# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761063Orig1s000

# 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: | September 26, 2018 |
| Reviewer: | Hongliu Ding, MD, PhD, MPH<br>Division of Epidemiology I |
| Team Leader: | Kira Leishear, PhD, MS<br>Division of Epidemiology I |
| Division Deputy Director: | Sukhminder K. Sandhu, PhD, MS, MPH<br>Division of Epidemiology I |
| Subject: | ARIA Sufficiency Memo for Pregnancy Safety Concerns |
| Drug Name: | Emgality (Galcanezumab) |
| Application Type/Number: | BLA 761063 |
| Applicant/sponsor: | Eli Lilly and Company |
| OSE RCM #: | 2018-878 |

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Emgality (galcanezumab) is a calcitonin-gene related peptide (CGRP) with a proposed indication for the prophylaxis of episodic and chronic migraine in adults. This drug is a humanized immunoglobulin (subclass) G4 (IgG4) monoclonal antibody that binds CGRP and inhibits its activity as a sensory neuropeptide in the trigeminal system.[1] Galcanezumab is administered via subcutaneous injection only. The dosing regimen is a 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg.

### 1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure 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.[8] Animal studies did not show evidence of embryolethality, teratogenicity, or fetotoxicity and no effect was observed on female fertility. In the clinical trials, pregnant women were excluded, and women of reproductive potential were required to use birth control during the trials and for an additional 5 months after the final drug exposure. However, 13 women exposed to galcanezumab became pregnant during the trials (all had first trimester exposure), and an additional 3 women became pregnant after completion of treatment (the timing between the last exposure and the start of the pregnancy was not reported). Of these 16 women exposed to galcanezumab, their pregnancy outcomes as of 5/25/18 are as follows: 8 term births (7 had no complications; 1 newborn had low blood glucose at birth which resolved [mother had gestational diabetes]); 1 premature birth without complications [mother became pregnant post-treatment and had preeclampsia]; 1 spontaneous abortion [mother became pregnant after completing treatment, was 38 years old and had a history of fibroids]; 1 missed abortion; 1 elective termination; 4 unknown/lost to follow up.

Currently, there are insufficient human data to establish the safety of galcanezumab during pregnancy. However, human IgG is known to cross the placental barrier,[9] thus galcanezumab may be transmitted from the mother to the developing fetus. The long half-life of galcanezumab (27 days) likely increases the potential developmental risk to the fetus. Therefore, galcanezumab exposure in women with migraine who are pregnant or of childbearing potential is a safety concern.

In the current proposed labeling, as of September 26, 2018, the Risk Summary in Section 8.1 Pregnancy, states: “There are no adequate data on the developmental risk associated with the use of EMGALITY in pregnant women. Administration of galcanezumab-gnlm to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at plasma exposures greater than that expected clinically did not result in adverse effects on development *(see Animal Data)*.”

### 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 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: *Click here to enter text.*

### 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:*

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: Current ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

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

The Division of Neurology Products requests two PMRs related to pregnancy outcomes. As of September 26, 2018, the proposed PMR language for these are:

3498-3 "*Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Emgality during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Emgality before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life."*

*and*

3498-4 "*Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3498-3 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Emgality during pregnancy compared to an unexposed control population.*"

## 3. References


1. Edvinsson L, Haanes KA, Warfvinge K, et al. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol. 2018.
2. Skljarevski V, Oakes TM, Zhang Q, et al. Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine Prevention: A Randomized Clinical Trial. JAMA Neurol. 2018;75(2):187-193.
3. Dodick DW, Goadsby PJ, Spierings EL, et al. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Neurol. 2014;13(9):885-892.
4. Ayer DW, Skljarevski V, Ford JH, et al. Measures of Functioning in Patients With Episodic Migraine: Findings From a Double-Blind, Randomized, Placebo-Controlled Phase 2b Trial With Galcanezumab. Headache. 2018.
5. Monteith D, Collins EC, Vandermeulen C, et al. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the CGRP Binding Monoclonal Antibody LY2951742 (Galcanezumab) in Healthy Volunteers. Front Pharmacol. 2017;8:740.
6. Oakes TMM, Skljarevski V, Zhang Q, et al. Safety of galcanezumab in patients with episodic migraine: A randomized placebo-controlled dose-ranging Phase 2b study. Cephalalgia. 2018;38(6):1015-1025.
7. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018.
8. 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 May 2, 2018.
9. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104(1):228-233.

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/s/
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HONGLIU DING
09/26/2018

KIRA N LEISHEAR
09/26/2018

WEI HUA on behalf of SUKHMINDER K SANDHU
09/26/2018

JUDITH W ZANDER
09/27/2018

MICHAEL D NGUYEN
09/27/2018

ROBERT BALL
09/27/2018

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

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

# Memorandum

**Date:** September 10, 2018

**To:** Suhail Kasim, M.D.
Division of Neurology Products (DNP)

E. Andrew Papanastasiou, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

**From:** Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Aline Moukhtara, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use

**BLA:** 761063

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In response to DNP consult request dated October 3, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFUs), and carton and container labeling for the original BLA submission for EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use (Emgality).

**PI:** OPDP's comments on the proposed labeling are based on the draft PI, PPI and IFUs received by electronic mail from DNP (E. Andrew Papanastasiou) on August 28, 2018, and are provided below.

**PPI and IFUs:** A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFUs were sent under separate cover on September 6, 2018.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 3, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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DHARA SHAH
09/10/2018

**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: | September 6, 2018 |
| To: | William Dunn, MD<br>Director<br>**Division of Neurology Products (DNP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Sharon W. Williams, MSN, BSN, RN<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Dhara Shah, PharmD, RAC<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU) |
| Drug Name (established name): | EMGALITY (galcanezumab-gnlm) |
| Dosage Form and Route: | injection, for subcutaneous use |
| Application Type/Number: | BLA 761063 |
| Applicant: | Eli Lilly and Company |

# 1 INTRODUCTION

On September 26, 2017, Eli Lilly and Company submitted for the Agency's review a Biologics License Application (BLA) for EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use. The proposed indication for EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use is preventive treatment of migraine in adults.

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 Neurology Products (DNP) on October 3, 2017, for DMPP and OPDP to review the Applicant's proposed (b) (4) IFUs for EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on March 30, 2018.

# 2 MATERIAL REVIEWED

- Draft EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use (b) (4) IFUs received on September 26, 2017, and received by DMPP and OPDP on August 28, 2018.
- Draft EMGALITY (galcanezumab-gnlm) Prescribing Information (PI) received on September 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 28, 2018.
- Submitted review of IFUs for IND 111295 (b) (4) dated August 2, 2016.

# 3 REVIEW METHODS

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 (b) (4) and IFU documents using the Arial font, size 10.

In our collaborative review of the (b) (4) IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the (b) (4) IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the (b) (4) IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language

- (b) (4)
- ensured that the (b) (4) IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the (b) (4) IFUs are consistent with the approved comparator labelings where applicable.

## 4 CONCLUSIONS

The (b) (4) 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 (b) (4) IFUs is 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 (b) (4) IFUs.

Please let us know if you have any questions.

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SHARON W WILLIAMS
09/06/2018

DHARA SHAH
09/06/2018

# MEMORANDUM

**REVIEW OF REVISED LABEL AND LABELING**

Division of Medication Error Prevention and Analysis (DMEPA)
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 5, 2018 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | BLA 761063 |
| **Product Name and Strength:** | Emgality (galcanezumab-gnlm) injection<br>120 mg/mL |
| **Applicant/Sponsor Name:** | Eli Lilly and Company |
| **FDA Received Date:** | May 3, 2018; June 29, 2018 |
| **OSE RCM #:** | 2017-2045-1 |
| **DMEPA Safety Evaluator:** | Chad Morris, PharmD, MPH |
| **DMEPA Team Leader:** | Lolita White, PharmD |

## 1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised 1-count and 2-count prefilled syringe and prefilled pen carton and the prefilled syringe and prefilled pen container labels for Emgality (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 revised 1-count and 2-count prefilled syringe and prefilled pen carton and the prefilled syringe and prefilled pen container labels for Emgality are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Whaley, E. Label and Labeling Review for Emgality (BLA 761063). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 30. RCM No.: 2017-2045.



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/s/
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JOHN C MORRIS
09/05/2018

LOLITA G WHITE
09/05/2018

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | 07/30/2018 |
| **From** | Cara Alfaro, Clinical Analyst<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Emilios (Andrew) Papanastasiou, Regulatory Project Manager<br>Suhail Kasim, Medical Officer<br>Division of Neurology Products |
| **BLA #** | 761063 |
| **Applicant** | Eli Lilly and Company |
| **Drug** | Galcanezumab |
| **NME** | Yes |
| **Proposed Indication** | Prophylaxis of migraine in adults |
| **Consultation Request Date** | 11/6/2017 |
| **Summary Goal Date** | 7/27/2018, Extension granted to 08/10/2018 |
| **Advisory Committee Meeting** | None |
| **Action Goal Date** | 9/27/2018 |
| **PDUFA Date** | 9/27/2018 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Stickler, Taylor, Dolezil, and Rizova, and the Clinical Research Organization (CRO), (b) (4) were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final compliance classification of the clinical site inspections of Drs. Taylor, Dolezil, and Rizova was No Action Indicated (NAI), and the final compliance classification of the inspection of Dr. Stickler was Voluntary Action Indicated (VAI, due to some drug accountability issues). The final compliance classification of the CRO, (b) (4) was NAI.

(b) (4)

(b) (4).

Additionally, two clinical investigator sites enrolling subjects in Protocol 15Q-MC-CGAI were inspected by (b) (4) Dr. Freddy Guillermo Castro Farfan (Site #825/Mexico) and Dr. Bibiana Saravia (Site #727/Argentina). The (b) (4) inspectional findings for these two clinical site inspections were communicated to OSI. (b) (4)

## II. BACKGROUND

Galcanezumab injection is a human monoclonal antibody being developed for the prophylaxis of migraine in adults under BLA 761063 (IND 111295). The sponsor has submitted two Phase 3 studies in *episodic* migraine (Protocols 15Q-MC-CGAG and 15Q-MC-CGAH) and one Phase 3 trial in *chronic* migraine (Protocol 15Q-MC-CGAI) to support the efficacy and safety of galcanezumab for the prophylaxis of migraine in adults. At the time of BLA submission, the post-treatment follow-up washout phases of these studies were ongoing.

Protocol 15Q-MC-CGAG

*Title*: "A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 [galcanezumab] in patients with episodic migraine – the EVOLVE-1 study"

*Subjects*: 862 randomized

*Sites*: United States (81 sites, including 6 sites in Puerto Rico) and Canada (8 sites)

*Study Initiation and Completion Dates*: 1/11/2016 to 3/22/2017

This was a randomized, double-blind, placebo-controlled study in subjects with episodic migraine. Included were male or female subjects, 18 to 65 years of age, diagnosis of migraine, history of migraine headaches at least one year prior to screening, and migraine onset prior to 50 years of age.

The study consisted of four study phases: screening phase (3 – 45 days), baseline phase (30 – 40 days) to determine eligibility, 6-month double-blind treatment phase, and a 4-month post-treatment follow-up washout phase (currently ongoing). Prior to Visit 1 (screening), subjects were to have had a history of 4 to 14 migraine headache days (MHD) and at least 2 migraine attacks per month on average within the past 3 months. During the baseline phase, subjects must have had 4 to 14 MHDs, had at least 2 migraine attacks, and achieved 80% compliance with the electronic diary (ePRO).

Eligible subjects were randomized 1:1:2 to one of three treatment groups:

- Galcanezumab 120 mg once per month by subcutaneous injection
- Galcanezumab 240 mg once per month by subcutaneous injection
- Placebo once per month by subcutaneous injection

Patient-reported outcome assessments were collected by subjects using a handheld electronic diary (ePRO). The *primary efficacy endpoint* was the mean change from baseline in the number of monthly MHDs during the 6-month double-blind treatment phase.

Protocol 15Q-MC-CGAH

*Title*: "A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 [galcanezumab] in patients with episodic migraine – the EVOLVE-2 study"

*Subjects*: 922 randomized

*Sites*: 109 sites in 11 countries; United States (49 sites, including 2 sites in Puerto Rico), Western Europe (29 sites), Asia/Pacific (12 sites), Latin America (9 sites), Eastern Europe (6 sites), Middle East/Central Asia (4 sites)

*Study Initiation and Completion Dates*: 1/29/2016 to 3/29/2017

The study design for Protocol CGAH was the same as the design for Protocol CGAG.

Protocol 15Q-MC-CGAI

*Title*: "A phase 3, randomized, double-blind, placebo-controlled study of LY2951742 [galcanezumab] in patients with chronic migraine – the REGAIN study"

*Subjects*: 1117 randomized

*Sites*: 116 sites in 12 countries; United States (55 sites including 4 sites in Puerto Rico), Western Europe (30 sites), Latin America (13 sites), Eastern Europe (5 sites), Asia/Pacific (5 sites), Canada (4 sites), Middle East/Central Asia (4 sites)

*Study Initiation and Completion Dates*: 1/12/2016 to 3/16/2017

This was a randomized, double-blind, placebo-controlled study in subjects with chronic migraine. Included were male or female subjects 18 to 65 years of age, diagnosis of chronic migraine, history of at least one headache-free day per month for the previous three months prior to screening, and migraine onset prior to 50 years of age.

The study consisted of five phases: screening (3 – 45 days), baseline (30 – 40 days) phase to determine eligibility, a 3-month double-blind treatment phase, an optional 9-month open-label extension phase (currently ongoing), and a 4-month post-treatment follow-up washout phase (currently ongoing). Subjects who do not enter the open-label extension phase would continue into the 4-month washout phase. During the baseline phase, subjects had to have at least 15 headache days of which at least 8 had features of migraine headache and achieve 80% compliance with the e-diary (ePRO).

Eligible subjects were randomized 1:1:2 to one of three treatment groups:

- Galcanezumab 120 mg once per month by subcutaneous injection
- Galcanezumab 240 mg once per month by subcutaneous injection
- Placebo once per month by subcutaneous injection

The *primary efficacy endpoint* was the mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind phase.

**Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects, prior inspectional history, and data anomalies.

## III. RESULTS

| Site #/ Name of CI/ Address | Protocol #/ # of Enrolled Subjects | Inspection Dates | Compliance Classification |
|---|---|---|---|
| Site #235<br><br>**David Stickler, M.D.**<br>2695 Elms Plantation Blvd<br>Suite D<br>Charleston, SC 29406 | 15Q-MC-CGAG<br>Subjects: 27<br><br>15Q-MC-CGAI<br>Subjects: 21 | 11-15 Dec 2017 | VAI |
| Site #238<br><br>**Kelly Taylor, M.D.**<br>2700 Old Winter Garden Rd.<br>Ocoee, FL 34761 | 15Q-MC-CGAG<br>Subjects: 37<br><br>15Q-MC-CGAH<br>Subjects: 9 | 27 Nov – 8 Dec 2017 | NAI |
| Site #601<br><br>**David Dolezil, M.D.**<br>Budecska 33<br>Praha 2, 120 00<br>Czech Republic | 15Q-MC-CGAH<br>Subjects: 14<br><br>15Q-MC-CGAI<br>Subjects: 18 | 29 Jan – 7 Feb 2018 | NAI |
| Site #602<br><br>**Yuliya Rizova, M.D.**<br>Pocernicka 1427/16<br>Praha 10, 100 00<br>Czech Republic | 15Q-MC-CGAH<br>Subjects: 30<br><br>15Q-MC-CGAI<br>Subjects: 15 | 29 Jan – 7 Feb 2018 | NAI |
| CRO<br><br>(b) (4) | 15Q-MC-CGAG<br><br>15Q-MC-CGAH<br><br>15Q-MC-CGAI | (b) (4) | NAI |

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.
VAI = Voluntary Action Indicated, deviation(s) from regulations.
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

Protocols 15Q-MC-CGAG, 15Q-MC-CGAH, and 15Q-MC-CGAI were considered ongoing at the time the BLA was submitted (follow-up washout phases were ongoing). As such, the sponsor had not sent the final certified CD of ePRO data to the clinical sites. During the clinical site inspections, FDA field investigators verified sponsor data listings with printouts or excel spreadsheets of ePRO data, none of which included an audit trail. An information request was sent to the sponsor on February 15, 2018 requesting a certified copy, with audit trails, of the ePRO raw data for subjects enrolled in the four inspected clinical sites. The sponsor submitted these data on March 5, 2018. These data were reviewed as a further data integrity verification of ePRO headache data submitted with the BLA application.

