that they were unsure how thorough they needed to be with the simulation. They added that they previously worked in a hospital and knew that used injection devices belong in sharps containers. C09 also explained that they did not see the disposal information in the QRI. They had focused on QRI Steps 1-3 and did not read all information in the QRI, adding that they would typically read more thoroughly at home. When asked, C09 demonstrated that they understood		

			the disposal information in the QRI.		
Repeat Injection Steps with Second Pen for a Complete Dose [C]	Use Errors (n=8; 4 injection-experienced patients; 3 injection-experienced caregivers, 1 injection-naïve caregiver) Use Difficulty (n=2; 1 injection-experienced patient; 1 injection-naive caregiver)	<u>Use Errors</u> -P02, P14, P18, P26, C13, C19, C28, and C32 completed the first injection and indicated they were done with the task. They did not complete the second injection. <u>Use Difficulties</u> -P31 and C14 initially administered one dose, asked the moderator what to do next, read the QRI, and proceeded to administer the second injection.	<u>Use Errors</u> -P02, P14, P18, P26, C13, C19, and C28 described that the device was similar to the injection devices they currently use. They described that their existing devices come in 2-pack or 4-pack carton configurations, but the regimen only requires one injection for a full dose. P02 noted that they rely on the prescription to know what their dose is and, as this was not provided in the study, they did not know how much to administer. P02 said they did not see the text in the QRI nor IFU stating both pens were required for a full dose and assumed only one injection was needed. They reported glancing at the QRI and being focused on Steps 1-3 in the IFU. P02 initially glanced at '100 mg + 100 mg = 1 full dose' in the IFU and	In the validation study, the occurrence rate of not administering both injections was 8 out of 75 attempts. Lilly's risk management process identified underdose as a potential hazard of not administering both injections to complete the dose. This hazard could lead to reduced therapeutic benefit (severity 3). Of the eight (8) use errors during this task, seven (7) participants attributed insufficient prominence or misinterpretation as a root cause for not choosing to use the second pen. Lilly identified an opportunity to make additional changes to the labeling components of the UI to make dosing information more prominent and understandable. Seven (7) QRI modifications were made to mitigate use problems associated with task 10, Repeat injection steps with second pen for complete dose. These modifications to the user interface are expected to reduce this use-related risk	Based on the URRA, we note the potential harm associated with these use issues include negative impact on efficacy due to an underdose (missed dose or partial dose). We acknowledge the current mitigation strategies in place including dedicated statements that are boxed in the IFU at the beginning and the end, along with a figure depicting two injections equal one dose at the beginning of the QRI and a dedicated highlighted statement at the end of the QRI. Based on the subjective feedback, we note several of the participants attributed the use issues due to negative transfer and the information not being salient. Therefore, we agree with the Sponsor's assessment, proposed additional mitigations, and proposal to conduct a supplemental HF validation study to evaluate the effectiveness of the implemented mitigations.

			interpreted incorrectly that 100 mg was a full dose. C13, C28, C32 stated that they did not see the dosing information in the QRI during the task because they did not look at the top of the QRI, instead focusing on the steps of use and assuming only one injection was needed. P26 admitted that they did not read the instructions and when they saw information about two pens being required for a full dose, they assumed that it was about the contents of the box rather than the dosage. They stated, "I didn't realize both [pens] were for the same time." C19 said they saw the diagram during the task but interpreted it as two separate doses. When asked, P02, C13, C19, C28, and C32 understood the	and will be evaluated in a supplemental validation study.	

			IFU text stating that two injections are required for a full dose. <u>Use Difficulties</u> -P31 and C14 noted that they had initially believed that one injection constituted a full dose due to past experiences with injections. P31 also explained that they had initially glanced at the QRI but had not really looked at the diagram illustrating both pens were required for a full dose. They added that they had been in "default mode" in administering one injection after seeing the words, "one full dose" in the QRI.		

Table 5. HF Validation Study Knowledge Task Assessment Results

Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Inspection Instructions [C]	Use Errors (n=10; 2 injection-experienced	-C11 stated that	-C11 noted he did not expect to see information to check	In the validation study, the error rate for the knowledge question about inspecting	Based on the URRA, we note the potential harm associated with these use issues include

	caregivers; 2 injection-naïve caregivers; 3 HCPs)	he had read the expiration date but could not find information to check this date in the IFU. -C15, C27, H10, H12 and H14 did not mention to check for damage on the device. -C08, C15, H10 and H14 did not mention to check for frozen medication.	the expiration date under the "Inspect" section of the IFU. He explained that he typically checks the expiration date when first receiving the medication, rather than right before injecting, and so did not consider it part of inspecting the device. -C15 and H12 explained that they did not think they needed to read out all the information in that section when responding to the question. He confirmed he saw this information during the knowledge assessment and understood it. C27 noted he expected this device would not become damaged due to its "sturdy" design and packaging during the study. H14 noted she thought the moderator's question was specific to the	the device before use was 7 out of 75. Lilly risk management process identified the following as potential hazards for accepting a device that's expired, damaged or frozen: degraded drug product, drug with reduced potency, device inoperable, underdose, broken device, and injection of silicone particulates. These hazards could lead to minor immune response/injection site reaction (severity 2), minor pain/discomfort (severity 2), reduced therapeutic effect (severity 3), or major immunogenic reaction (severity 4). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. Manufacturing controls provide assurance that the drug product will not be defective and that the labeling will be accurate. The IFU instructs to inspect the Pen to make sure that the pen is not damaged or expired, and it instructs to	immune response or lack of drug effect or immunogenic reaction due to injection of drug degradation products or frozen drug, negative impact on efficacy due to injection of expired product, delay in treatment or pain/discomfort due to damaged device. We acknowledge the current mitigation strategies in place including dedicated statements under the storage section of the IFU, dedicated statements instructing users to inspect the solution and expiration date along with a figure displaying where to find the expiration date. We note some participants were confused by the task prompt which may have contributed to the errors seen. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			medication rather than about the device. She confirmed that she saw and understood the information but did not include it as part of her answer because she was focused on the medicine, instead of the device as well. C27 explained that he had focused on the paragraph in this section and had overlooked the bullet points, instead looking throughout the back of the IFU for more inspection information. H10 noted she had skipped over (i.e., not seen) the bullet point about damage because it was not bolded. However, she added that, as an experienced nurse, she would not use a damaged device. -C15 explained that he did not think he needed to read out all the information in that section when	make sure the medicine is not frozen, does not contain particulates, and is not cloudy/discolored. Additional instructions regarding storage and expiration are also listed on the outside of the carton and the device label. Of the seven (7) people who responded incompletely to the question (use error), six (6) participants noted study artifact as a contributing root cause: misinterpreting the task prompt (C15, H12, H14), not mentioning an item due to expecting to do it on their own without reading this section (C11, H10), or not expecting the study team would present a damaged device (C27). Lilly determined that the wording of the moderator prompt was a contributing factor for these six (6) participants. The prompt has been edited to clarify the scope of the task, and the task with this updated prompt was evaluated in the supplemental HF study in order to confirm whether the product labeling supports	