**1. David Stickler, M.D.**

At this site for Protocol 15Q-MC-CGAG, 42 subjects were screened, 27 subjects were enrolled, and 23 subjects completed the double-blind phase of the study. The EIR did not specify reasons for the 4 subjects who discontinued the study. Per sponsor data listings, these subjects discontinued due to: withdrawal by subject (2), physician decision (noncompliance), and pregnancy (Subject # (b) (6) randomized to galcanezumab). The pregnancy for this subject was disclosed and included in the BLA submission.

For Protocol 15Q-MC-CGAI, 34 subjects were screened, 21 subjects were enrolled, and 16 subjects completed the double-blind phase of the study. The EIR did not specify reasons for the 5 subjects who discontinued the study. Per sponsor data listings, these subjects discontinued due to: loss to follow-up (2), adverse event (squamous cell carcinoma), adverse event (hair loss), and withdrawal by subject.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 14 of 27 (52%) subjects enrolled in Protocol 15Q-MC-CGAG and 10 of 21 (48%) subjects enrolled in Protocol 15Q-MC-CGAH was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, concomitant medications, adverse event reports, laboratory results, protocol deviations and primary efficacy endpoint (daily headache count). (b) (4) was responsible for clinical monitoring for both protocols.

Primary efficacy endpoint data, i.e. daily headache counts and associated symptoms, were recorded by subjects using an e-diary (ePRO). A certified CD of this data was not sent to the clinical site since the studies were considered ongoing. For this inspection, ePRO data from line listings were compared to a spreadsheet provided by one of the clinical coordinators. This spreadsheet did not contain audit trail information. There were no discrepancies between the line listings and ePRO data in the spreadsheet for either protocol. Of note, there was no evidence of under-reporting of adverse events in either protocol.

As part of a data integrity check, this reviewer performed some verification of the primary efficacy endpoint data using certified ePRO daily headache source data obtained from the sponsor. Headache data from a random sample of 5 of 27 (18%) randomized subjects for

Protocol 15Q-MC-CGAG and 4 of 21 (19%) randomized subjects for Protocol 15Q-MC-CGAI were verified. No discrepancies were identified.

A Form FDA 483 was issued at the conclusion of the inspection for inadequate investigational drug disposition records. Only 4 of 14 (28%) subject drug accountability records reviewed for Protocol 15Q-MC-CGAG and 1 of 10 (10%) subject drug accountability records reviewed for Protocol 15Q-MC-CGAI had accurate and complete documentation. In his response, Dr. Stickler noted that study coordinators documented dispensation of investigational drug on subject drug logs but failed to document dispensation on the Master Drug Accountability Logs. The site has implemented a corrective action plan to address this issue for future clinical trials.

**2. Kelly Taylor, M.D.**

At this site for Protocol 15Q-MC-CGAG, 79 subjects were screened, 37 subjects were enrolled, and 29 subjects completed the double-blind phase of the study. The EIR did not specify reasons for the 8 subjects who discontinued the study. Per sponsor data listings, these subjects discontinued due to: loss to follow-up (2), withdrawal by subject, adverse event (redness at injection site), physician decision (subject started prohibited medication), and pregnancy (Subject (b) (6), randomized to placebo). For Protocol 15Q-MC-CGAH, 28 subjects were screened, 9 subjects were enrolled, and 8 subjects completed the double-blind phase of the study. One subject was lost to follow-up.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 25 of 37 (66%) subjects enrolled in Protocol 15Q-MC-CGAG and all 9 subjects enrolled for Protocol 15Q-MC-CGAH was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, concomitant medications, adverse event reports, laboratory results, protocol deviations and primary efficacy endpoint (daily headache count). (b) (4) was responsible for clinical monitoring for both protocols.

Primary efficacy endpoint data, i.e. daily headache count and associated symptoms, were recorded by subjects using an e-diary (ePRO). A certified CD of this data was not sent to the clinical site since the studies were considered ongoing. For this inspection, ePRO data from line listings were compared to a spreadsheet provided by one of the clinical coordinators. This spreadsheet did not contain any audit trail information. There were no discrepancies between the line listings and ePRO data in the spreadsheet for either protocol. Of note, there was no evidence of under-reporting of adverse events in either protocol.

As part of a data integrity check, this reviewer performed some verification of the primary efficacy endpoint data using certified ePRO daily headache source data obtained from the sponsor. Headache data from a random sample of 7 of 37 (19%) randomized subjects for Protocol 15Q-MC-CGAG and 2 of 9 (22%) randomized subjects for Protocol 15Q-MC-CGAH were verified. One discrepancy was noted for Subject (b) (6) participating in Protocol 15Q-MC-CGAG and randomized to galcanezumab. For this subject, a headache (mild) was recorded on (b) (6) (double-blind period) per sponsor ePRO data while the data listing in the BLA does

not have an entry for that day (date was skipped, indicating that no diary entry was available for that day).

Of note, for one of 25 subject records reviewed for Protocol 15Q-MC-CGAG, there was one episode of a subject receiving study drug approximately 10 minutes prior to having their labs drawn (Visit 5, Subject # (b) (6). Per protocol, labs were to be drawn prior to study drug administration. At Visit 5, labs were drawn for immunogenicity, biomarker storage sample, CGRP plasma sample, and pharmacokinetic sample. The site noted the deviation on the CRF, and Dr. Taylor reported this protocol deviation to the IRB. This protocol deviation is not included in the listing of important protocol deviations submitted with the BLA.

*Reviewer Comment: A data check for daily headaches during the baseline and 6-month double-blind periods noted one instance of discrepancy, as described above, among a random sample of subjects for Protocols 15Q-MC-CGAG and 15Q-MC-CGAH. It is very unlikely that this single instance of data discrepancy would impact the overall efficacy analyses for this application. In addition, for Protocol 15Q-MC-CGAG, there was one episode of a subject receiving study drug before having their labs drawn (by approximately 10 minutes) in violation of the protocol. It is unlikely that this single instance would impact the overall safety or PK analyses for this application.*

**3. David Dolezil, M.D**

At this site for Protocol 15Q-MC-CGAH, 20 subjects were screened, 14 subjects were randomized, and 14 subjects completed the double-blind phase of the study. For Protocol 15Q-MC-CGAI, 20 subjects were screened, 18 subjects were randomized, and 16 subjects completed the double-blind phase of the study. One subject ((b) (6)) discontinued the study approximately one month after randomization due to pregnancy. Study drug (placebo) was stopped immediately, and the pregnancy was followed to term.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects for both protocols was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IEC/sponsor communications, test article accountability, inclusion/exclusion criteria, adverse event reports, protocol deviations, and primary efficacy endpoint (daily headache count). (b) (4) was responsible for clinical monitoring for both protocols.

Primary efficacy endpoint data, i.e. daily headache count and associated symptoms, were recorded by subjects using an e-diary (ePRO). The site was not able to provide a certified copy of the final ePRO data because the post-treatment follow-up phase for these studies was still ongoing. For this inspection, the ePRO data line listings were compared to a printout from the Trial Manager database provided by the site. This printout did not contain any audit trail information. No discrepancies were noted for either protocol. Of note, there was no evidence of under-reporting of adverse events for either protocol.

As part of a data integrity check, this reviewer performed some verification of the primary efficacy endpoint data using certified ePRO daily headache source data obtained from the

sponsor. Headache data from a random sample of 3 of 14 (21%) randomized subjects for Protocol 15Q-MC-CGAH and 4 of 18 (22%) randomized subjects for Protocol 15Q-MC-CGAI were verified. No discrepancies were identified.

Of note, this site was chosen, in part, due to data anomalies identified in the blood pressure data. This site had a last digit preference for 0's and 5's and less blood pressure variability compared to other sites participating in these clinical trials. Per protocol, blood pressure measurements were to be taken using a calibrated machine. During the inspection, it was noted that 99% of blood pressure readings ended in multiples of 5. The FDA field investigator learned that the study nurse had been rounding the readings.

**4. Yuliya Rizova, M.D**

At this site for Protocol 15Q-MC-CGAH, 44 subjects were screened, 30 subjects were randomized, and 27 subjects completed the double-blind phase of the study. The EIR did not specify the reasons for the three subjects who discontinued the study. According to sponsor line listings, the reason for discontinuation was "withdrawal by subject." For Protocol 15Q-MC-CGAI, 19 subjects were screened, 15 subjects were randomized, and 15 subjects completed the double-blind phase of the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 20 of 30 (67%) randomized subjects for Protocol 15Q-MC-CGAG and all randomized subjects for Protocol 15Q-MC-CGAH was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, training documents, IEC/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, concomitant medications, adverse event reports, laboratory results, subject diaries, protocol deviations, and primary efficacy endpoint (daily headache count). (b) (4) was responsible for clinical monitoring for both protocols.

Primary efficacy endpoint data, i.e. daily headache count and associated symptoms, were recorded by subjects using an e-diary (ePRO). For this inspection, ePRO data from line listings were compared to a printout from the TrialManager database provided by the site. This printout did not contain audit trail information. There no discrepancies were noted for either protocol. Of note, there was no evidence of under-reporting of adverse events in either protocol.

As part of a data integrity check, this reviewer performed some verification of the primary efficacy endpoint data using certified ePRO daily headache source data obtained from the sponsor. Headache data from a random sample of 6 of 30 (20%) randomized subjects for Protocol 15Q-MC-CGAH and 3 of 15 (22%) randomized subjects for Protocol 15Q-MC-CGAI were verified. No discrepancies were identified.

The FDA field investigator did note that there was a missing serum pregnancy test for Subject (b) (6), randomized to galcanezumab, at Visit 14 for Protocol 15Q-MC-CGAH. Visit 14 corresponds to the 4-month follow-up washout phase of the study.

*Reviewer comments: One subject participating in Protocol 15Q-MC-CGAH did not have the required serum pregnancy test completed at Visit 14. This deviation was not included in the listing of Protocol Deviations, although other missing labs for this subject are included in this listing. This subject did have all the required urine and serum pregnancy tests completed at Visits 3 – 12, during the double-blind phase of the study. Visit 14 corresponds to the 4-month follow-up washout phase of the study in which no investigational drug is administered. Therefore, though a protocol violation, missing a serum pregnancy test four months after the last dose of study medication was received poses little risk to the subject.*

**5.** (b) (4)

**6.** (b) (4) **Findings**

(b) (4) (b) (4) (b) (4). Additionally, two clinical investigator sites enrolling subjects in Protocol 15Q-MC-CGAI were inspected (b) (4): Dr. Freddy

Guillermo Castro Farfan (Site #825/Mexico) and Dr. Bibiana Saravia (Site #727/Argentina). The (b) (4) inspectional findings for these two clinical site inspections were communicated to OSI. (b) (4)

(b) (4) did not identify any critical findings during these clinical site inspections but did note major inspectional findings. Most of the major findings for Sites #825 and #727 were deemed the responsibility of the sponsor and not the clinical investigator.

The major inspectional findings for Site #727 for which the clinical investigator/site were responsible included: routine maintenance program for the equipment (e.g. freezer for samples) was not in place; formal procedure to prevent problems with investigational drug integrity were not in place; late updating of delegation list.

The major inspectional findings for Site #825 for which the clinical investigator/site was responsible included electronic system for continuous recording of temperatures for investigational product storage was temporarily broken such that the system could not be verified; two syringes of investigational product were administered one in one arm and the other in the other arm and not per operations manual; hybrid process to create and manage the medical chart at site was not adequate (sponsor and CRO had responsibility as well)

Of note, during the clinical inspection of Site #825, (b) (4) noted that the database for interim analysis was unlocked and changed. (b) (4) The date of the CSR submitted with the BLA is (b) (4) September 18, 2017. It was noted that a consistent review and correction of data happened in February 2018, while the date of database lock was March 5, 2017. This finding was graded major (not critical) as there was no evidence that the changes could have had an impact on the benefit/risk evauation for assessment (b) (4). These changes included, but were not limited to, changes in concomitant medications for two subjects and corrections in medical history for two subjects (medical history entered for wrong subject; subjects had similar names). The sponsor noted that discrepancies between source documentation and InForm were detected during a review of site documentation in February 2018. The site requested the relevant CRFs to be unlocked so that the site could make the changes. The study team then evaluated the changes and concluded that the changes did not impact the efficacy or safety conclusions reported in the interim CSR. Thus, the data was not re-analyzed.

*{See appended electronic signature page}*

Cara Alfaro, Pharm.D.
Clinical Analyst
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
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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

**cc:**

Central Document Room/BLA 761063
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Heather Fitter
DNP/Medical Officer/Suhail Kasim
DNP/Project Manager/Emilios Papanastasiou
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analyst/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/s/
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CARA L ALFARO
07/30/2018

PHILLIP D KRONSTEIN
07/30/2018

KASSA AYALEW
07/30/2018

**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**

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DATE: May 10, 2018

TO: Billy Dunn, M.D.
Director
Division of Neurology Products (DNP)
Office of New Drugs

FROM: Gopa Biswas, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Amendment: Surveillance inspection of (b) (4)

**Inspection Summary**

The EIR review dated April 24, 2018 is being amended to correct a typographical error in Discussion item #1.

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies I5Q-MC-CGAQ (BLA 761063) (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Thus, I recommend that the data from studies I5Q-MC-CGAQ (b) (4) and other studies using similar methods be accepted for further Agency review.

**Inspected Studies:**

**BLA 761063**

**Study Number:** I5Q-MC-CGAQ (b) (4) (b) (4) )
**Study Title:** "Pharmacokinetics and Pharmacodynamics of LY2951742 (Galcanezumab) in Healthy Subjects Following Subcutaneous Administration of LY2951742 (Galcanezumab) Solution in a Prefilled Syringe or an Autoinjector"

**Dates of conduct:** (b) (4)

**Studies not yet associated with an application**

**Study Number:** (b) (4)
**Study Title:**

**Dates of conduct:**

**Analytical site:**

OSIS scientist Gopa Biswas audited the analytical portion of the above studies at (b) (4)

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, I did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site. However, I discussed several items with the firm's management.

**Discussion items:**

(b) (4)

(b) (4)

**Conclusion:**

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Therefore, I recommend that the data from studies I5Q-MC-CGAQ (BLA 761063) (b) (4) be accepted for further review. In addition, the data from

studies using similar methods submitted to pending applications (**Attachment 1**) should be accepted for further Agency review.

Based on the inspectional findings, studies using similar methods conducted between the previous inspection (b) (4) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gopa Biswas, Ph.D.
Lead Pharmacologist

**Final Classification:**

**NAI-** (b) (4)
**FEI#:** (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft Amend: 05/10/2018
Edit: CB 05/10/2018

ECMS: Cabinets/CDER OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ (b) (4)

OSIS File #: (b) (4)

**FACTS:** (b) (4)

## Attachment 1
## Studies in support of Pending Applications

| Application # | Study # | Study Type (in vitro/in vivo) | Drug Name | Dates of conduct |
|---|---|---|---|---|
| BLA 761063 | I5Q-MC-GAQ | In vivo | Galcanezumab | (b) (4) |
| (b) (4) | | | | |

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/s/
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GOPA BISWAS
05/10/2018

CHARLES R BONAPACE
05/11/2018

**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: May 7, 2018

TO: Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I, OND

FROM: Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Routine inspection of (b) (4)

## Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of Study I5Q-MC-CGAQ (BLA 761063) conducted at (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. Thus, the data from Study I5Q-MC-CGAQ and other studies of similar design are acceptable for further Agency review.

## Inspected Study

## BLA 761063

**Study Number:** Study I5Q-MC-CGAQ
**Study Title:** "Pharmacokinetics and Pharmacodynamics of LY2951742 (Galcanezumab) in Healthy Subjects

Following Subcutaneous Administration of LY2951742 (Galcanezumab) Solution in a Prefilled Syringe or an Autoinjector"

**Dates of conduct:** (b) (4)

**Clinical site:** (b) (4)

ORA investigator (b) (4) (b) (4)

The inspection included a thorough examination of study records, including the informed consent process, protocol compliance, institutional review board records, drug accountability and storage, and adverse events.

At the conclusion of the inspection, investigator (b) (4) did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

## Conclusion

After reviewing the EIR and inspectional findings, I conclude the data from the audited study are reliable. Therefore, I recommend accepting the data from Study I5Q-MC-CGAQ for further review. In addition, the data from studies of similar design submitted to pending applications (Attachment 1) are acceptable for further Agency review.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (b) (4) and the end of the current surveillance interval are acceptable for review by the Agency without an inspection.

Himanshu Gupta, Ph.D.
Staff Fellow

**Final Classification:**

**NAI-** (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au/Gupta

Draft: HG 04/25/2018, 4/30/2018, 5/7/2018
Edit: SA 04/26/2018; 05/01/2018, 5/3/2018; JC 5/3/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES/(b) (4) (b) (4) BLA 761063_Galcanezumab

OSIS File #: (b) (4) (BLA 761063), (b) (4)

**FACTS:** (b) (4)

**Attachment 1**
**Studies in support of Pending Applications**

| Application # | Study # | Drug Name(s) | Dates of conduct |
|---|---|---|---|
| BLA 761063 | Study I5Q-MC-CGAQ | galcanezumab | (b) (4) |
| (b) (4) | | | |

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/s/
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HIMANSHU GUPTA
05/07/2018

STANLEY AU
05/07/2018
Acting Team Lead

SEONGEUN CHO
05/07/2018

**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**

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DATE: April 23, 2018

TO: Billy Dunn, M.D.
Director
Division of Neurology Products (DNP)
Office of New Drugs

FROM: Gopa Biswas, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4)

**Inspection Summary**

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of studies I5Q-MC-CGAQ (BLA 761063) (b) (4)

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Thus, I recommend that the data from studies I5Q-MC-CGAQ (b) (4) and other studies using similar methods be accepted for further Agency review.

**Inspected Studies:**

**BLA 761063**

**Study Number:** I5Q-MC-CGAQ (b) (4) # (b) (4))
**Study Title:** "Pharmacokinetics and Pharmacodynamics of LY2951742 (Galcanezumab) in Healthy Subjects

Following Subcutaneous Administration of LY2951742 (Galcanezumab) Solution in a Prefilled Syringe or an Autoinjector”

**Dates of conduct:** (b) (4)

**Studies not yet associated with an application**

**Study Number:** (b) (4)
**Study Title:**

**Dates of conduct:**

**Analytical site:**

OSIS scientist Gopa Biswas audited the analytical portion of the above studies at (b) (4)

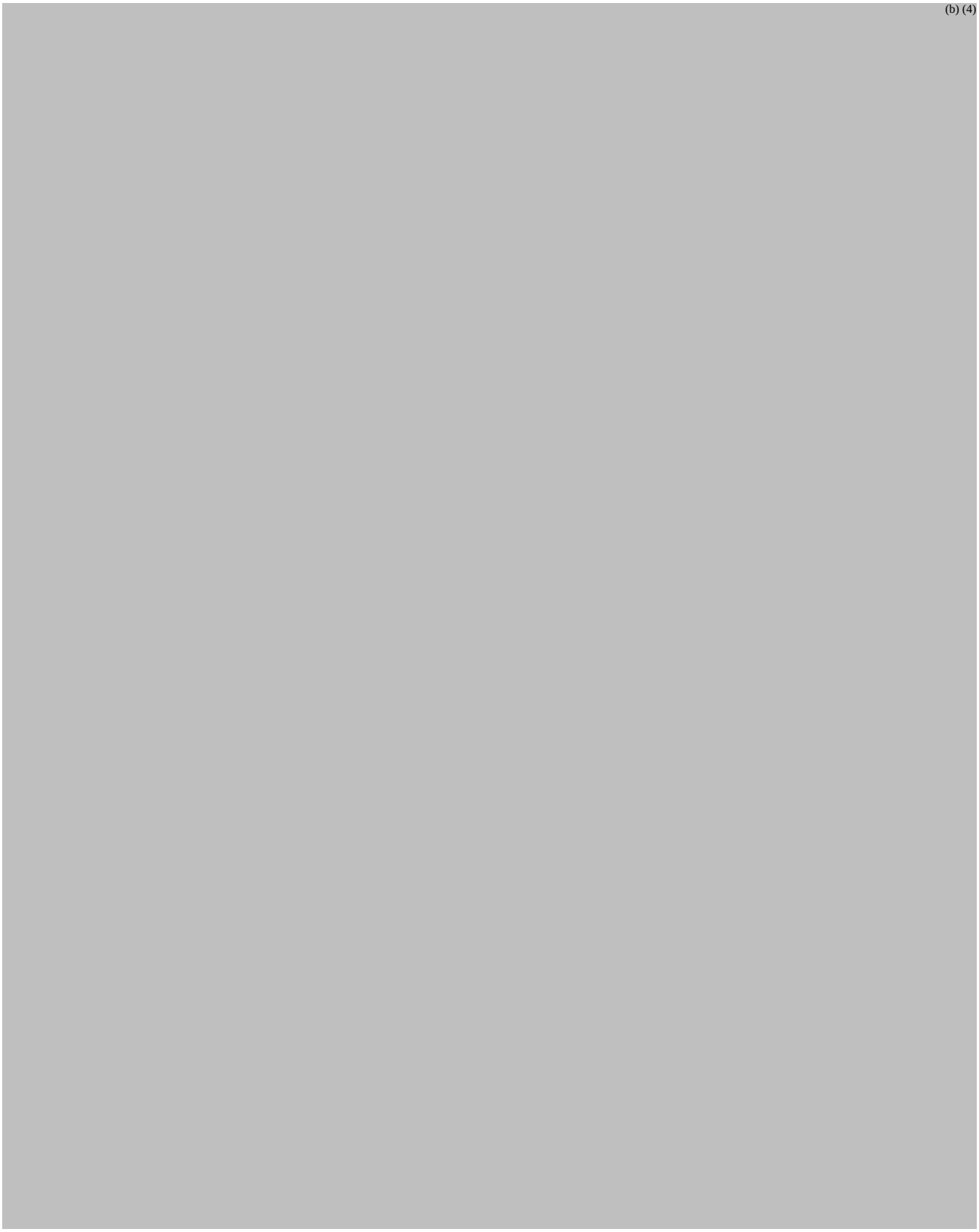
The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm’s management and staff.

At the conclusion of the inspection, I did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site. However, I discussed several items with the firm’s management.

**Discussion items:**

(b) (4)

(b) (4)



(b) (4)

**Conclusion:**

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable. Therefore, I recommend that the data from studies I5Q-MC-CGAQ (BLA 761063) (b) (4) be accepted for further review. In addition, the data from studies using similar methods submitted to pending applications (**Attachment 1**) should be accepted for further Agency review.

Based on the inspectional findings, studies using similar methods conducted between the previous inspection [redacted] and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

Gopa Biswas, Ph.D.
Lead Pharmacologist

**Final Classification:**

**NAI-** [redacted]
**FEI#:** [redacted]

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: 04/17/2018
Edit: 04/20/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ [redacted]

OSIS File #: [redacted]

**FACTS:** [redacted]

## Attachment 1
## Studies in support of Pending Applications

| Application # | Study # | Study Type (in vitro/in vivo) | Drug Name | Dates of conduct |
|---|---|---|---|---|
| BLA 761063 | I5Q-MC-GAQ | In vivo | Galcanezumab | (b) (4) |

(b) (4)

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/s/
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GOPA BISWAS
04/23/2018

CHARLES R BONAPACE
04/23/2018

**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)
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:** | March 30, 2018 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | BLA 761063 |
| **Product Name and Strength:** | Emgality (galcanezumab-gnlm[a]) injection, 120 mg/mL |
| **Product Type:** | Single-ingredient Combination product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Eli Lilly and Company |
| **Submission Date:** | September 26, 2017 |
| **OSE RCM #:** | 2017-2045 |
| **DMEPA Safety Evaluator:** | Ebony Whaley, PharmD, BCPPS |
| **DMEPA Team Leader:** | Lolita White, PharmD |

[a] Proper name for Emgality BLA 761063 found conditionally acceptable on February 16, 2018.

## 1 REASON FOR REVIEW

As part of the approval process for Emgality (galcanezumab-gnlm) injection BLA 761063, the Division of Neurology Products (DNP) requests that we review the proposed Prescriber Information (PI), container label, carton labeling, and Instructions for Use (IFU) for areas of vulnerability that could lead to medication error.

## 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 Label and Labeling Review**

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

N/A=not applicable for this review
*We do not typically search FAERS 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

Emgality (galcanezumab-gnlm) is a prefilled syringe and prefilled pen intended for monthly subcutaneous injection for the prophylaxis of migraine in adults. The intended doses, 120 mg and 240 mg, are provided by one or two injections using the 120 mg/mL prefilled syringe or 120 mg/mL prefilled pen.

Our review of the proposed PI, IFU, container labels, and carton labeling for Emgality (galcanezumab-gnlm) injection identified the following areas of needed improvement that may contribute to medication errors:

Highlights of Prescribing Information and Full Prescribing Information

1. The Dosage and Administration section of the Highlights of Prescribing Information and Section 2.1 Migraine of the Full Prescribing Information do not prominently describe the loading dose as part of the dosing regimen. We are concerned that users may overlook the information regarding the 240 mg loading dose.

Instructions for Use (prefilled pen and prefilled syringe)

1. The IFU does not inform users that 2 injections may be required for a 240 mg dose.

Container labels (prefilled pen and prefilled syringe)

1. The strength statement is not prominent.
2. (b) (4)

Carton labeling (prefilled pen and prefilled syringe)

1. The strength statement is not prominent.
2. (b) (4)
3.

We provide specific recommendations regarding these areas below in section 4.1 for revisions to the PI and in section 4.2 for revisions to the container labels and carton labeling to help minimize the potential for medication errors to occur with the use of this product.

## 4 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed container label, carton labeling, PI, and IFU and identified areas where information should be revised to help ensure safe use of the product. We provide recommendations below in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations be implemented prior to approval of this product.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. Highlights of Prescribing Information and Section 2.1 Migraine of the Full Prescribing Information
        i. The instructions to administer a loading dose is not prominently stated.

(b) (4)

### 4.2 RECOMMENDATIONS FOR ELI LILLY

We recommend the following be implemented prior to approval of BLA 761063:

A. Instructions for Use (prefilled pen and prefilled syringe)
   1. (b) (4)

B. Container labels (prefilled pen and prefilled syringe)
   1. The strength statement is not prominent and may be overlooked. We recommend that the prominence (e.g. font size) is increased to mitigate the risk of user confusion regarding the product strength per 21 CFR 201.15(a)(6).
   2. (b) (4) (b) (4) (b) (4) We recommend that the container labels are updated throughout to include the conditionally approved nonproprietary name suffix 'gnlm'.

C. Carton labeling
   1. See recommendation B.1. and B.2. and revise accordingly.
   2. (b) (4) (b) (4) (b) (4)

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

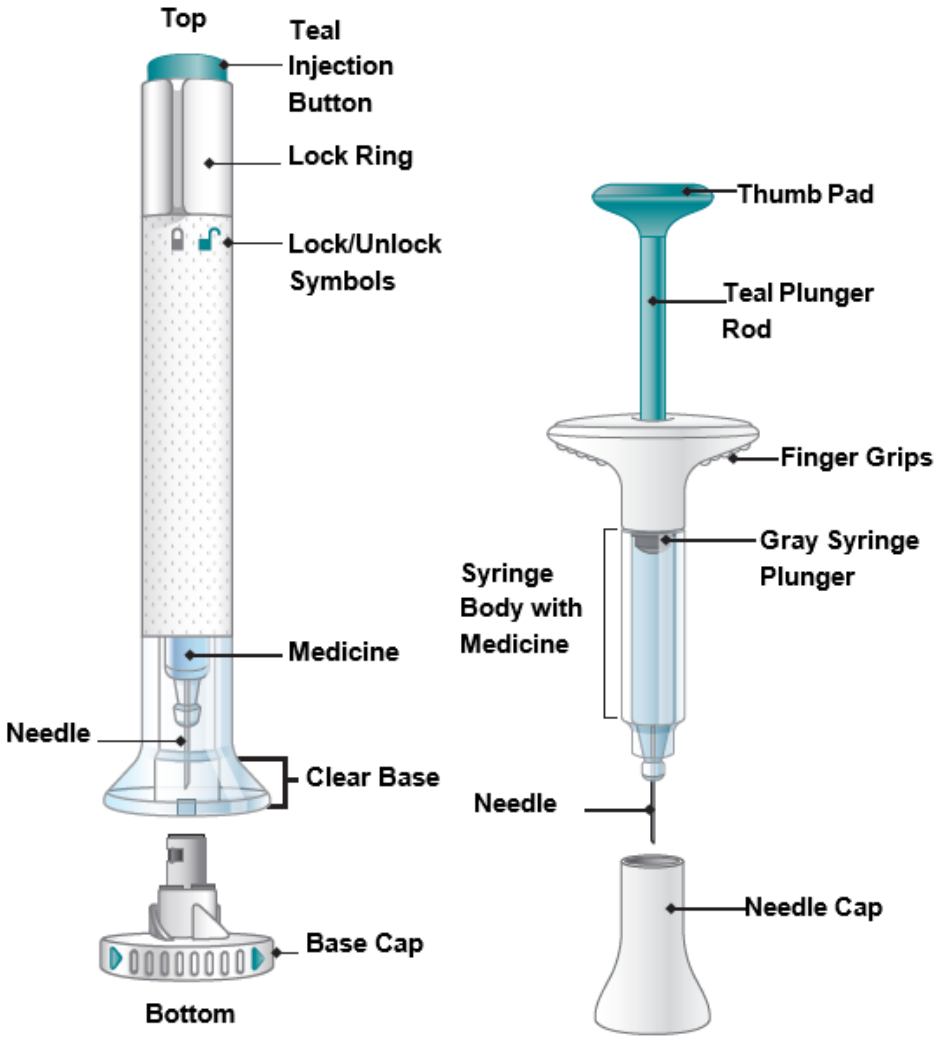
## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Emgality that Eli Lilly and Company submitted on September 27, 2017.

**Table 2. Relevant Product Information for Emgality**

| | |
|---|---|
| **Initial Approval Date** | N/A |
| **Active Ingredient** | galcanezumab |
| **Indication** | prophylaxis of migraine in adults |
| **Route of Administration** | subcutaneous |
| **Dosage Form** | injection solution |
| **Strength** | 120 mg/mL |
| **Dose and Frequency** | The recommended dose is 120 mg injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose. (b) (4) |
| **How Supplied** | |
| **Storage** | - Store refrigerated at 2°C to 8°C (36°F to 46°F).<br>- Protect EMGALITY from light until use.<br>- Do not freeze. Do not shake.<br>- EMGALITY may be stored outside of refrigeration for up to 7 days when stored at temperatures up to 30°C (86°F).<br>- Discard the EMGALITY single-dose prefilled pen or syringe after use in a puncture-resistant container. |

| | Pack Size | NDC |
|---|---|---|
| **Prefilled pen** | | |
| 120 mg single-dose | Carton of 1 | 0002-1436-11 |
| 120 mg single-dose | Carton of 2 | 0002-1436-27 |
| **Prefilled syringe** | | |
| 120 mg single-dose | Carton of 1 | 0002-2377-11 |
| 120 mg single-dose | Carton of 2 | 0002-2377-27 |

| | |
|---|---|
| **Container Closure** |  |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 8, 2017, we searched DMEPA's previous reviews using the term, galcanezumab. Our search identified 3 previous reviews[bcd] and we confirmed that our previous recommendations were implemented or considered.

| OSE Review RCM | DMEPA Recommendations |
|---|---|
| (b) (4) | |
| 2016-1807 | We reviewed the human factors data for the proposed galcanezumab 120 mg/mL prefilled syringe and 120 mg/mL autoinjector and determined that HF validation studies are not needed for the proposed products. We also collaborated with DMPP for review of the draft IFU and provided recommendations. |
| (b) (4) | |

(b) (4)

[c] Whaley, E. Human Factors Protocol Review for Galcanezumab IND 111295. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 13. RCM No.: 2016-1807.