			responding to the question. He confirmed he saw this information during the knowledge assessment and understood it. H10 stated that she had seen the information not to use the device if frozen and was unsure why she had not said it earlier, adding that she would know not to use frozen medication. H14 noted he thought the moderator's question was specific to the medication rather than about the device. She confirmed that she saw and understood the information but did not include it as part of her answer because she was focused on the medicine, instead of the device as well.	appropriate device inspection. Notably, every participant found the section on inspecting the device before use without moderator assistance. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk level to be reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Warm Up Instructions [C]	Use Errors (n=1; 1 HCP)	H01 located the proper IFU section but did not locate the proper information within that section to answer the question.	-H01 noted she had focused on the bold sub-headings as the "big takeaways" and did not see the non-bold	In the validation study, the error rate for the knowledge question about warming up the pen before use was 1 out of 75.	Based on the URRA, we note the potential harm associated with these use issues include an immune response, immunogenic reaction, or lack of drug effect due to injection of

			information for “Take the Pens from the refrigerator.”	Lilly risk management process identified that the observed use problem could result in the following as potential hazards: injection of cold drug product and longer than expected injection times (still under 10 seconds specification). These hazards could lead to the following harms: minor pain/discomfort (severity 2) and reduced therapeutic effect (severity 3). Additionally, degraded drug product, underdose, device inoperable, injection of heated drug product, loss of sterility in primary container closure, and broken devices were identified as potential hazards for improperly heating up the device. These hazards could lead to minor immune response/injection site reaction (severity 2), minor pain/discomfort (severity 2), minor infections (severity 2), reduced therapeutic benefit (severity 3), major infection (severity 4), or major immunogenic reaction (severity 4).	degraded drug product. Additional potential harm related to these use issues include negative impact on efficacy/underdose due to loss of drug product volume, delay in treatment or negative impact on efficacy due to inoperable device, pain/discomfort due to exposure to high temperatures or syringe breaking, infection due to injection from non-sterile container, underdose or pain/discomfort due to cold drug and potentially lengthening injection time. We acknowledge the current mitigation strategies in place including dedicated instructions on the correct use. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

				Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. 'Take the Pens from the refrigerator' is listed as the first step on the 'Preparing to inject (b) (4) panel. The IFU instructs to leave the pens out at room temperature for 30 minutes to allow the autoinjector to warm up before use. The IFU also warns users to not heat up the device using inappropriate means, like a microwave, direct sunlight, or hot water. H01 found the appropriate section in the IFU, read and correctly interpreted the section heading, but did not read further into the section to learn additional information. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	

Table 6. HF Supplemental Study Simulated Use Results					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Choose Injection Site [C]	Use Errors (n=2; 2 injection-naïve patients)	-P05 referenced the QRI and placed the injection pad on their upper arm. The moderator redirected the participant to place the injection pad on the thigh. -P14 initially placed the injection pad on their forearm and stated they would self-inject in the upper arm in real life. The moderator directed them to place the injection pad on their thigh. They administered both injections with the injection pad on the thigh.	-P05 said they chose their arm because all vaccines and other injections they have seen have been in the arm and they expected this would be the same. The participant stated that they did not see anything in the materials instructing a particular injection site. Once pointed to this part of the QRI, they noted the information was clear but that they had not thought to look at it earlier. -P14 stated that they initially placed the injection pad on their forearm because they thought it would be easier to	The occurrence rate of choosing the incorrect injection site observed in the validation study was 2 out of 58 total attempts (31 for injection 1, 27 for injection 2). Two (2) participants who attempted both injections could not be assessed (marked TNA) on the second injection, due to use errors choosing the injection site in the first injection. Lilly's risk management process identified that the observed use problem (self-injection into the back of the arm) could lead to the following hazards: intramuscular, intravenous, or intradermal injection. These hazards could lead to minor pain or discomfort (severity 2), minor immune response/injection site reaction (severity 2), possible development of antibodies (severity 2), or higher than	Based on the use-related risk analysis (URRA), we note the potential harm associated with these use issues include pain/discomfort due to an intramuscular injection or due to an injection at the same site, along with potential for antibody development or higher expected bioavailability due to intradermal or intravenous injection. We acknowledge the current mitigation strategies in place including dedicated figures and statements in the IFU and the Quick Reference for Injection (QRI) on the inner carton lid. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			demonstrate an injection to the moderator. P14 explained they chose the upper arm because they thought this would be less painful than the stomach. P14 stated that they did not read the injection site text in the QRI earlier, because they were focused on steps 1-2-3.	expected bioavailability (severity 2). Both participants were marked unsuccessful for indicating they would self-inject into the back of their arm. While Lilly recommends that patients do not self-inject into the back of the arm, this recommendation is to increase user comfort (i.e., patient user avoids operating device at an uncomfortable angle) and to reduce the occurrence of this discomfort leading to injection in an incorrect tissue layer. If the user holds the device flat and firmly against the skin for the entire duration of the injection, they will successfully complete dose administration into the correct tissue layer in the back of the arm, which is an acceptable injection site for administration by a caregiver or HCP. Selecting an improper injection site is a use error common to all medication delivery devices and the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU have dedicated sections for	