(b) (4)

## APPENDIX G. LABELS AND LABELING

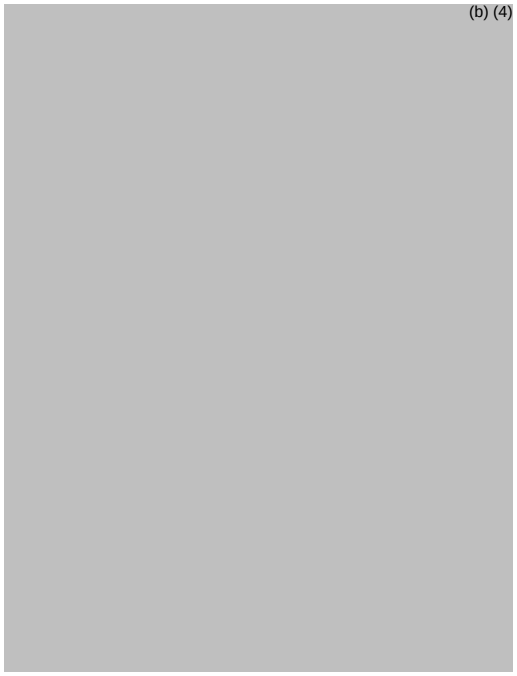
### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Emgality labels and labeling submitted by Eli Lilly and Company on September 27, 2017.

- Container labels
- Carton labeling
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

### G.2 Label and Labeling Images

- Container label (prefilled syringe)




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



5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/s/

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EBONY A WHALEY
03/30/2018

LOLITA G WHITE
03/31/2018

**OFFICE OF DEVICE EVALUATION**

**DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**

**GENERAL HOSPITAL DEVICES BRANCH**

**INTERCENTER CONSULT MEMORANDUM**

| | |
|---|---|
| **Date** | March 26, 2018 |
| **To** | Emilios Papanastasiou, Regulatory Health Project Manager,<br>CDER/OND/ODEI/DNP |
| **Requesting Division** | DNP |
| **From** | CDR Keith Marin<br>CDRH/ODE/DAGRID/GHDB |
| **Through<br>(Team Lead)** | John McMichael, ICC Team Lead<br>CDRH/ODE/DAGRID/GHDB |
| **Through<br>(Branch Chief)** | CAPT Alan Stevens<br>CDRH/ODE/DAGRID/GHDB |
| **Subject** | Consult for Submission # BLA 761063<br>ICCR #2017-01684<br>ICC#1700797 |
| **Recommendation** | Device constituent parts of the combination product are Approvable. |

| Digital Signature Concurrence Table | |
|---|---|
| Reviewer | Keith G. Marin -S<br>Digitally signed by Keith G. Marin -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=0011250397<br>Date: 2018.05.10 11:37:08 -04'00' |
| Team Lead | John C. Mcmichael -S<br>2018.05.10 11:58:16 -04'00' |
| Branch Chief | Alan M. Stevens -S<br>Digitally signed by Alan M. Stevens -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S<br>Date: 2018.05.15 07:25:08 -04'00' |

# 1. Submission Overview

| Table 1. Submission Information | |
|---|---|
| ICCR # (Lead) | ICCR #2017-01684 |
| ICCR SharePoint Link | http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1910 |
| ICC tracking # (Lead) | ICC1700797 |
| Submission Number | BLA 761063 |
| Sponsor | Eli Lilly and Company |
| Drug/Biologic | Emgality (galcanexumab) |
| Indications for Use | prevention of migraines. |
| Device Constituent | Prefilled syringe and Autoinjector |
| Related Files | None |

| Table 2. Review Team | |
|---|---|
| CDER/CBER Lead Review Division | DNP |
| Submission RPM | Emilios Papanastasiou |
| Lead Device Reviewer | CDR Keith Marin |
| The CDRH review is being managed under ICC #: ICC1700797 | |

| Table 3. Important Dates | | |
|---|---|---|
| **Interim Due Dates** | **Meeting Date** | **Due Date** |
| Filing | 11/2/2017 | 11/2/2017 |
| 74-Day Letter | 12/08/2017 | 12/08/2017 |
| Mid-Cycle | 2/27/2018 | 2/27/2018 |
| Primary Review | 3/14/2018 | 3/14/2018 |
| Internal Meeting | 5/27/2018 | 5/27/2018 |
| Sponsor Meeting | 06/15/2018 | 06/15/2018 |

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# 2. PURPOSE/BACKGROUND

## 2.1. Scope

Eli Lilly and Company (Lilly) is submitting this initial Biologics License Application (BLA) to gain United States (US) regulatory approval for galcanezumab for the following indication: Galcanezumab is indicated for the prophylaxis of migraine in adults. CDER has requested on the Intercenter consult form the following information:

"This consult request is for attendance at the planning filing meeting scheduled on 11/2/2017."

***Reviewer's Note:*** *CDER has not requested any other information but it is the assumption of this reviewer that a complete review of BLA 761063 will be needed.*

This memo will provide a comprehensive review of the prefilled syringe and autoinjector that will be used to deliver Galcanezumab. Drug device compatibility (i.e. plunger stopper) will be deferred to CDER.

## 2.2. Prior Interactions

### *2.2.1. Related Files*

*IND 111295*

ICC1600808: CDER requested that CDRH provide written comments on the proposed auto-injector vs. prefilled syringe delivery system for IND111295. This review was initially conducted by Janice Ferguson. In ICC1600808, CDER's request was to address a response to a CDRH IR, specifically questions 2b and 3. Based on review of the responses, the response to the IR was deemed acceptable as the sponsor has stated the information requested will be provided in the future BLA. The sponsor stated that they will provide appropriate stability testing in the future BLA to support the time the device will be stored. Additioanlly, the sponsor stated that they would include the necessary testing according to ISO 11608-1 and ISO 11608-5. However, they did not make mention that they would include the specifications within their release criteria. The sponsor was instructed that they need to include needle extension length as release criteria, or explain how their IPC are adequate to control this requirement.

ICC1700560: DNP held a face to face Pre-BLA meeting with Eli Lily to discuss IND 111295 (galcanezumab) on July 18,

2017. In this submission, we were consulted with little lime before the scheduled meeting. It was agreed that CDRH could provide reviewer general post meeting comments in anticipation of the BLA submission. The goal of this submission was to provide general comments on what CDRH will expect to see in a future marketing submission. The following was communicated to the sponsor:

*"Within your submission it was observed that there are no specific questions pertaining to the device constituent parts of the combination product. Additionally, no information on the device was included in the current submission. It appears that a similar syringe and autoinjector were used in BLA 125469. If you are making no changes to the device and plan on referencing the information from this BLA, please ensure all of the necessary information to support your submission is included within the referenced BLA. We recommend that you conduct testing to verify the essential performance requirements of the combination product presentations (e.g. dose accuracy, activation force, extended needle length, dispensing time, breakloose/glide force, etc.) with the to-be-marketed version of the device and the intended biologic; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended biologic (i.e. fluid characteristics, viscosity, etc.). If you are not going to reference BLA 125469, please ensure all of the necessary design requirements, verification, validation testing, and risk analysis are included within your submission."*

***Reviewer's Note:*** *The sponsor has included device information for the prefilled syringe and autoinjector that was referened in the earlier IND. This will be reviewed in the current submission.*

### 2.3. Indications for Use

| Combination Product | Indications for Use |
|---|---|
| Galcanezumab | Galcanezumab is indicated for the prophylaxis of migraine in adults. |
| Prefilled syringe<br>Autoinjector | The prefilled syringe is intended to inject galcanezumab drug product into the body.<br>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. |

## 3. ADMINISTRATIVE

### 3.1. Documents Reviewed

| Document Title | Date - Version | Location |
|---|---|---|
| BLA 761063 | 09/27/2017 | \\cdsesub1\evsprod\BLA761063\0001 |

## 4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The primary container closure for both the prefilled syringe is described below:


Figure 3.2.P.7.1-1 Primary Container Closure System

Table 3.2.P.7.2-1 Identification for Galcanezumab Injection

| Component | Description |
|---|---|
| Syringe Barrel | (b) (4) |
| Plunger | |

**Prefilled Syringe**

The prefilled syringe is a prefilled, single-use, injection device that enables patients, caregivers or health care professionals to administer a fixed-dose of galcanezumab drug product via subcutaneous injection. Galcanezumab is indicated for migraine prevention in adults 18 and older and can be injected in the abdomen, thigh or back of the arm. The syringe system complies with the requirements of ISO 11040-4 and ISO 7864. (b) (4) Table 3.2.P.2.4-1 provides more information regarding the container closure system components.

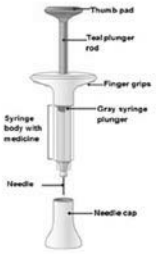



Figure 3.2.R.2.2-1 Galcanezumab Prefilled Syringe

(b) (4)

Figure 3.2.R.2.2-2 Prefilled Syringe Used in Clinical Studies

Table 3.2.R.2.2-1 Material Identification

| | Component | Material |
|---|---|---|
| Patient Contact Components | Plunger rod | (b) (4) |
| | Finger grips | |
| | Syringe body (b) (4) | |
| | Needle cap components<br>Needle cap<br>Cap insert | |
| | Flange cap | |
| Internal Component | | |

Abbreviation: (b) (4)

Table 3.2.P.2.4-1 Galcanezumab Injection Container Closure System Components

(b) (4)

## Syringe and Autoinjector Device Specifications:

Table 3.2.P.5.1-2 Specifications for the Prefilled Syringe

| Test | Analytical Procedure | Acceptance Criteria |
|---|---|---|
| Identity | CEX | Conforms to reference standard [1] |
| Dose Accuracy | Volume by Weight | Not less than (b) (4) and not more than (b) (4) |
| Visual Inspection | Visual | Pass |

Abbreviation: CEX=cation exchange chromatography.
[1] Conforms with reference standard indicates that the sample chromatographic profile compares favorably to the reference standard with no new peaks and/or no absence of peaks based on examples in the methods and clinical experience.

Table 3.2.P.5.1-3 Specifications for the Autoinjector

| Test | Analytical Procedure | Acceptance Criteria |
|---|---|---|
| Identity | CEX | Conforms to reference standard [1] |
| Dose Accuracy | Volume by Weight | Not less than (b) (4) and not more than (b) (4) |
| Injection Process Time | Activation to retraction timing | Not more than (b) (4) |
| Visual Inspection | Visual | Pass |

Abbreviation: CEX=cation exchange chromatography.
[1] Conforms with reference standard indicates that the sample chromatographic profile compares favorably to the reference standard with no new peaks and/or no absence of peaks based on examples in the methods and clinical experience.

| Other Tests (continued) | | | |
|---|---|---|---|
| Volume of Injection | USP <1><br>Ph. Eur. 2.9.17 | Meets compendial requirements<br>Not less than (b) (4) | - - |
| Bacterial Endotoxins | USP <85><br>Ph. Eur. 2.6.14<br>or<br>End-point fluorescence | Not more than (b) (4) EU/mg | - - |
| Sterility | USP <71><br>Ph. Eur. 2.6.1 | Meets compendial requirements | Meets compendial requirements |
| Break-loose Force | Compression Test | Not more than (b) (4) | Not more than (b) (4) |
| Glide Force | Compression Test | Not more than | Not more than |

(b) (4)

***Reviewer's Note:*** *While the sponsor has provided the comparison table, it use is limited as the syringes are not identical and the manufacturers of the syringes are not the same. The sponsor will still need to validate the function of their syringe.*

Syringe device description information comes from 3.2.R of BLA 761063\0001.

**Autoinjector:**

The autoinjector is designed for use with parenteral drug products that are filled in a (b) (4) When activated, the autoinjector delivers the entire volume (b) (4) in a single injection. The fluid path from the prefilled syringe is through the (b) (4) needle component of the primary drug container.

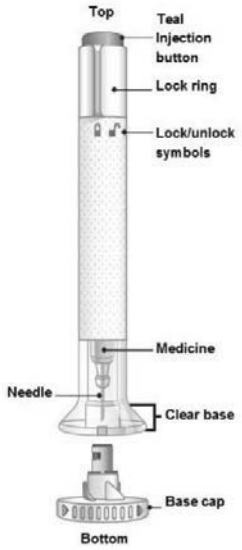



Table 3.2.R.2.2-2 Material Identification

| | 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 | | |

(b) (4)

***Reviewer's Note:*** *While the sponsor has provided the comparison table, it use is limited as the injectors are not identical and the manufacturers of the syringes are not the same. The sponsor will still need to validate the function of their syringe.*

Autoinjector device description information comes from 3.2.R of BLA 761063\0001.

# CLINICAL DEVELOPMENT

## 4.1. Current Study Summary

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Subjects Who Were Randomized and Received ≥1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| **Bioavailability and Bioequivalence Studies** | | | | | | |
| I5Q-MC-CGAO; 5.3.3.1 Full; Complete; United States | Part A: Assess the tolerability of GMB following SC administration of GMB 240 mg as a solution formulation in a PFS<br>Part B: Determine the relative bioavailability of GMB 300 mg after SC administration of the lyophilized formulation (reference) and the solution formulation in a PFS | Phase 1, single-center, randomized, single dose study in healthy subjects in two parts; Part A: double-blind, placebo-controlled Part B: open-label, parallel group | Part A: GMB 240 mg (administered as wo GMB 120mg SC injections) or PBO as a solution formulation Following dose administration, 5-month monitored washout phase<br><br>Part B: GMB 300 mg (administered as three GMB 100 mg SC injections) in a lyophilized formulation or a solution formulation. Following dose administration, 5-month monitored washout phase | **Part A** N = 18<br>GMB 240 mg 15<br>PBO 3<br><br>**Part B** N = 160<br>GMB 300 mg lyophilized formulation 80<br><br>GMB 300 mg solution formulation 80 | Healthy adult subjects aged 18 to 65 years inclusive with a BMI 19 to 35 kg/m$^2$ inclusive | Single dose |

**Tabular Listing of Clinical Studies for Migraine Prevention**

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Subjects Who Were Randomized and Received ≥1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| I5Q-MC-CGAQ; 5.3.3.4 Full; Complete; United States | Determine the relative bioavailability of GMB 240 mg after SC administration of GMB as solution via a manual PFS (reference) or autoinjector (test). | Phase 1, multicenter, randomized, open-label, two-arm parallel group study | GMB 240 mg (administered as two GMB 120 mg SC injections) via a manual PFS or via an autoinjector. Following dose administration, 5-month monitored washout phase | N = 160<br>GMB 240 mg via PFS 80<br>GMB 240 mg via AI 80 | Healthy adult subjects aged 18 to 65 years inclusive with a BMI 19 to 35 kg/m$^2$ inclusive | Single dose |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Subjects Who Were Randomized and Received ≥1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| **Healthy Subject Pharmacokinetic and Initial Tolerability Studies** | | | | | | |
| I5Q-MC-CGAA; 5.3.3.1 Full; Complete; Belgium | Evaluate the safety and tolerability of single and multiple doses of GMB administered via SC injection in healthy subjects | Phase 1, single-center, randomized, double-blind, placebo-controlled, single dose escalation and multiple dose study | Part A single dose escalation: GMB 1 mg, GMB 5 mg, GMB 25 mg, GMB 75 mg, GMB 200 mg or GMB 600 mg GMB or PBO administered via SC injection<br>Following dose administration, 54-129 days postdose monitored washout phase, depending on dose<br><br>Part B multiple dose: GMB 150 mg or PBO SC injection Q2W<br>Following treatment phase, 4-month monitored (washout) phase | **Part A Single Dose** N = 54<br>GMB 1 mg 7<br>GMB 5 mg 7<br>GMB 25 mg 7<br>GMB 75 mg 7<br>GMB 200 mg 7<br>GMB 600 mg 7<br>PBO 12<br><br>**Part B Multi-Dose** N = 9<br>GMB 150 mg 7<br>PBO 2 | Healthy male subjects aged 18 to 55 years inclusive with a BMI equal to or greater than 19 kg/m$^2$ | Part A: Single dose Part B: 2 months |

**Tabular Listing of Clinical Studies for Migraine Prevention**

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Subjects Who Were Randomized and Received ≥ 1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| I5Q-MC-CGAE; 5.3.3.1 Full; Complete; United States | Evaluate the safety and tolerability of GMB administered as a single and multiple SC injections in healthy subjects, including Japanese subjects | Phase 1, single-center, randomized, double-blind, placebo-controlled, single and multiple dose study | Part A single dose escalation: GMB 5 mg, GMB 50 mg, GMB 120 mg or GMB 300 mg or PBO administered via SC injections.<br>Following dose administration, 5-month monitored washout phase<br><br>Part B multiple dose: GMB 300 mg (administered as two GMB 150 mg SC injections) or PBO monthly<br>Following treatment phase, 5-month post-treatment (washout) phase | **Part A Single Dose** N = 35<br>GMB 5 mg 6<br>GMB 50 mg 6<br>GMB 120 mg 7<br>GMB 300 mg 8<br>PBO 8<br><br>**Part B Multi-Dose** N = 10<br>GMB 300 mg 8<br>PBO 2 | Japanese and Caucasian healthy subjects aged 20 to 65 years inclusive with a BMI of 18 to 35 kg/m$^2$ inclusive. | Part A: Single dose Part B: 3 months |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| **Controlled Clinical Studies Pertinent to Migraine Prevention** | | | | | | |
| I5Q-MC-CGAG (Pivotal Study); 5.3.5.1 Full; Ongoing (double-blind treatment phase complete); Canada, United States | Determine if GMB is superior to PBO in the prevention of migraine in patients with episodic migraine | Phase 3, multicenter randomized, double-blind, placebo-controlled, parallel group study | Monthly: GMB 120 mg (with GMB 240mg loading dose), GMB 240 mg or PBO administered via SC injection<br>Following double-blind treatment phase, 4-month post-treatment (washout) phase | N = 858<br>Treatment Group / ITT[c] / Safety[d]<br>GMB 120mg: 213 / 206<br>GMB 240mg: 212 / 220<br>PBO: 433 / 432 | Patients with episodic migraine aged 18 to 65 years inclusive who meet ICHD-3 beta 1.1 or 1.2 as confirmed during a prospective baseline period[e] | 6 months |
| I5Q-MC-CGAH (Pivotal Study); 5.3.5.1 Full; Ongoing (double-blind treatment phase complete); Argentina, Czech Republic, Germany, Israel, Republic of Korea, Mexico, Netherlands, Spain, Taiwan, United Kingdom, United States | Determine if GMB is superior to PBO in the prevention of migraine in patients with episodic migraine | Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study | Monthly: GMB 120 mg (with GMB 240 mg loading dose), GMB 240 mg or PBO administered via SC injection<br>Following double-blind treatment phase, 4-month post-treatment (washout) phase | N = 915<br>Treatment Group / ITT[c] / Safety[d]<br>GMB 120mg: 231 / 226<br>GMB 240mg: 223 / 228<br>PBO: 461 / 461 | Patients with episodic migraine aged 18 to 65 years inclusive who meet ICHD-3 beta 1.1 or 1.2 as confirmed during a prospective baseline period[e] | 6 months |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| I5Q-MC-CGAI (Pivotal Study); 5.3.5.1 Full; Ongoing (double-blind treatment phase complete); Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, United Kingdom, United States | Determine if GMB is superior to PBO in the prevention of migraine in patients with chronic migraine | Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study | Double-Blind dosing monthly:<br>GMB 120 mg (with GMB 240 mg loading dose), GMB 240 mg or PBO administered via SC injection<br>Open-Label dosing monthly:<br>1st OL dose: GMB 240 mg<br>2nd OL dose: GMB 120 mg<br>Thereafter monthly:<br>GMB 120 mg or GMB 240 mg per clinical judgment<br>Following open-label extension, 4-month post-treatment (washout) phase | N = 1,113<br>Double-Blind Treatment Phase<br>Treatment Group / ITT[c] / Safety[d]<br>GMB 120mg: 278 / 273<br>GMB 240mg: 277 / 282<br>PBO: 558 / 558<br>N = 1021<br>Open-Label Treatment Phase<br>Treatment Group[f]<br>GMB 120mg/GMB: 259<br>GMB 240mg/GMB: 261<br>PBO/GMB: 501 | Patients, 18-65 years inclusive who meet ICHD-3 beta for chronic migraine (1.3) as confirmed in prospective baseline period[g] | Double-Blind Treatment Phase: 3 months<br>Open-Label Treatment Phase: 9 months |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients Who Were Randomized and Received ≥ 1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| I5Q-AR-ART1; 5.3.5.1 Full; Complete; United States | Assess the efficacy and safety of GMB in the prevention of migraine in migraine patients with or without aura over a 3-month period | Phase 2a, proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study | GMB 150 mg or PBO administered via SC injection Q2W Following double-blind treatment phase, 3-month post-treatment (washout) phase | N = 217<br>GMB 150mg 107<br>PBO 110 | Patients aged 18 to 65 years inclusive with a history of migraine meeting ICHD-II criteria for at least one year prior to enrollment in study and with an onset of migraine prior to age 50 as confirmed during a prospective baseline period[e] | 3 months |
| I5Q-MC-CGAB; 5.3.5.1 Full; Complete; United States | Assess the efficacy and safety of GMB in the prevention of migraine and determine the GMB dose(s) for future Phase 3 development | Phase 2b, dose-ranging multicenter, randomized, double-blind, placebo-controlled study | Monthly (Q4W): GMB 300 mg, GMB 120 mg, GMB 50 mg, GMB 5 mg or PBO administered via SC injection Following double-blind treatment phase, 3-month post-treatment (washout) phase | N = 410<br>GMB 5 mg 68<br>GMB 50 mg 68<br>GMB 120 mg 70<br>GMB 300 mg 67<br>PBO 137 | Patients aged 18 to 65 years inclusive with a history of migraine meeting ICHD-3 beta criteria for at least one year prior to enrollment in the study and a frequency of 4 to 14 migraine headache days and at least 2 migraine attacks per month as confirmed during a prospective baseline period, and onset of migraine prior to age 50[e] | 3 months |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients Who Were Randomized and Received ≥ 1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| (b) (4) | | | | | | |

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients Who Were Randomized and Received ≥ 1 Dose of Study Treatment | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| (b) (4) | | | | | | |

Tabular Listing of Clinical Studies for Migraine Prevention

| Study Identifier; Location of Report; Report Type; Status[a]; Participating Countries[b] | Objective | Design; Control Type | Treatment and Regimen: Dose/Route/Frequency | Number of Patients | Diagnosis or Inclusion Criteria | Treatment Duration |
|---|---|---|---|---|---|---|
| **Uncontrolled Clinical Study** | | | | | | |
| I5Q-MC-CGAJ; 5.3.5.2 Full; Ongoing (open-label treatment phase complete); Belgium, Canada, France, Hungary, United States | Evaluate the long-term safety and tolerability of GMB in migraine patients for 1 year of treatment | Phase 3, multicenter, randomized open-label, long-term safety study | Monthly: GMB 120 mg (with GMB 240 mg loading dose) or GMB 240 mg administered via SC injection For second monthly dose administration and all dose administrations thereafter, patients were allowed to self-inject GMB using PFS and then autoinjector, when it became available to patients. Following open-label treatment phase, 4-month post-treatment (washout) phase | N = 270<br>Treatment Arm / ITT[c] / Safety[d]<br>GMB 120mg / 135 / 129<br>GMB 240mg / 135 / 141 | Patients aged 18 - 65 years inclusive who meet ICHD-3 beta for episodic or chronic migraine (1.1, 1.2 or 1.3) and have an average of 4 or more migraine headache days per month for previous 3 months | 12 months |

#### *4.1.1. Specific Study Issues*

None noted.

# 5. DESIGN CONTROL REVIEW

## 5.1. Design Review Summary

#### *5.1.1. Design Control Documentation Check*

| Design Control Requirement* | Signed/Dated Document Present | | Submission Location |
|---|---|---|---|
| | Yes | No | |
| Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer | X | | 0001 (1) 09/27/2017, 3.2.P.5.1 |
| Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file. | X | | 0001 (1) 09/27/2017, 3.2.R |
| Risk Analysis supplied in the NDA / BLA by the Combination Product Developer | X | | 0001 (1) 09/27/2017, 3.2.R |
| Validation Data | X | | 0001 (1) 09/27/2017, 3.2.R, 5.2 |
| • Human factors<br>• Clinical data | X | | |

*5.1.2. Design Control Review*

# 6. DESIGN VERIFICATION AND VALIDATION REVIEW

## 6.1. Summary of Design V&V Attributes

| Design Verification / Validation Attributes | Yes | No | N/A |
|---|---|---|---|
| Validation of essential requirements covered by clinical and human factors testing | X | | |
| To-be-marketed device was used in the pivotal clinical trial | | | |
| Verification methods relevant to specific use conditions as described in design documents and labeling | X | | |
| Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study) | | | X |
| Traceability demonstrated for specifications to performance data | X | | |

| Standards / Guidance Conformance | | YES | NO | N/A |
|---|---|---|---|---|
| Conformance to Standards | ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods | X | | |
| | ISO 11608-2:2012 – Needles | | | X |
| | ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors | | | X |
| | ISO 11608-5:2012 – Automated Functions | X | | |

| | | | | |
|---|---|---|---|---|
| Adherence to FDA Guidance | Infusion Pumps Total Product Life Cycle – Guidance for Industry and FDA Staff (2014) | | | X |
| | Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005) | | | X |
| | Guidance for Industry and FDA Staff – Intravascular Administration Sets Premarket Notification Submissions (2008) | | | X |
| | Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013) | X | | |
| | Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002) | | | X |
| | Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017) | X | | |
| | Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015) | | | X |

*This table does NOT include discipline specific Guidance / Standards that may be applicable to the review

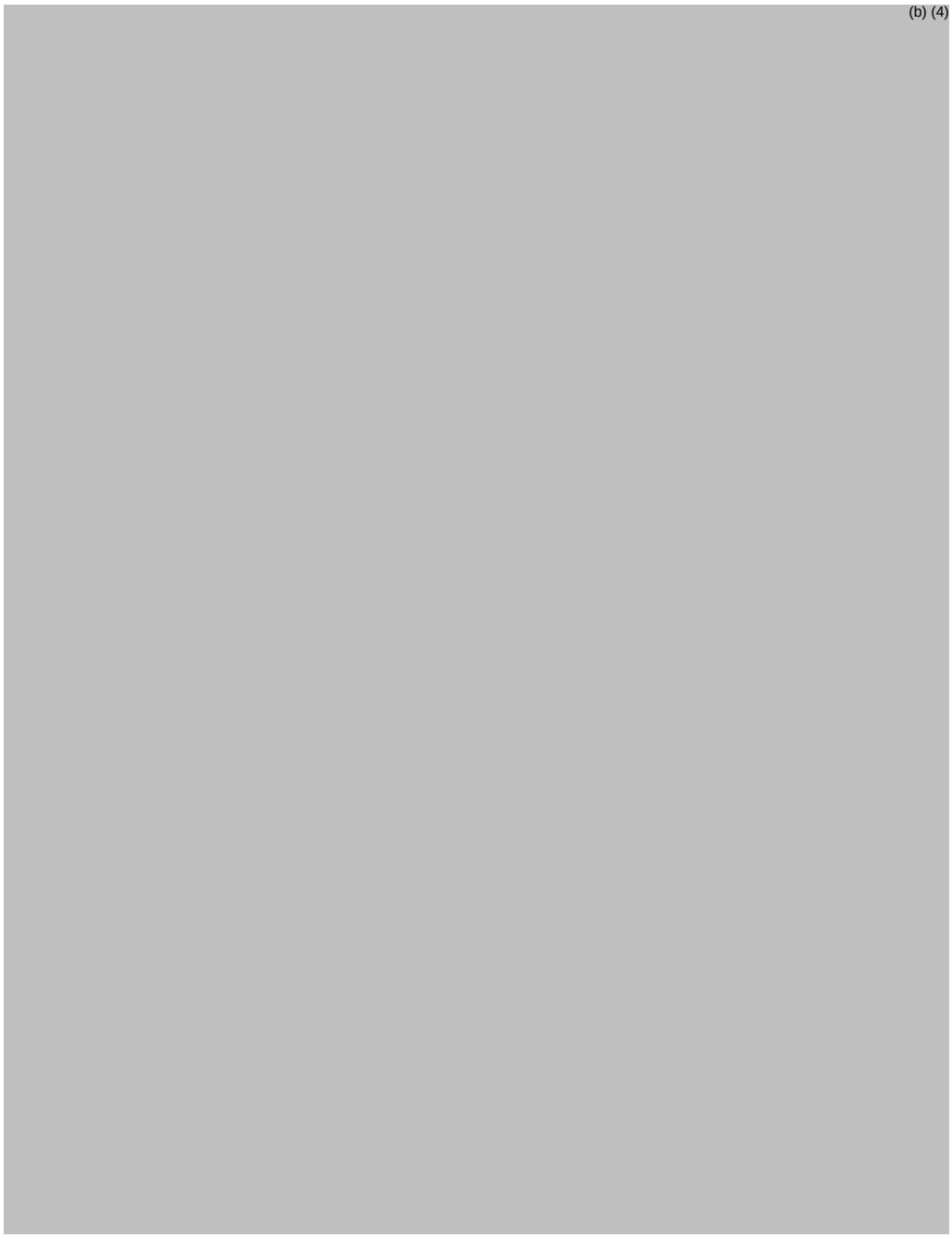
## 6.2. Design Validation Review

| Design Validation Attributes | Yes | No | N/A |
|---|---|---|---|
| Phase I/II/III Study utilized the to-be-marketed device | X | | |
| Bioequivalence Study utilized to-be-marketed device | X | | |
| Simulated Actual Use Study utilized to-be-marketed device | X | | |

## 6.3. Design Verification Review

Prefilled Syringe Verification Testing

(b) (4)


(b) (4)

(b) (4)

(b) (4)

(b) (4) Syringe Performance

Break-loose and glide forces were evaluated for galcanezumab injection (b) (4) at both long-term (2°C to 8°C) and accelerated (30°C/60% RH) conditions (Section 3.2.P.8, Stability). The data indicate acceptable performance of the (b) (4) at both storage conditions. The break-loose force was observed to slightly increase at both storage conditions, but remains below the specification limit.