				injection site instructions. Both appropriately describe through graphics and text the proper selection of the acceptable injection sites.	
Remove Base Cap [C]	Use Errors (n=2; 1 injection-experienced caregiver)	-C09 did not view any of the instructional material before starting the injection. C09 did not remove the base cap, then unlocked the device and pressed the button causing the device to actuate into the base cap over the table. During the second injection, C09 did not view any of the instructional material before starting the injection. C09 did not remove the base cap, then unlocked the device, and proceeded to attempt to inject into the injection pad that was strapped to the manikin.	-C09 said they did not use any of the instructional material, focusing only on the numbers (pad printing) on the pen. When directed to use the labeling in the second trial, the participant performed all tasks successfully with no use errors. C09 realized when reading the QRI that the base cap must be pulled off. They added that if this happened in real life, they would call Lilly customer service. Notably, they stated during the task, "Sorry, I am not familiar with this device."	In the validation study, the occurrence rate of not removing the base cap was 2 out of 60 total attempts (31 for injection 1, 29 for injection 2). Lilly's risk management process identified no dose delivered as a potential hazard of not removing the base cap. This hazard could lead to a delay in treatment/reduced therapeutic benefit (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The QRI and IFU instruct to remove the gray base cap by twisting, and both show a redundant directional arrow to indicate	Based on the URRA, we note the potential harm associated with these use issues include a delay in treatment or negative impact on efficacy due to no dose delivered. We acknowledge the current mitigation strategies in place including a dedicated step incorporating instructions and a figure displaying removal of the base cap in the IFU and QRI. We note this participant did not reference any of the labeling and just the numbers. . Therefore, we recommend the user interface be revised to address this use issue. See section 5.3 for our recommendation.

				the direction to twist. The pen includes sequential numbering on various parts of the pen, starting with '1' on the gray base cap. The gray base cap also includes a directional arrow to indicate the direction to twist, consistent with the illustrated instructions. In the QRI and IFU, the illustrations for steps after removing the base cap depict devices without base caps. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Place Device against Injection Site [C]	Use Error (n=1; 1 injection-naïve patient)	-P05, during the first injection, placed the device upside down on the injection pad with no part of their body over the needle area. The moderator paused the participant, at which point the participant realized their mistake and reoriented the device correctly.	-P05 said that they initially placed the device upside down because they did not see the text or illustration in the QRI stating to place the clear base on the injection site. P05 added that they had assumed that the base cap would be taken off the top of	In the validation study, the occurrence rate of placing the device upside down on the injection site was 1 out of 58 total attempts (30 for injection 1, 28 for injection 2). One (1) participant who attempted both injections could not be assessed (marked TNA) on this task for either injection, due to use errors when removing the base cap.	Based on the URRA, we note the potential harm associated with these use issues include an injection site reaction due to wrong injection site, delay in treatment or negative impact on efficacy due to no dose, or possible development of antibodies due to injection into unintended user. We acknowledge the current mitigation strategies in place including dedicated statements

			the device, like taking a lid from a jar. P05 stated that they initially believed the number 1 on the base cap indicated to press on that end to administer the injection but then realized that the 1 indicated that the cap should be removed first. After injection, they noticed the QRI instruction to place the clear side down and stated that it was clear.	Lilly's risk management process identified that the observed use problems could lead to the following hazards: no dose (to patient) and unintended dose to someone other than the patient. These hazards could lead to the following harms: delay in treatment/reduced therapeutic benefit (severity 3) or immune response to someone other than the patient (no adverse events expected) (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU appropriately describe through graphics and text the proper operational sequence and technique. The IFU parts diagram states which end contains the needle and the location of the clear base. The QRI and IFU consistently shows the device with the needle end/clear base oriented downwards or towards the skin. The QRI and IFU instruct to	and figures displaying the correct orientation in the IFU and QRI. However, we note this participant would have injected into their thumb/wrong injection site. Therefore, we recommend the user interface be revised to address this use issue. See section 5.3 for our recommendation.

				place the clear base flat and firmly against the skin. Illustrated instructions include labels showing 'needle' when removing the base cap and 'clear base' when placing the device against the stomach. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Hold at Injection Site until Injection is Complete [C]	Use Errors (n=2; 1 injection-naive patient)	-P12 lifted both pens from the injection site before the second click sounded: Injection 1: Lifted pen 0.4 seconds before the second click and no liquid appeared to come out after liftoff. Injection 2: Lifted pen 2.5 seconds before the second click and liquid did come out after liftoff. P12 saw the liquid and placed the pen back on the injection site until the second click sounded.	-P12 explained that they heard only one click during the first injection but felt the needle retraction mechanism activate and so knew the device was done and they could remove it. For the second injection, P12 stated that they heard the first click, then felt a "vibration" (the needle releasing) and so believed the pen had finished and lifted it, but then they realized they had	In the validation study, the occurrence rate of not holding the device until the injection was complete was 1 out of 58 total attempts (30 for injection 1, 28 for injection 2). One (1) participant who attempted both injections could not be assessed (marked TNA) on this task for either injection, due to use errors when removing the base cap. Lilly's risk management process identified that the observed use problems could lead to the following hazards: underdose,	Based on the URRA, we note the potential harm associated with these use issues include negative impact of efficacy due to an underdose (missed dose or partial dose). We acknowledge the current mitigation strategies in place including a dedicated step with instructions and figures presenting the correct use in the IFU and QRI. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			lifted the pen too early and subsequently did hear the second click. During root cause investigation, P12 found and correctly interpreted the QRI statement that the injection may take 10 seconds, noting that they did not see this in the QRI earlier as they had instead been focused on the text below each illustration.	intradermal injection, unintended needle movement, or needle breaking during the injection. These hazards could lead to reduced therapeutic benefit (severity 3), minor pain or discomfort (severity 2), or infection that may require antibiotics (severity 3). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The pen provides auditory feedback indicating when the injection starts (first click) and when the injection is complete (second click). The QRI and IFU instruct to hold the clear base flat and firmly against the skin during the injection, and to press and hold the blue button for 10 seconds or until a second loud click is heard. The pen provides visual feedback through the clear base, where the user can watch the gray plunger travel as the dose is administered. The IFU also states that a	

				complete injection can be confirmed by ensuring the gray plunger is visible in the clear base. One (1) participant lifted both devices early. However, for the first device, the participant lifted the device from the injection site 0.4 seconds before the second click was heard (C06). No surrogate liquid was observed to be present on the injection pad after the participant lifted the device from the site, indicating that the full contents were likely administered into the injection pad prior to liftoff. Additionally, the Lilly mechanical engineering team determined that, at 0.4 seconds prior to hearing the second click, the full medication has been delivered. When medication administration is approximately 0.1 seconds from completion, a delay mechanism lasting approximately 0.6 seconds is activated to ensure that the medication is fully delivered. The needle retracts after this delay, and the second click occurs when the needle has finished	