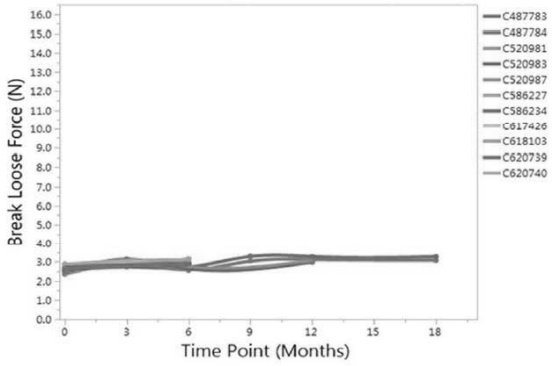



Figure 3.2.P.2.4.1.4-6 Break-Loose Force Data Stored at 5°C

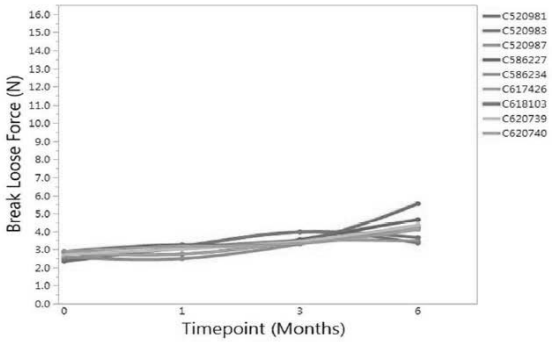



Figure 3.2.P.2.4.1.4-7 Break-Loose Force Data Stored at 30°C

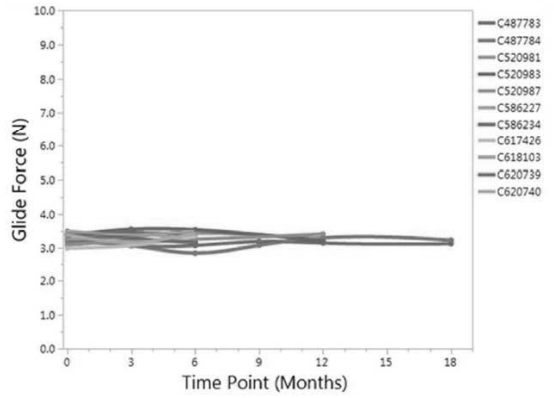



Figure 3.2.P.2.4.1.4-8 Glide-Force Data Stored at 5°C

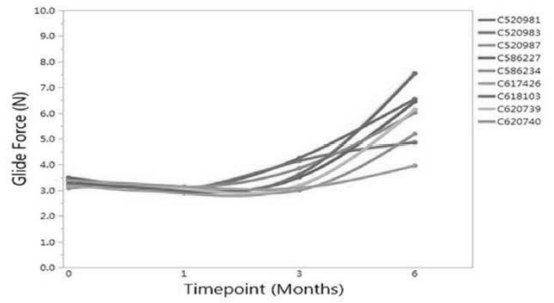



Figure 3.2.P.2.4.1.4-9 Glide-Force Data Stored at 30°C

Needle performance: (b) (4) has certified the needle to meet the relevant performance requirements, including pull-out force, patency, stiffness, resistance to breakage, and resistance to corrosion, as indicated in the industry standards ISO 9626: 1991 with Amd 1: 2001, Stainless steel needle tubing for manufacture of medical devices, and ISO 7864: 1993, Sterile hypodermic needles for single use. The needle also meets the dimensional requirements of ISO 9626, with the exception that the maximum outer diameter is slightly larger than specified for a (b) (4). The tip end of the syringe barrel is closed with a rigid needle shield composed of a proprietary (b) (4).

*Reviewer's Note: The sponsor has provided all requested performance testing and it meets the established acceptance criteria. I have no further questions.*

<u>Biocompatiblity</u>


The materials in the plunger rod are shown in the below table. These materials represent all the materials used in the exterior components of the device. No plasticizers, additives, cross-linkers, reagents, surfactants, or detergents are used to manufacture the exterior components. The process used to assemble the (b) (4) with the prefilled syringe components uses no additional chemicals or materials.

**Table 3.2.R.2.4-1 Plunger Rod Materials**

| Component | Material | CAS# |
|---|---|---|
| Plunger Rod - 1st injection shot | (b) (4) | Trade secret |
| | | (b) (4) |
| Plunger Rod - 2nd injection shot | | Trade Secret |
| | | Trade Secret |
| | | (b) (4) |

Abbreviation: (b) (4)
(b) (4)

**Table 3.2.R.2.4-2 Flange Cap Materials**

| Component | Material | CAS# |
|---|---|---|
| Flange Cap Plastic | (b) (4) | Trade Secret |
| | | (b) (4) |

Abbreviation: (b) (4)

**Table 3.2.R.2.4-3 Syringe Body Materials**

| Component | Material | CAS# |
|---|---|---|
| Body 1st injection shot (Syringe Body) | (b) (4) | (b) (4) |
| Body 2nd injection shot (Finger Grips) | | Trade secret |
| | | Trade secret |
| | | (b) (4) |

Abbreviation (b) (4)

**Table 3.2.R.2.4-4 Needle Cap Materials**

| Component | Material | CAS# |
|---|---|---|
| Needle Cap - 1st Injection Shot | (b) (4) | Trade secret |
| | | (b) (4) |
| Needle Cap - 2nd Injection Shot | | Trade secret |
| | | Trade secret |
| | | (b) (4) |

Abbreviation: (b) (4)
(b) (4)

**Table 3.2.R.2.4-5 Cap Insert Materials**

| Component | Material | CAS# |
|---|---|---|
| Cap Insert | (b) (4) | Trade secret |
| | | (b) (4) |

Abbreviation: (b) (4)

***Reviewer's Note:*** *It is a little odd that some of the component materials CAS numbers are a trade secret. Not sure why the number cannot be disclosed especially in a BLA application. However, ultimately it is the biocompatibility testing reports that are what is critical and ultimately what will be evaluated.*

Test Reports

## Cytotoxicity Testing per ISO 10993-5

### L929 Minimum Essential Medium (MEM) Elution Test

- Extraction liquid: 10% Fetal Bovine Serum supplemented MEM
- Extraction condition: 37°C for 24 hours
- Cell line: Mouse fibroblast (LA929) cell line
- Qualitative evaluation as defined in the standard

### Results

There was no biological reactivity (Grade 0) of the cells exposed to the test article extract. The response obtained from the positive and negative control article extracts confirmed the suitability of the test system.

Based on ISO 10993-5 guidelines, the test article met the requirements of the test and is not considered to have a cytotoxic effect.

## Irritation Test per ISO 10993-10 (Primary Skin Irritation)

- Extraction liquids: 0.9% USP Saline for injection (polar), Cottonseed Oil (non-polar)
- Extraction condition: 50°C for 72 hours

### Results

The USP 0.9% NaCl and Cottonseed Oil (CSO) extracts of the test article were evaluated for their potential to produce Primary Skin Irritation after a single topical 4-hour application to the skin of New Zealand White rabbits. No signs of erythema or edema were noted at any observation period.

Based on ISO 10993-10 guidelines, the test article extracts were considered negligible irritants.

## Sensitization Test per ISO 10993-10 (Kligman [Guinea Pig] Maximization Test)

- Extraction liquids: 0.9% USP Saline for injection (polar), Cottonseed Oil (non-polar)
- Extraction condition: 50°C for 72 hours

### Results

The USP 0.9% NaCl and CSO extracts of the test article elicited no reaction at the challenge (0% sensitization), following an induction phase. Therefore, as defined by the scoring system of Kligman, this is a Grade I reaction and the test article is classified as having weak allergenic potential.

Based on the ISO 10993-10 guidelines, a Grade 0 sensitization rate is not considered significant and the test article meets the requirements of the ISO 10993-10.

Autoinjection Verification Testing

Verification testing was conducted according to ISO 11608-1. Results of testing are as follows:

**Table 3.2.R.2.3.1-2 Testing Conditions and Number of Prefilled Syringes Tested**

| Condition | Temperature | Humidity (%) | Exposure (hours) | Number of PFS |
|---|---|---|---|---|
| Standard Atmosphere | 23°C ± 5°C | 50 ± 25 | 4 | 60 |
| Cool Atmosphere | 5°C ± 3°C | N/A | 4 | 60 |
| Warm Atmosphere | 40°C ± 2°C | 50 ± 10 | 4 | 60 |
| Dry Heat / Cold Storage[1] | 5°C ± 3°C | N/A | 96 | 60 |
| Free Fall | N/A | N/A | N/A | 21 |
| Vibration | N/A | N/A | N/A | 20 |

Abbreviations: IFU = Instructions for Use; ISO = International Organization for Standardization; N/A = not applicable; NIS = needle-based injection system; PFS = prefilled syringe.

[1] For NIS containing manufacturer filled, integrated, non-replaceable containers, ISO 11608-1:2012 requires the system to be subjected to preconditioning at the acceptable high and low storage conditions that are stated in the IFU. For the galcanezumab prefilled syringe, the storage conditions stated on the carton are 2°C to 8°C.

**Table 3.2.R.2.3.1-3 Dose Accuracy Testing Results**

| Test Condition | Specification Limits (mL) | Sample Size | Mean $\bar{X}$ (mL) | SD σ (mL) | Tolerance Interval $\bar{X}$±Target k*σ | Test Result (Pass/Fail) |
|---|---|---|---|---|---|---|
| Standard Atmosphere | (b) (4) | 60 | 1.061 | 0.005 | 1.05-1.07 | Pass |
| Cool Atmosphere | | 60 | 1.060 | 0.003 | 1.05-1.07 | Pass |
| Warm Atmosphere | | 60 | 1.045 | 0.005 | 1.03-1.06 | Pass |
| Dry Heat/Cold Storage | | 60 | 1.053 | 0.005 | 1.04-1.07 | Pass |
| Free Fall | | 21 | 1.059 | 0.003 | 1.05-1.07 | Pass |
| Vibration | | 20 | 1.055 | 0.005 | 1.04-1.07 | Pass |

Abbreviation: SD = standard deviation.

**Table 3.2.R.2.4.1-7 Actuation**

| Name | LQL (%) | Sample Size | Target k | Specification | Mean $\bar{X}$ | SD σ | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Base Cap Removal Torque, Twist Off (in-oz) | ≤5.5 | 25 | 2.583 | (b) (4) | 10.540 | 0.781 | 8.5 - 12.6 | Pass |
| Base Cap Removal Force, Straight Pull (lbf) | ≤5.5 | 25 | 2.583 | | 1.946 | 0.185 | 1.47 - 2.42 | Pass |
| Torque to Unlock (in-oz) | ≤5.5 | 25 | 2.583 | | 12.925 | 0.703 | 11.1 - 14.7 | Pass |
| Peak Activation Force (lbf) | ≤5.5 | 25 | 2.583 | | 2.150 | 0.257 | 1.5 - 2.8 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.

**Table 3.2.R.2.4.1-8 Lock Mechanism Integrity**

| Name | LQL (%) | Sample Size | Acceptance Criteria | Maximum Acceptable Number of Non-conforming | Total Non-conforming Devices Observed | Pass/Fail |
|---|---|---|---|---|---|---|
| Lock Security | ≤5.5 | 70 | Accept: (b) (4)<br>Reject: | 0 | 0 | Pass |
| Locked Device Integrity | ≤5.5 | 70 | Accept:<br>Reject: | 0 | 0 | Pass |

Abbreviation: LQL = limiting quality level.

**Table 3.2.R.2.4.1-9 Exposed Needle Length**

| Name | LQL (%) | Sample Size | Target k | Specification Limits (in) | Mean $\bar{X}$ (in) | SD σ (in) | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass /Fail |
|---|---|---|---|---|---|---|---|---|
| Exposed Needle Length | ≤3.5 | 25 | 2.837 | (b) (4) | 0.224 | 0.003 | 0.216 - 0.233 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.
[1] Specification in inches corresponds to design specification (b) (4) mm.

**Table 3.2.R.2.4.1-10 Needle Damage**

| Name | LQL (%) | Sample Size | Acceptance Criteria | Maximum Acceptable Number of Non-conforming | Total Non-conforming Devices Observed | Pass/Fail |
|---|---|---|---|---|---|---|
| Needle Shielding Before Injection Cycle | ≤3.5 | 90 | Accept: (b) (4)<br>Reject: | 1 | 0 | Pass |
| Base Cap Removal | ≤5.5 | 90 | Accept:<br>Reject: | 2 | 0 | Pass |

Abbreviation: LQL = limiting quality level.

**Table 3.2.R.2.4.1-11 Dose Delivery**

| Name | LQL (%) | Sample Size | Target k | Specification Limits (mL) | Mean $\bar{X}$ (mL) | SD σ (mL) | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Delivery Amount | ≤3.5 | 25 | 2.837 | (b) (4) | 1.053 | 0.003 | 1.04 - 1.06 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.

**Table 3.2.R.2.4.1-12 Injection of the Medicinal Product**

| Name | LQL (%) | Sample Size | Target k | Specification Limits (mL) | Mean $\bar{X}$ (mL) | SD σ (mL) | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Cool Atmosphere Delivery Amount | 2.5 | 60 | 2.670 | (b) (4) | 1.054 | 0.003 | 1.05 - 1.06 | Pass |
| Warm Atmosphere Delivery Amount | 2.5 | 60 | 2.670 | | 1.046 | 0.004 | 1.04 - 1.06 | Pass |
| Standard Atmosphere Delivery Amount | 2.5 | 60 | 2.670 | | 1.049 | 0.004 | 1.04 - 1.06 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.

**Table 3.2.R.2.4.1-13 Needle Shielding**

| Name | LQL (%) | Sample Size | Acceptance Criteria | Maximum Acceptable Number of Non-conforming | Total Non-conforming Devices Observed | Pass/Fail |
|---|---|---|---|---|---|---|
| Needle Shielding after Injection Cycle | ≤3.5 | 90 | Accept: (b) (4)<br>Reject: | 1 | 0 | Pass |

Abbreviation: LQL = limiting quality level.

**Table 3.2.R.2.4.1-14 Needle Retraction Position**

| Name | LQL (%) | Sample Size | Target k | Acceptance Criteria (mm) | Mean $\bar{X}$ (mm) | SD σ (mm) | One sided Tolerance Bound, $\bar{X}$ - Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Retraction Position[1] | ≤5 | 25 | 2.638 | (b) (4) | 7.685 | 0.163 | 7 | Pass |

Abbreviation: LQL = limiting quality level; SD = standard deviation.
[1] Data from approved autoinjector testing.

**Table 3.2.R.2.4.1-15 Disabling Autoinjector after Retraction**

| Name | LQL (%) | Sample Size | Acceptance Criteria | Maximum Acceptable Number of Non-conforming | Total Non-conforming Devices Observed | Pass/Fail |
|---|---|---|---|---|---|---|
| Clockwise Torque Override after Retraction | ≤5.5 | 70 | Accept: (b) (4)<br>Reject: | 1 | 0 | Pass |
| Counter Clockwise Torque Override after Retraction[1] | ≤10 | 32 | Accept:<br>Reject: | 0 | 0 | Pass |

Abbreviation: LQL = limiting quality level.
[1] Data from approved autoinjector testing.

Injection Time:

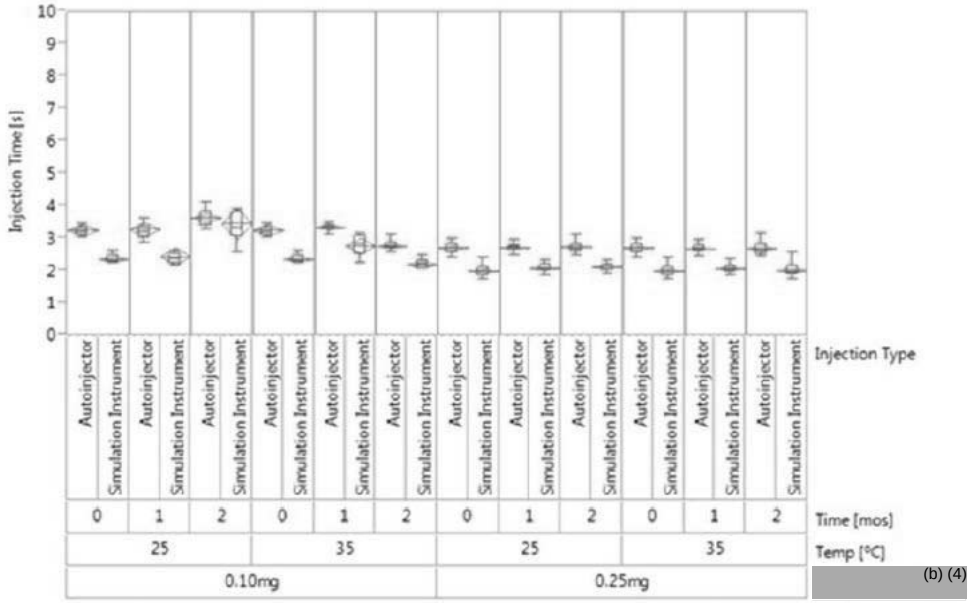



**Figure 3.2.P.2.4.1.4-1 Comparison of Autoinjector Simulation Instrument and Autoinjector Injection Time Results**

**Table Q2-1 Actuation**

| Name | LQL (%) | Sample Size | Target k | Specification | Mean $\bar{X}$ | SD σ | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Peak Activation Force (lbf) | ≤5.5 | 25 | 2.583 | (b) (4) | 2.150 | 0.257 | 1.5 - 2.8 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.