				retracting. As such, when lifting at 0.4 seconds before the second click, this participant would likely have received the full contents from their first injection. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Discard Device [C]	Use Errors (n=2; 1 injection-naive patient; 1 injection-experienced patient) Close Call (n=1; 1 caregiver)	<u>Use Errors</u> -P14 and P17 disposed of both pens into the trash. <u>Close Call</u> -C14 initially disposed of both pens into the trash and then attempted to self-correct their error after reviewing the IFU. Moderator paused them before they reached into the trash as a safety precaution.	<u>Use Errors</u> -P14 explained that they remembered the QRI stating to throw away the used pen once done and understood this as: throw the used pen into the trash and do not use that pen again. They could not find this statement again during root cause investigation. P14 stated that, thinking more about disposal, they know that products with needles should be disposed in a	In the validation study, the occurrence rate of disposing of the device incorrectly was 4 out of 58 total attempts (30 for injection 1, 28 for injection 2). One (1) participant who attempted both injections could not be assessed (marked TNA) on this task for either injection, due to the moderator needing to retrieve the device from the participant earlier in the session for safety reasons. Lilly's risk management process identified the following as potential hazards of disposing of the device incorrectly: a used needle stick to another	Based on the URRA, we note the potential harm associated with these use issues include transfer of infectious agent, infection, and pain/discomfort due to used needle stick to another person and broken glass. We acknowledge the current mitigation strategies in place including dedicated instructions, a figure in the IFU, a dedicated statement in the QRI, and the needle retraction mechanism. We note one participant was able to self-correct, and another participant did notice the disposal information but threw it in the trash because the moderator stated "do what you would do at home."

			sharps container rather than the household trash. The moderator pointed to the disposal statement in the QRI, and P14 noted that they had read “Throw away” because it was in boldface but had not read the rest of the sentence and for that reason did not realize to use the sharps container. When reading the full sentence, P14 interpreted it correctly. P17 stated that at home, they would have put the devices back in the carton and throw them in the household trash. P17 did notice the disposal section in the IFU during simulated use but did not read the information. They stated that the moderator told them to ‘do what they would normally do at home’ and thus,	person or a broken syringe. These hazards could lead to major infection requiring medical intervention (severity 4) or minor pain or discomfort as a result of cuts from broken glass (severity 2). Inappropriate device disposal is a use error common to all medication delivery devices and the mitigations implemented to reduce its occurrence are appropriate. The primary mitigation to reduce used needle sticks after injection is the needle retraction feature. Once all the medication has been fully delivered from the device into the skin, the needle will automatically retract from the skin and up into the clear base. The needle orifice of the pen’s clear base is minimized to restrict user access both before and after use. The QRI and IFU instruct to put the used pen in a sharps container. The IFU also follows the FDA guidance by detailing through graphics and text disposal procedures and options for a sharps container in a dedicated	Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

			chose to follow current practices instead of the labeling. <u>Close Call</u> -C14 stated that they originally thought the devices needed to be disposed in the trashcan but then saw the use step regarding proper disposal in the IFU. After seeing this step in the IFU, they intended to grab them out of the trash can and properly dispose of them devices in the sharps container. They were unfamiliar with sharps containers based on experiences caretaking their stepfather but understood that the IFU instructed them to dispose of medical waste in something other than a trashcan.	section for Disposing of [redacted] (b) (4) Pen. For the participants who either did not dispose of the device correctly or experienced difficulties disposing during simulated use, they were asked Question E: "What do these materials say about how to dispose the device after use?" All participants who were asked Question E located and comprehended how to properly discard the devices within the QRI or IFU. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	
Repeat Injection Steps with Second Pen for a Complete Dose [C]	Use Errors (n=2; 1 patient; 1 injection-experienced caregiver)	-C06 did not use the second pen to complete the full dose. During Trial 2, C06 completed the full dose with both pens with no observations.	-When asked "Did you give the full dose today?", C06 said it was two pens (after looking back at the box) and noted that	In the validation study, the occurrence rate of not administering both injections was 2 out of 30 attempts. One participant (C09) could	Based on the URRA, we note the potential harm associated with these use issues include negative impact on efficacy due to an underdose (missed dose or partial dose).

		-P11 did not continue to the second dose. They were accurately able to communicate that a full dose was two injections when asked.	they did not give the full dose. C06 initially stated that all injections they've seen are one (1) pen for a full dose. C06 also explained that they had been focused on the 100 mg on the top of the carton and the steps 1-2-3 in the QRI. They did not read the blue banner nor step 4. -P11 was accurately able to communicate that a full dose was two injections, stating that "I did see on the top of the box on the lid that it said you will two injections to get your full dose [participant pointed to blue banner on QRI]. Means that if the doctor had ordered a full dose you would have to do the two pens." They noted as part of root cause that the carton mentioned refrigeration and wondered about leaving the unused	not be evaluated for injecting the full dose because of a use error on task 4, Remove base cap, on both devices. Lilly's risk management process identified underdose as a potential hazard of not administering both injections to complete the dose. This hazard could lead to reduced therapeutic benefit (severity 3). Of the two (2) use errors during this task, one (1) participant attributed insufficient prominence as a root cause for not choosing to use the second pen. Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. The QRI and IFU instruct that two (2) injections are required for a full dose and to inject one (1) pen followed right away by the other pen; in the QRI, this information is presented in large font and high contrast at the upper left. Step 4 in the QRI also instructs to inject the second pen immediately after the first to	We acknowledge the current mitigation strategies in place including dedicated statements that are boxed in the IFU at the beginning and the end, along with a figure depicting two injections equal one dose at the beginning of the QRI and a dedicated highlighted statement at the end of the QRI. However, we note a participant focused on the 100 mg at the top of the carton and the steps 1-2-3 in the QRI," but did not read the blue banner or step 4. Therefore, we recommend the user interface be revised to address this use issue. See section 5.3 for our recommendation.

			device in the refrigerator, as they do with Humira. During the root cause, they were unsure if they should administer the second pen immediately or wait 5-10 minutes before the second injection. P11 stated that, during Trial 1, they read only the Step 4 header in the QRI ("Inject 2nd Pen) because they believed the task was to see how they would go about using the pen, including sharing what they currently do with Humira, rather than administering both pens for a full dose. P11 only read the contents of Step 4 after moderator probing and saw 'immediately' at that time. When the moderator asked if they knew earlier in the session to administer the second pen immediately, the	give a full dose. Additionally, the IFU includes graphics and text showing what constitutes a full dose (100mg / mL + 100mg / mL = Full dose). Notably, all participants provided successful responses to Knowledge Assessment F, What is the full dose. One (1) participant did not see that the second pen should be administered immediately after the first and wondered if they should wait some time (5-10 minutes) before administering the second injection (P11). The Lilly medical team determined that there is no harm associated with separating the 2 injections by 5 or 10 minutes. This timeframe would not be unexpected, giving the patient time to prepare the site and syringe for a second injection. After analyzing the root causes, controls, and the severity of harm, Lilly determined the residual use-related risk has been reduced to as low as possible. Further modification of the user	

			participant stated "No, because I didn't read [Step 4 contents] until a few minutes ago. I did see about the 'inject the second pen', but I didn't read in the instructions how soon you had to do it…I didn't think I was going to need to do a second injection, so I didn't pay attention to [Step 4 contents] down there." When asked about the overall goal of the first trial, P11 stated "I'm just showing you how I would have administered, you know, the procedure that I would have done to prep it and actually give the injection…I thought I was just showing you how I would go about holding it and what I would do…That was what I was doing, like I would usually do at home."	interface is not likely to reduce this use error.	

			Additionally, for Trial 2, P11 only gave one injection again, indicating they thought the task was to administer the second injection to complete the full dose (where the first injection occurred in Trial 1).		

Table 7. HF Supplemental Study Knowledge Task Assessment Results					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Sponsor's Root Cause Analysis	Sponsor's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Inspection Instructions [C]	Use Difficulty (n=1; 1 injection-naïve patient)	-P14 struggled to find information on expecting the materials, noting information on damaged devices, but ultimately was able to find instructions for inspecting devices.	-P14 stated that they were unsure where they would expect to find this information in the IFU. P14 explained that they had been focused on the illustrations and did not initially notice the "Preparing to inject (b) (4)" header. P14 stated they noticed the inspection information once they had started thoroughly reading the IFU.	The error rate for the knowledge question about inspecting the device before use was 0 out of 31. Lilly risk management process identified the following as potential hazards for accepting a device that's expired, damaged, frozen, or has drug product that is discolored, cloudy or has particulates: degraded drug product, drug with reduced potency, device inoperable, underdose, broken device, injection of silicone particulates (caused by	Based on the URRA, we note the potential harm associated with these use issues include immune response or lack of drug effect or immunogenic reaction due to injection of drug degradation products or frozen drug, negative impact on efficacy due to injection of expired product, delay in treatment or pain/discomfort due to damaged device. We acknowledge the current mitigation strategies in place including dedicated statements under the storage section of the IFU, dedicated statements instructing users to inspect the

				freezing), and injection of particulate contaminants. These hazards could lead to minor immune response/injection site reaction (severity 2), minor pain/discomfort (severity 2), reduced therapeutic effect (severity 3), or major immunogenic reaction (severity 4). Lilly has analyzed the test results with the associated root causes and has concluded that the mitigations implemented to reduce its occurrence are appropriate. Manufacturing controls provide assurance that the drug product will not be defective and that the labeling will be accurate. The IFU instructs to inspect the Pen to make sure that the pen is not damaged or expired, and it instructs to make sure the medicine is not frozen, does not contain particulates, and is not cloudy/discolored. Additional instructions regarding storage and expiration are also listed on the outside of the carton and the device label. After analyzing the root causes, controls, and the	solution and expiration date along with a figure displaying where to find the expiration date. Therefore, we find the residual risk acceptable, and we have no recommendations at this time.

				severity of harm, Lilly determined the residual use-related risk level to be reduced to as low as possible. Further modification of the user interface is not likely to reduce this use error.	

5 CONCLUSION & RECOMMENDATIONS

5.1 HF VALIDATION AND SUPPLEMENTAL STUDY RESULTS

The results of the HF validation study and supplemental study demonstrate that representative users can use the product safely and effectively. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Section 5.3 below for Eli Lilly. We ask that the Division of Gastroenterology convey the below recommendations to Eli Lilly so that the recommendations are implemented prior to approval of this Application.

5.2 COMPARATIVE ANALYSES (b) (4)

Considering the totality of the information provided in the Comparative Analyses (b) (4) (b) (4) we agree with the Applicant's determination (b) (4) (b) (4) However, we have a recommendation for the proposed (b) (4) IFU in Section 5.3 below for Eli Lilly.

5.3 RECOMMENDATIONS FOR ELI LILLY & COMPANY

We recommend the following be implemented prior to approval of this BLA:

A. (b) (4) IFU

1. (b) (4)

B. Quick Reference for Injection (QRI)

1. Based on the subjective feedback provided in the HF summative study results related to the task of repeat injection steps with second pen for a complete dose, consider adding an image to step 4 to improve emphasis and understanding of this task.

C. Device

1. Based on the subjective feedback provided in the HF summative study results related to the task of removing the base cap, we recommend adding the statement “twist to remove cap” by the “1” to improve understanding and clarity of the cap removal task.
2. Based on the subjective feedback provided in the HF study results related to the task of placing the device against the injection site, we recommend adding a “needle end” label to the device to further improve understanding and clarification.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Omvoh received on March 30, 2022 from Eli Lilly & Company.

Table 2. Relevant Product Information for Omvoh

Initial Approval Date	N/A
Nonproprietary Name	mirikizumab-xxxx
Indication	indicated for the treatment of adult patients with moderately to severely active ulcerative colitis
Route of Administration	subcutaneous
Dosage Form	injection
Strength	100 mg/mL
Dose and Frequency	Induction Dosing: • 300 mg infused intravenously for at least 30 minutes at Weeks 0, 4, and 8 Maintenance Dosing: • 200 mg (given as two consecutive 100 mg subcutaneous injections) starting after completion of induction dosing, then every 4 weeks thereafter.
How Supplied	See nested table below
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use if it has been frozen. Do not shake. Keep in the original carton to protect from light.