**Table Q2-2 Design Verification Results for Injection Process Time**

| Name | LQL (%) | Sample Size | Target k | Specification | Mean $\bar{X}$ | SD σ | One-Sided Tolerance Bound, $\bar{X}$ + Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Injection Process Time Maximum (Seconds) | ≤3.5 | 25 | 2.502 | (b) (4) | 3.93 | 0.30 | 4.7 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.

**Table Q2-3 Exposed Needle Length**

| Name | LQL (%) | Sample Size | Target k | Specification Limits | Mean $\bar{X}$ | SD σ | Tolerance Interval $\bar{X}$ ± Target k*σ | Pass /Fail |
|---|---|---|---|---|---|---|---|---|
| Exposed Needle Length (in) | ≤3.5 | 25 | 2.837 | (b) (4) | 0.224 | 0.003 | 0.216 - 0.233 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.
[a] Specification in inches corresponds to design specification (b) (4) mm.

**Table Q2-4 Needle Retraction Position**

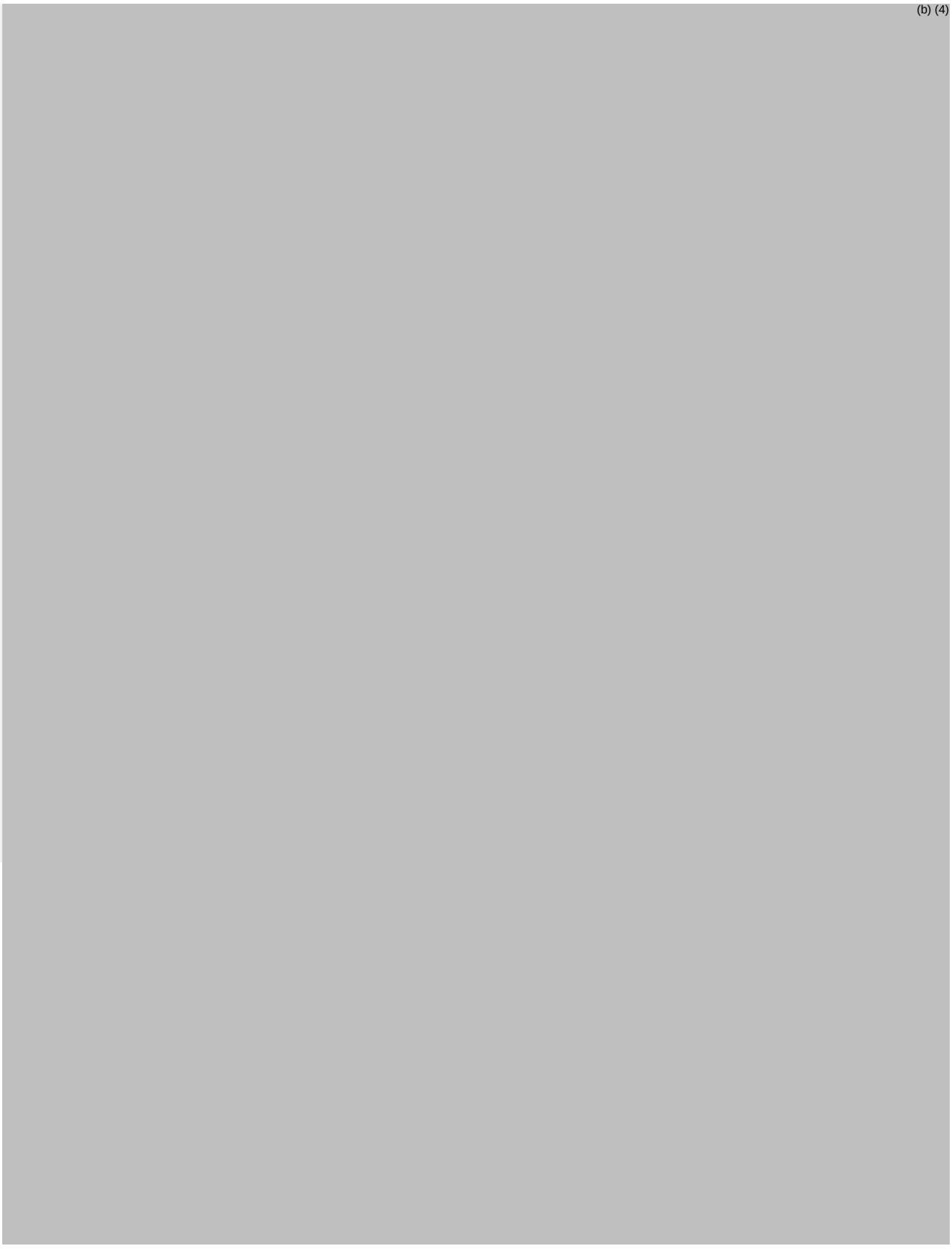
| Name | LQL (%) | Sample Size | Target k | Acceptance Criteria | Mean $\bar{X}$ | SD σ | One-Sided Tolerance Bound, $\bar{X}$ - Target k*σ | Pass/Fail |
|---|---|---|---|---|---|---|---|---|
| Retraction Position (mm)[a] | ≤5 | 25 | 2.638 | (b) (4) | 7.685 | 0.163 | 7 | Pass |

Abbreviations: LQL = limiting quality level; SD = standard deviation.
[a] Data from approved autoinjector testing.

*Reviewer's Note: The sponsor has provided a summary report on the dose accuracy testing for the autoinjector and provided all necessary testing. I have no further questions.*

Biocompatiblilty

The materials of the injection button and base cap are provided in the below tables. These materials represent all the materials used in the exterior components of the device. No plasticizers, additives, crosslinkers, reagents, surfactants, or detergents are used to manufacture the device.


(b) (4)


Testing:

## Cytotoxicity Testing per ISO 10993-5

### L929 Minimum Essential Medium Elution Test

- Extraction liquid: 10% fetal bovine serum supplemented minimum essential medium
- Extraction condition: 37°C for 24 hours
- Cell line: Mouse fibroblast (L929) cell line
- Qualitative evaluation as defined in the standard

### Results

There was no biological reactivity (Grade 0) of the cells exposed to the test article extract. The response obtained from the positive and negative control article extracts confirmed the suitability of the test system.

Based on the criteria of the protocol, a Grade of 0 for the test articles is not considered to have a cytotoxic effect and the ISO 10993-5 guidelines, the test article meets the requirements of ISO 10993-5 guidelines.

## Irritation Test per ISO 10993-10 (Primary Skin Irritation)

- Extraction liquids: 0.9% USP saline for injection (polar), cottonseed oil (CSO, non-polar)
- Extraction condition: 50°C for 72 hours

### Results

The USP 0.9% sodium chloride for injection (NaCl) and CSO extracts of the test article were evaluated for their potential to produce primary skin irritation after a single topical 4-hour application to the skin of New Zealand White rabbits. No signs of erythema or edema were noted at any observation period.

Based on the criteria of the protocol, a score of 0 for skin reactions to the test articles is not considered significant and the test article meets the requirements of ISO 10993-10 guidelines.

## Sensitization Test per ISO 10993-10 (Kligman (Guinea Pig) Maximization Test)

- Extraction liquids: 0.9% USP saline for injection (polar), CSO (non-polar)
- Extraction condition: 50°C for 72 hours

### Results

The USP 0.9% NaCl and CSO extracts of the test article elicited no reaction at the challenge (0% sensitization), following an induction and topical application phase. Therefore, as defined by the scoring system of Kligman, this is a Grade I reaction and the test article is classified as having weak allergenic potential.

Based on the criteria of the protocol, a Grade 0 sensitization score for the test articles is not considered significant and the test article meets the requirements of the ISO 10993-10 guidelines.

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review:

| **Reference Standard / Guidance** | **Description / Extent of FDA Recognition** | **Documentation Adequate** | |
|---|---|---|---|
| | | **Yes** | **No** |
| IEC62366 | Medical devices – Application of usability engineering to medical devices (2007) | X | |
| ISO 14971 | Risk Management | X | |

Shipping Studies:

(b) (4)

(b) (4)


# 7. RISK ANALYSIS

## 7.1. Risk Analysis Attributes

| Risk Analysis Attributes | Yes | No | N/A |
|---|---|---|---|
| Risk analysis conducted on the combination product | X | | |
| Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.) | X | | |
| Mitigations are adequate to reduce risk to health | X | | |
| Version history demonstrates risk management throughout design / development activities | X | | |

User specifications for Pen and Syringe:

**Intended Device Users**

The intended users of the galcanezumab prefilled syringe and pen include patients, caregivers, and healthcare providers.

**Patients**

Patients are individuals 18 years of age or older with a history of migraines. Patients may self-inject, or may receive injections from a caregiver or healthcare professional.

**Caregivers**

Caregivers are individuals 18 years of age or older who administer injections to patients in a non-professional capacity (e.g., parents, spouses, neighbors, teachers).

**Healthcare Providers**

Healthcare providers are individuals 18 years of age or older who are qualified by education, training, certification, or licensure to administer (e.g., nurses, medical assistants), prescribe (e.g., physicians, nurse practitioners, physician assistants), or dispense (e.g., pharmacists) galcanezumab to patients.

**User Capabilities**

Users may have a range of perceptual, cognitive, and physical characteristics which may affect their interactions with the devices:

**Injection Experience**

Patients and caregivers may have a range of previous experience with injecting medications. Some may have no experience with using injection devices (injection-naïve), while others may have more extensive experience, potentially including the use of vial and syringe, prefilled syringes, autoinjectors, or other devices (injection-experienced).

**Education**

The education level of patients and caregivers is expected to reflect that of the general population, and may range from less than high school education to postgraduate or professional degrees.

**Visual Acuity**

Visual acuity in patients and caregivers is expected to reflect that of the general population.

**Hand Functionality**

Hand functionality (strength, dexterity, and range of motion) in patients and caregivers is expected to reflect that of the general population.

***Reviewer's Note:*** *Stated use specifcations are appropriate for these device types.*

## Identified Use Errors and mitigations

**Table 1: Known use problems for the galcanezumab prefilled syringe and pen**

| Use Problem | Mitigations (Prefilled Syringe) | Mitigations (Pen) |
|---|---|---|
| General confusion over how to operate the device | • The device has a standard user interface, to minimize the potential for confusion or errors resulting from negative transfer.<br>• The IFU includes illustrated step-by-step instructions describing the correct use. | • The device was designed to minimize the number of use steps.<br>• The IFU includes illustrated step-by-step instructions describing the correct use. |
| Differentiation errors | • The device and carton afford sufficient visual cues to allow intended users to successfully differentiate the product in the intended use environment.<br>• The IFU contains directions to confirm correct drug before use. | Same as prefilled syringe. |
| Device sharing (Using the same device for multiple patients) | • The device is designed for single use only.<br>• The device label, carton, and IFU include the statement, "One time use only". | • The device is designed to expel the full deliverable volume when the injection button is depressed.<br>• The device label, carton, and IFU include the statement, "One time use only". |
| Using expired drug | • The device label and carton include the expiration date.<br>• The IFU includes instructions to check the expiration date before use. | Same as prefilled syringe. |
| Removing the cap too early (needle clogging) | • The IFU includes instructions to leave the cap on until ready to inject. | Same as prefilled syringe. |
| Needle handling errors | • The device is designed with an integrated needle to eliminate risks associated with attaching and removing needles.<br>• The IFU includes instructions to not put the needle cap back on. | • The device is designed to automatically retract the needle after injection of the drug is complete to reduce the likelihood of contact with the used needle. |
| Using damaged devices | • The device is designed with clear components to allow for inspection before use.<br>• The IFU includes instructions to inspect before use, and to not use if it looks damaged. | Same as prefilled syringe. |

| Use Problem | Mitigations (Prefilled Syringe) | Mitigations (Pen) |
|---|---|---|
| Choking hazard (cap) | • The cap is designed to meet ISO11540:1993 vent area requirements for choking hazards; the IFU includes instructions to throw the cap away after removing it. | Not applicable |
| Air ingress | • The device is designed with a back-stop to prevent plunger removal and the plunger rod is designed to withstand tensile forces of 33N.<br>• The IFU includes illustrated instructions for correct use. | Not applicable |
| Dose splitting errors (not taking all injections to complete a dose) | • The carton is designed so that one carton holds one complete dose.<br>• The IFU includes instructions to take devices from the refrigerator, and to repeat the instructions each time with a new device for each injection. | Same as prefilled syringe. |
| Injection site errors (e.g., wrong injection site, not rotating injection sites). | • The IFU includes illustrated directions for choosing correct injection sites, rotating injection sites, and inserting the needle into the skin. | The IFU includes illustrated directions for choosing correct injection sites, rotating injection sites, and holding the device in place during injection. |
| Injection technique errors | • The IFU includes illustrated directions for performing an injection. | Same as prefilled syringe. |
| Incomplete injection | • The device is designed to allow visibility of full contents of syringe.<br>• The IFU includes illustrated instructions to ensure the complete volume of the syringe is delivered. | • The device is designed to click once when the injection button is pressed, and again when the injection is complete.<br>• The IFU includes illustrated directions to hold the device in place until the second click. |
| Disposal errors | • The device is designed to fit in standard sharps containers.<br>• The IFU includes illustrated instructions for safe disposal after use. | Same as prefilled syringe. |
| General care and storage errors. | • The device contains a cap to protect the medication before use.<br>• The IFU general information section includes information related to recommended care and storage before use. | Same as prefilled syringe. |
| Upside down injection (i.e. injection into thumb) | Not applicable | • The injection button has a shape and a contrasting color which are designed to indicate where the hand is placed during injection. |

***Reviewer's Note:*** *Use errors and mitigations are appropriate for these device types.*

## 7.2. Summary of Risk Analysis

The sponsor has stated that the residual risk for individual failure modes is determined through the FMEA process. The overall residual risk assessment evaluates the cumulative effect of all associated failure modes on patient risk. There were a total of 928 risks identified in the galcanezumab autoinjector FMEAs. In accordance with the risk acceptability criteria of PDS-SOP-PDS4025, 864 of those risks are acceptable based on the severity (SEV) and probability of harm (Prob.). The mitigations of 59 (Sev 3 Prob > 2) risks were evaluated by DQLT to confirm the risks had been reduced as far as possible. Five risks (yellow items in Table 2) were identified and required rationale for risk acceptability and DQLT approval. All risks have been presented to DQLT, and have been accepted without requiring further mitigation. There are no residual risks that fall in the unacceptable (red) zone (Table 2).