	Strength	Pack Size	NDC Code
For Intravenous Infusion			
Single-dose Vial	20 mg/mL (300 mg/15 mL)	Carton of 1	0002-7575-01
For Subcutaneous Use			
Single-patient-use prefilled syringe	100 mg/mL	Carton of 2	0002-8870-27
[redacted]			(b) (4)

Container Closure	Vial; (b) (4) Prefilled Pen

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 26, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, (b) (4) and 125444. Our search identified 3 previous reviews[h,i,j], and we confirmed that our previous recommendations were implemented.

[h] Schlick J. URRA review for mirikizumab (IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 July 11. RCM No.: 2019-1172.

[i] Schlick J. Review of URRA Response for mirikizumab (IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 07. RCM No.: 2019-1172-1.

[j] Barlow, M. HF Validation Study Protocol Review for mirikizumab (IND (b) (4) and IND 125444). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 DEC 03. RCM No.: 2020-2064.

APPENDIX C. HUMAN FACTORS STUDY & COMPARATIVE ANALYSES

C.1 Study Design & Results

- HF Validation Study Result Report: \\CDSESUB1\EVSPROD\bla761279\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\hfe-02-validation-report-rpt-555002.pdf
- HF Supplemental Study Result Report: \\CDSESUB1\EVSPROD\bla761279\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\hfe-02-supplemental-validation-report-rpt-601954.pdf

C.2 Comparative Analyses

- Comparative Analyses Report: (b) (4)

APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F. SPONSOR RESPONSE TO AGENCY INFORMATION REQUESTS

- Sponsor's May 26, 2022 response to Agency's May 24, 2022 IR: \\CDSESUB1\EVSPROD\bla761279\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\regulatory-response-us-uc-hf.pdf
- Sponsor's July 21, 2022 response to the Agency's July 18, 2022 IR: \\CDSESUB1\EVSPROD\bla761279\0020\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\regulatory-response-human-factors-jul-2022.pdf
- Sponsor's August 19, 2022 response to the Agency's August 16, 2022 IR:
    - \\CDSESUB1\EVSPROD\bla761279\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\regulatory-response-uc-ctd-15-aug-2022.pdf
    - \\CDSESUB1\EVSPROD\bla761279\0025\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ulcerative-colitis\5354-other-stud-rep\hfe\regulatory-response-uc-ctd-15-us-urra-report.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Omvoh labels and labeling submitted by Eli Lilly & Company.

- Container label received on March 30, 2022
- Carton labeling received on March 30, 2022
- Instructions for Use received on March 30, 2022
    - PFP IFU available from: \\CDSESUB1\EVSPROD\bla761279\0001\m1\us\proposed-ifu-100mg-pen.docx (b) (4)
- Prescribing Information (Image not shown) received on March 30, 2022, available from: \\CDSESUB1\EVSPROD\bla761279\0001\m1\us\proposed-uspi.docx
- Medication Guide received on March 30, 2022, available from: \\CDSESUB1\EVSPROD\bla761279\0001\m1\us\proposed-medguide.docx

G.2 Label and Labeling Images

Container Label – PFP

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 2, 2022
To:	Kelly Richards, RN, MSN, RAC Senior Regulatory Health Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	OMVOH (mirikizumab-xxxx)
Dosage Form and Route:	injection, for intravenous or subcutaneous use
Application Type/Number:	BLA 761279
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On March 30, 2022, Eli Lilly and Company, submitted for the Agency's review Biologics License Application (BLA) # 761279 for OMVOH (mirikizumab-xxxx). The proposed indication for OMVOH (mirikizumab-xxxx) is for the treatment of adult patients with moderately to severely active ulcerative colitis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on April 12, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for OMVOH (mirikizumab-xxxx) injection, for intravenous or subcutaneous use.

2 MATERIAL REVIEWED

- Draft OMVOH (mirikizumab-xxxx) MG and IFUs received on March 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 25, 2022.
- Draft OMVOH (mirikizumab-xxxx) Prescribing Information (PI) received on March 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 25, 2022.
- Approved EMGALITY IFU comparator labeling dated May 24, 2022.
- Approved TALTZ comparator labeling dated July 27, 2022.
- Approved STELARA comparator labeling dated July 29, 2022.
- Approved SKYRIZI IFU comparator labeling dated September 23, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFUs:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG are IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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DMPP-OPDP review of mirikizumab-xxxx (OMVOH) BLA 761279 MG and IFUs

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Clinical Inspection Summary

Date	12/1/2022
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch Office of Scientific Investigations (OSI)
To	Kelly Richards, Clinical Analyst Aysegul Gozu, M.D., Medical Officer Matthew Kowalik, M.D., Team Leader Jessica Lee, M.D., Director Division of Gastroenterology Products (DGP)
BLA	761279
Applicant	Eli Lilly and Company
Drug	Mirikizumab (proposed name (b) (4))
NME/Original BLA	Yes
Proposed Indication	Treatment of active (moderate/severe) ulcerative colitis
Consult Request	5/20/2022
CIS Goal Date	12/7/2022
Action Goal Date	3/30/2023
PDUFA Date	3/30/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In this original Biologics License Applications (BLA), Eli Lilly and Company seeks the approval of mirikizumab (proposed name (b) (4)) for the treatment of active moderate/severe ulcerative colitis (UC). T major supporting studies (I6T-MC-AMAN, I6T-MC-AMBG) were audited at good clinical practice (GCP) inspections of two clinical investigators (CI), Drs. Martinez and Pokrotnieks. The CIs were selected for inspections based on large subject enrollment, high treatment response, each CI having conducted both studies, and no recent inspection history. The non-US CI, Dr. Pokrotnieks in Latvia, was selected also for insufficient domestic data.

No significant GCP violations were observed. The two audited studies appear to have been conducted in compliance with GCP principles and regulations. The audited data for the two CIs appear acceptable in support of using mirikizumab as proposed in the BLA.

II. BACKGROUND

UC is a chronic disease of the rectum progressing to the more proximal contiguous colon characterized by unpredictable flares and remissions of mucosal inflammation, clinically evident as diarrheal urgency and colorectal bleeding. Therapy typically begins with 5-aminosalicylate or corticosteroids, with escalation to cytotoxic agents or biologic immunomodulators for adequate symptom control. Refractory disease often requires colectomy. The overall treatment goal is to induce and maintain disease remission for mucosal quiescence and symptom control. Successful remission maintenance obviates colectomy and reduces the risk colorectal cancer.

Interleukin-23 (IL-23) is an inflammatory cytokine important to UC disease activity. Inhibition of IL-23 appears to mitigate UC disease activity, as has been seen also in other immune disorders including Crohn's disease, rheumatoid arthritis, and multiple sclerosis. Mirikizumab is a humanized anti-IL-23 monoclonal antibody that appears to be effective in managing immune disorders involving IL-23, notably including UC.

This BLA supports the approval of mirikizumab for the treatment of moderate to severely active UC refractory to conventional UC therapies. The two pivotal studies supporting this BLA were audited at GCP inspections of two CIs. The major audited study features are described below.

I6T-MC-AMAN: *A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis*

This randomized double-blind study was conducted from 2018 to 2021 (31 months) in 1281 subjects randomized at 163 centers world-wide. The primary study objective was to demonstrate that mirikizumab is superior to placebo in inducing clinical remission (CR) at Week 12 in moderate to severely active UC.

Subject Inclusion:

- Adults (age18 – 80 years) with UC for at least 3 months
- Endoscopic and histopathologic evidence of extra-rectal UC
- Modified Mayo score (MMS) 4 – 9 and endoscopic subscore ≥2 within 14 days
- Refractory to (or intolerant of) conventional or biologic UC agents

Subject Exclusion:

- Non-UC IBD or other small/large intestinal disease/lesions, including dysplasia
- UC-like immune deficiency, extensive colectomy, or gastrointestinal cancer
- Three or more prior biologic therapies for UC (excluding tofacitinib)

Randomization: 3/1 mirikizumab or placebo, respectively, stratified by:

- Response to prior biologic therapy (failed or not)
- Corticosteroid use (yes/no)
- Severity of baseline disease (MMS 4 – 6 or 7 – 9)
- Geographic region (North America, Europe, Other)

Treatment Regimen:

- Mirikizumab 300 mg intravenous (IV) every 4 weeks (Q4W) for 12 weeks
- Placebo matched for appearance on identical regimen

Primary Endpoint: Subscores of *Modified Mayo Score* (MMS) at Week 12, to determine the proportion of subjects in CR at Week 12, where CR is defined as meeting all of the following MMS subscores:

- Stool frequency subscore (SF) = 0 or 1
- Rectal bleeding subscore (RB) = 0
- Endoscopic subscore (ES) = 0 or 1

Major Secondary Endpoint: MMS subscores at Week 12, to determine the proportion of subjects in alternate CR (ACR) at Week 12, where ACR = SF 0/1, RB 0, and ES 0/1.

I6T-MC-AMBG: *A Phase 3, Multicenter, Randomized, Double-blind, Parallel-arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients with Moderately to Severely Active Ulcerative Colitis*

This randomized double-blind study provided continued (maintenance) therapy for the subjects completing the induction study (I6T-MC-AMBG) and was conducted in parallel with the induction study (I6T-MC-AMAN) from 2018 to 2021 (37 months) in 1178 subjects randomized at 368 centers world-wide. The primary study objective was to show that mirikizumab is superior to placebo in achieving (sustaining) CR at Week 40, after achieving CR with mirikizumab, after the successful induction of CR in I6T-MC-AMAN.

- Subjects achieving CR on mirikizumab in the induction study were randomized 2/1 (blinded) to subcutaneous (SC) mirikizumab (200 mg Q4W) or placebo.
- Subjects responding to placebo in the induction study remained on placebo. Open-label rescue mirikizumab (300 mg Q4W IV, 3 doses) was given for loss of response (LOR).
- For any LOR (either arm), rescue induction was attempted with open-label mirikizumab (300 mg IV Q4W, Weeks 12 – 28, 3 doses; discontinued if rescue induction unsuccessful).
- Subjects who did not respond to either blinded mirikizumab or blinded placebo in the induction study received open-label extended induction with mirikizumab (300 mg Q4W IV, 3 doses at Weeks 0, 4, and 8).
- Non-responders to the initial induction (16T-MC-AMAN) who then responded to the extended induction (delayed CR) received open-label mirikizumab (200 mg Q4W SC).
- Non-responders to initial induction who again did not respond to extended induction by Week 12 were discontinued from the maintenance study (16T-MC-AMBG).

Primary Endpoint: MMS subscores at Week 40, to determine the proportion of subjects in CR at Week 40, where CR = SF 0/1, RB 0, and ES 0/1.

Major Secondary Endpoint: MMS subscores at Week 40, to determine the proportion of subjects in ACR at Week 40, where ACR = SF 0/1, RB 0, and ES 0/1.

III. INSPECTION RESULTS

1. Nicholas Martinez, M.D.

8550 Datapoint Drive, Suite 230
San Antonio, Texas 78229

Inspection Dates: August 29 – September 6, 2022

I6T-MC-AMAN, Site 2822: 19 subjects were screened, 14 were enrolled, and 14 completed the study. Subject case records for all subjects were reviewed, including detailed review for the 14 subjects completing the study.

I6T-MC-AMBG, Site 2822: 14 subjects completing Study I6T-MC-AMAN were screened, 14 were enrolled, 5 were terminated early for lack of efficacy, and 9 completed the study. Subject case records for all subjects were reviewed in detail.

The inspection confirmed compliance with GCP principles and regulations; no significant GCP deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations or adverse events (AEs) were discovered. Evidence of unblinding was not observed for I6T-MC-AMAN. The observed efficacy endpoints for both studies (as noted in protocol summary, Section II) were audited in detail and determined to be verifiable against the data reported in the BLA, as were the audited AE data.

2. Juris Pokrotnieks, M.D.

Pilsonu Iela 13
Riga, Latvia

Inspection Dates: October 17 – 21, 2022

I6T-MC-AMAN, Site 2423: 39 subjects were screened, 27 were enrolled, and 27 completed the study. Subject case records for all subjects were reviewed, including detailed review for 13 subjects completing the study.

I6T-MC-AMBG, Site 2423: One subject not responding to mirikizumab (UC exacerbation) at completion of Study I6T-MC-AMAN was not screened for Study I6T-MC-AMAN. The remaining 26 subjects completing Study I6T-MC-AMAN were screened, 26 were enrolled, one was terminated early for lack of efficacy, and 25 completed the study. Subject case records for all subjects were reviewed, including detailed review for 12 subjects completing the study.

The inspection confirmed good compliance with GCP principles and regulations; no significant GCP deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations or AEs were discovered. Evidence of unblinding was not observed for I6T-MC-AMAN. The observed efficacy endpoints for both studies (as noted in protocol summary, Section II) were audited in detail and determined to be verifiable against the data reported in the BLA, as were the audited AE data.

{See appended electronic signature page}

John Lee, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DGP/Division Director/Jessica Lee
DGP/Team Leader/Matthew Kowalik
DGP/Clinical Reviewer/Aysegul Gozu
DGP/Regulatory Project Manager/Kelly Richards
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Regulatory Officer/LaKisha Williams
OSI/DCCE/GCPAB/Acting Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Primary Reviewer/John Lee
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 12, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name and Strength:	mirikizumab-xxxx injection, 300 mg/15 mL (20 mg/mL) vial, 100 mg/mL prefilled pen (b) (4)
Applicant/Sponsor Name:	Eli Lilly
OSE RCM/TTT #:	2022-630-1 and 2022-702-1
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 3, 2022 for mirikizumab-xxxx. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for mirikizumab-xxxx (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Vee, S. Label and Labeling Review for mirikizumab-xxxx (BLA 761279). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 AUG 31. RCM No.: 2022-630/2022-702.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 31, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761279
Product Name, Dosage Form, and Strength:	Mirikizumab-xxxx[a] injection, 300 mg/15 mL (20 mg/mL) vial, 100 mg/mL prefilled pen (b) (4) (b) (4)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	March 30, 2022
OSE RCM/TTT #:	2022-630/2022-702
DMEPA 1 Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder mirikizumab-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 REASON FOR REVIEW

As part of the approval process for mirikizumab-xxxx injection, the Division of Gastroenterology (DG) requested that we review the proposed mirikizumab-xxxx prescribing information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, MG, container label, and carton labeling for mirikizumab-xxxx injection to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We find the proposed PI and MG acceptable from a medication error perspective. We identified areas of the proposed container labels and carton labeling that could be revised to improve clarity and readability of important information. We provide recommendations for the Applicant in Section 4.1 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed PI and MG acceptable from a medication error perspective. We identified areas in the proposed container label and carton labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4.1 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)
    1. The established name is not at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
    2. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."
    3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

B. Carton Labeling (prefilled pen [redacted] (b) (4))
    1. Relocate the statement, "Discard if not used within 2 weeks." To after the statement: "Date removed from refrigerator __/__/__."
    2. Relocate the route of administration to right after the dosage form and increase the prominence.
    3. There are two instances of the net quantity statements on the principal display panel (PDP). Please delete one to reduce clutter.
    4. We recommend that the Rx Only statement is unbolded since it is more prominent than the important information such as the route of administration.

C. Carton Labeling (vial)
    1. Relocate the "keep refrigerated" statement to the side panel.
    2. Net quantity statement is missing from the PDP.

D. Container Label (prefilled pen)
    1. We recommend that the Rx Only, do not freeze, and do not shake, keep out of reach of children statements are unbolded since it is more prominent than the route of administration.
    2. Relocate the route of administration to right after the dosage form and increase the prominence.

E. Container Label (b) (4)

(b) (4)

F. Container Label (vial)

1. Relocate the “keep refrigerated” statement to the side panel.
2. Place “Single dose vial- Discard unused Portion” all on one line.
3. Increase the prominence of the route of administration.

Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of your human factors validation study results.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for mirikizumab-xxxx received on March 30, 2022 from Eli Lilly and Company.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for mirikizumab-xxxx</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Nonproprietary Name</td><td>mirikizumab-xxxx</td></tr>
<tr><td>Indication</td><td>indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).</td></tr>
<tr><td>Route of Administration</td><td>Intravenous injection and subcutaneous injection</td></tr>
<tr><td>Dosage Form</td><td>injection</td></tr>
<tr><td>Strength</td><td>300 mg/15 mL (20 mg/mL) vial, 100 mg/mL prefilled pen (b) (4) (b) (4)</td></tr>
<tr><td>Dose and Frequency</td><td><u>Induction Dosage</u>
The recommended induction dosage regimen is 300 mg infused intravenously for at least 30 minutes at Week 0, Week 4, and Week 8

<u>Maintenance Dosage</u>
The recommended maintenance dosage regimen is 200 mg (given as two consecutive subcutaneous injections of 100 mg each) every 4 weeks after completion of induction dosing</td></tr>
<tr><td>How Supplied</td><td>
<table>
<tr><th></th><th>Strength</th><th>Pack Size</th></tr>
<tr><td>For Intravenous Infusion</td><td></td><td></td></tr>
<tr><td>Single-dose Vial</td><td>20 mg/mL (300 mg/15 mL)</td><td>Carton of 1</td></tr>
<tr><td>For Subcutaneous Use</td><td></td><td></td></tr>
<tr><td colspan="3">(b) (4)</td></tr>
<tr><td>Single-patient-use prefilled pen</td><td>100 mg/mL</td><td>Carton of 2</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store refrigerated at 2°C to 8°C (36°F to 46°F).
Do not freeze. Do not use if it has been frozen.</td></tr>
</table>

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Proprietary name labels and labeling submitted by Eli Lilly and Company.

- Container label received on March 30, 2022
- Carton labeling received on March 30, 2022
- Instructions for Use received on March 30, 2022, available from \\CDSESUB1\evsprod\BLA761279\0001\m1\us
- Prescribing Information (Image not shown) received on March 30, 2022, available from \\CDSESUB1\evsprod\BLA761279\0001\m1\us
- Medication Guide received on March 30, 2022, available from \\CDSESUB1\evsprod\BLA761279\0001\m1\us

G.2 Label and Labeling Images

Container - Pen

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SARAH K VEE
08/31/2022 11:04:57 AM

IDALIA E RYCHLIK
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