**Table 1 - Residual Risk Summary Table**

| Where Identified | Number of Acceptable Residual Risks | Number of Residual Risks requiring mitigation evaluation (Sev 3 Prob ≥2) | Number of Residual Risks Requiring Justification | Number of Unacceptable Residual Risks |
|---|---|---|---|---|
| AFMEA | 156 | 18 | 5 | 0 |
| DFMEA | 244 | 3 | 0 | 0 |
| R0 PFMEA | 89 | 19 | 0 | 0 |
| DS-BL PFMEA | 35 | 0 | 0 | 0 |
| DS-D PFMEA | 62 | 5 | 0 | 0 |
| DS-R PFMEA | 278 | 14 | 0 | 0 |
| TOTAL | 864 | 59 | 5 | 0 |

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**User Capabilities**

Users may have a range of perceptual, cognitive, and physical characteristics which may affect their interactions with the devices:

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***Reviewer's Note:*** *Use errors and mitigations are appropriate for these device types.*

**Table 2 - Risk Acceptability Criteria Matrix**

| Probability of Harm | | | Negligible (SEV 1) (67) | Minor (SEV 2) (482) | Moderate (SEV 3) (157) | Major (SEV 4) (221) | Severe (SEV 5) (1) |
|---|---|---|---|---|---|---|---|
| | Frequent (Prob. 5) | AFMEA | 0 | 0 | 0 | 0 | 0 |
| | | DFMEA | | | | | |
| | | All PFMEAs | | | | | |
| | Probable (Prob. 4) | AFMEA | 0 | 4 | 0 | 0 | 0 |
| | | DFMEA | 0 | 0 | | | |
| | | R0 PFMEA | 0 | 0 | | | |
| | | DS-BL PFMEA | 0 | 0 | | | |
| | | DS-D PFMEA | 0 | 0 | | | |
| | | DS-R PFMEA | 0 | 0 | | | |
| | Occasional (Prob. 3) | AFMEA | 1 | 49 | 0 | 0 | 0 |
| | | DFMEA | 52 | 84 | 0 | | |
| | | R0 PFMEA | 0 | 2 | 0 | | |
| | | DS-BL PFMEA | 0 | 0 | 0 | | |
| | | DS-D PFMEA | 0 | 0 | 0 | | |
| | | DS-R PFMEA | 3 | 0 | 0 | | |
| | Remote (Prob. 2) | AFMEA | 4 | 79 | 18 | | 0 |
| | | DFMEA | 3 | 45 | 3 | 0 | |
| | | R0 PFMEA | 0 | 44 | 19 | 0 | |
| | | DS-BL PFMEA | 0 | 0 | 0 | 0 | |
| | | DS-D PFMEA | 0 | 17 | 5 | 0 | |
| | | DS-R PFMEA | 2 | 14 | 14 | 0 | |
| | Improbable (Prob. 1) | AFMEA | 0 | 4 | 0 | 23 | 1 |
| | | DFMEA | 0 | 6 | 0 | 54 | 0 |
| | | R0 PFMEA | 0 | 10 | 1 | 32 | 0 |
| | | DS-BL PFMEA | 0 | 13 | 11 | 11 | 0 |
| | | DS-D PFMEA | 0 | 30 | 7 | 8 | 0 |
| | | DS-R PFMEA | 2 | 85 | 79 | 93 | 0 |
| | | | Severity of Harm | | | | |

**Table 4** – Occurrence Rates of Key Hazardous Situations

| ID | FDA Hazardous Situation | Occurrence Rate | FTA Events (R/C #) |
|---|---|---|---|
| 1 | Delivery Error – Device Fluid Path Occlusion | 0.00417% | 11, 12, 13 |
| 2 | Delivery Error – Incomplete Drug Delivery | 0.29235% | 105, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 |
| 3 | Delivery Error – Unexpected Separation of Components | 0.00004% | 34, 35, 54, 56 |
| 4 | Delivery Error – Component Failure | 0.19673% | 14, 15, 16, 17, 18, 19, 32, 33, 38, 39, 40, 41, 42, 43, 53, 55, 59 |
| 5 | Delivery Error – Device Insufficiently Sealed to Environment | 0.00513% | 3, 100 |
| 6 | Delivery Error - Incorrect Device Preparation | 0.01271% | 7, 8, 9, 104 |
| 7 | Delivery Error – Insufficient / Inadequate Device Activation | 0.02567% | 20, 28 |
| 8 | Delivery Error – Injection Initiates Prior to Needle Reaching the Correct Tissue Depth of Penetration | 0.09621% | 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75 |
| 9 | Delivery Error - Incorrect Selection of Device | 0.00017% | 36, 37 |
| 10 | Delivery Error - Incorrect Injection Site | 0.00421% | 51, 52 |
| 11 | Delivery Error - Improper Shipping/Storage | 0.01671% | 19, 43 |
| 12 | Contamination - Device Insufficiently Sterile | 0.00543% | 1, 2, 3, 4, 10, 100 |
| 13 | Contamination - Inappropriate Storage | 0.04592% | 1, 5 |
| 14 | Contamination - Device Insufficiently Sealed to Environment | 0.00513% | 3, 100 |
| 15 | Contamination - Inappropriate or Insufficient Connection | 0.01721% | 3, 104 |
| 16 | Contamination - Incorrect Device Assembly/Preparation | 0.00021% | 2 |
| 17 | Contamination – Device Reuse | 0.00000% | 10 |
| 18 | Contamination - Failure to Use Aseptic Technique | 0.00000% | 7, 8, 9 |
| 19 | Contamination - Failure to Correctly Dispose of Device | 0.00000% | 6 |
| 20 | Trauma – Device Body Breakage | 0.04233% | 76, 77, 78, 79 |
| 21 | Trauma – Needle Fracture / Remains Embedded in Subcutaneous Tissue | 0.00000% | 80, 81, 82, 83 |
| 22 | Trauma - Device Exterior Surface Contains Sharp Edges | 0.06674% | 101 |
| 23 | Trauma - Insufficient Assembly/Preparation | 0.01965% | 76, 80, 103, 88, 90, 95, 97 |
| 24 | Trauma - Inadequate Disposal | 0.00000% | 6 |
| 25 | Trauma - Insufficient Activation | 0.00000% | 85, 86, 93 |
| 26 | Trauma – Unexpected Separation of Components | 0.03512% | 85, 102, 103 |
| 27 | Particulate Emboli - Particulate related from device. Device material present within injectable | 0.00450% | 3 |
| 28 | Particulate Emboli - Incorrect Device Assembly/Preparation | 0.00021% | 2 |
| 29 | Needle Stick | 0.04073% | 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 102, 103 |

Critical Tasks:

The critical tasks for the galcanezumab prefilled syringe are [1] uncap the device, [2] insert the needle into the injection site, and [3] inject the dose. The critical tasks for the galcanezumab pen are [1] uncap the device, [2] place the device at the injection site, [3] unlock the device, and [4] press and hold the injection button for 10 seconds.

Residual Risks that were followed up:

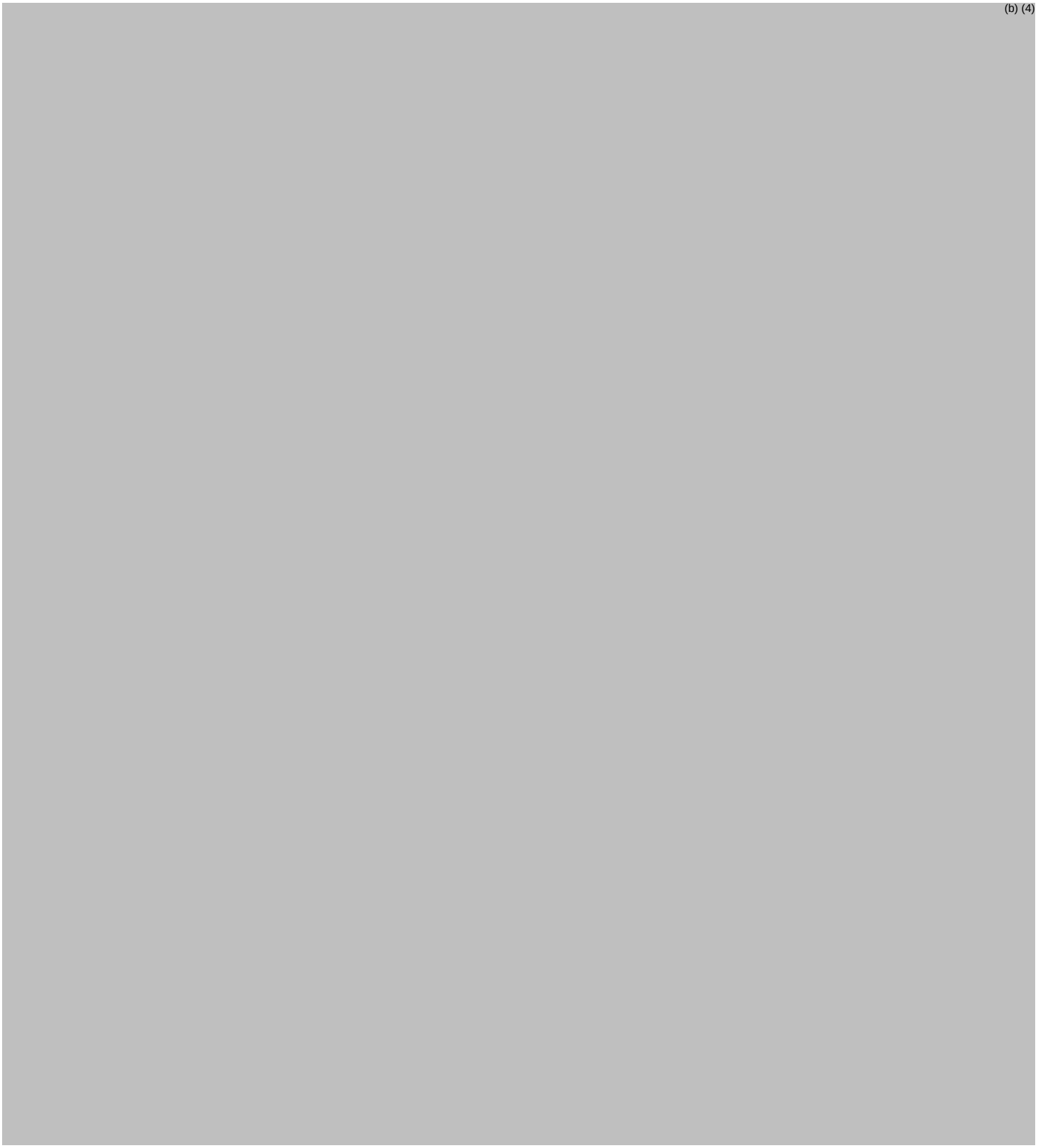
- Package deliberately contaiminated or adulterated
- Device operator reattaches base cap prior to dosing
- Device operator removes device while dosing
- Device operator injects before warming
- Needle stick due to error

***Reviewer's Note:*** *The sponsor has identified the critical task and medical risk from the residual risk with the use of the device include underdosing, overdosing, contamination, laceration, intramuscular/intravenous injection, injection of expired drug. The sponsor has provided rationale that adequately addresses these medical risks.*

## 8. LABELING

(b) (4)

(b) (4)



***Reviewer's Note:*** *Box labeling and insturctions for use are present within the application and appear appropriate for this device type.*

# 9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

Pre-filled syringe:

| Batch Number | | C620740C | C618103C | C618103D | C672272E | C672271D | C672270G |
|---|---|---|---|---|---|---|---|
| **Analytical Property** | **Acceptance Criteria** | **Results** | | | | | |
| **Purity Tests (continued)** | | | | | | | |
| Reduced Purity (Reduced CE-SDS) | NLT (b) (4)% | 98.6 | 98.5 | 98.7 | 98.7 | 98.6 | 98.6 |
| Non-Reduced Purity (Non-Reduced CE-SDS) | NLT %| 97.9 | 97.8 | 98.0 | 97.8 | 97.8 | 97.8 |
| **Other Tests** | | | | | | | |
| Description (Visual) | Clear to opalescent, colorless to slightly yellow to slightly brown solution, free of visible particles | Pass | Pass | Pass | Pass | Pass | Pass |
| Color (Ph. Eur. 2.2.2) | Not more than Color Standard (b) (4) | Pass | Pass | Pass | Pass | Pass | Pass |
| Clarity (Ph. Eur. 2.2.1) (instrumentation) | Not more than (b) (4) NTU (Less than the standard of opalescence) | 29.0 | 28.7 | 28.9 | 28.8 | 28.8 | 28.4 |
| Charge Heterogeneity Main Peak (CEX) | NLT (b) (4)% | 60.4 | 60.3 | 60.3 | 57.5 | 56.7 | 55.9 |
| Charge Heterogeneity Total Acidic Variants (CEX) | NMT %| 19.4 | 19.2 | 19.2 | 17.4 | 17.7 | 17.9 |
| Charge Heterogeneity Total Basic Variants (CEX) | NMT %| 20.2 | 20.5 | 20.5 | 25.1 | 25.6 | 26.2 |
| Particulate Matter ≥10 µm (light obscuration) (USP <788>, Ph. Eur. 2.9.19) | Meets pharmacopoeial requirements (NMT (b) (4) particles/container) | 8 | 9 | 15 | 13 | 17 | 21 |
| Particulate Matter ≥25 µm (light obscuration) (USP <788>, Ph. Eur. 2.9.19) | Meets pharmacopoeial requirements (NMT (b) (4) particles/container) | 0 | 0 | 0 | 0 | 0 | 0 |
| Break loose force | Not more than (b) (4) | 3.2 | 2.9 | 3.4 | 3.1 | 3.1 | 3.4 |

| Batch Number | | C620740C | C618103C | C618103D | C672272E | C672271D | C672270G |
|---|---|---|---|---|---|---|---|
| **Analytical Property** | **Acceptance Criteria** | **Results** | | | | | |
| **Device Tests** | | | | | | | |
| Dose Accuracy (Volume by Weight) | Not less than (b) (4) mL and not more than (b) (4) mL | 1.05 | 1.05 | 1.05 | 1.05 | 1.05 | 1.05 |
| Visual Inspection (visual) | Pass | Pass | Pass | Pass | Pass | Pass | Pass |

Abbreviations: CE-SDS = capillary electrophoresis-sodium dodecyl sulfate; CEX = cation exchange chromatography; NLT = not less than; NMT= not more than; NTU = nephelometric turbidity unit; SEC = size-exclusion chromatography; UV = ultraviolet.

Autoinjector:

| Batch Number | | C620740F | C620740E | C618103F | C672272C | C672271C | C672270E |
|---|---|---|---|---|---|---|---|
| **Analytical Property** | **Acceptance Criteria** | **Results** | | | | | |
| **Device Tests** | | | | | | | |
| Dose Accuracy (Volume by Weight) | Not less than (b) (4) mL and not more than (b) (4) mL | 1.05 | 1.05 | 1.05 | 1.05 | 1.05 | 1.05 |
| Injection Process Time (Activation to retraction timing) | Less than or equal to (b) (4) seconds | 4.0 | 3.9 | 4.6 | 4.4 | 4.3 | 4.6 |
| Visual Inspection (visual) | Pass | Pass | Pass | Pass | Pass | Pass | Pass |

Abbreviations: CE-SDS = capillary electrophoresis-sodium dodecyl sulfate; CEX = cation exchange chromatography; NLT = not less than; NMT= not more than; NTU = nephelometric turbidity unit; SEC = size-exclusion chromatography; UV = ultraviolet.

***Reviewer's Note:*** (b) (4)

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**Reviewer Comments: The sponsor has adequately addressed our questions that were raised interactively. I have no further questions.**

## 11.OUTSTANDING DEFICIENCIES

None

## 12.RECOMMENDATION

Approval

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

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/s/

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EMILIOS A PAPANASTASIOU
05/17/2018

**MEMORANDUM**

**NONPROPRIETARY NAME SUFFIX**

Division of Medication Error Prevention and Analysis (DMEPA)
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:** | February 16, 2018 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | BLA 761063 |
| **Product Name and Strength:** | Emgality (galcanezumab) injection<br>120 mg/mL |
| **Product Type:** | Single ingredient, combination product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Eli Lilly and Company |
| **Submission Date:** | September 26, 2017 |
| **OSE RCM #:** | 2017-2515 |
| **DMEPA Primary Reviewer:** | Chad Morris, PharmD, MPH |
| **OMEPRM Deputy Director:** | Lubna Merchant, MS, PharmD |

## 1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the suffixes proposed by Eli Lilly for the nonproprietary name and communicates our recommendation for the nonproprietary name.

## 2 ASSESSMENT OF THE NONPROPRIETARY NAME

On September 26, 2017, Eli Lilly submitted a list of ten suffixes, in order of preference, to be used in the nonproprietary name of their product. The suffixes were evaluated against the principles described in the applicable guidance[a]. We conducted an evaluation of the suffix candidates in the order of preference listed by the Sponsor.

**1. galcanezumab** (b) (4)

We note that the first proposed suffix, (b) (4)

Additionally, (b) (4) FDA finds that this proposed suffix, – (b) (4) is not devoid of meaning and inconsistent with the principles described in our final guidance.

There are several look-alike sound-alike medications that increase the risk for medication errors and numerous live trademarks contain the proposed suffix as a distinct word. The proposed suffix, (b) (4) In the study of HCPs submitted in support of this suffix, we note that 12.5% of study participants interpreted prescriptions or medication orders for "galcanezumab (b) (4) as " (b) (4) which indicates there is some potential for this suffix to be used and interpreted as an entity apart from the core name, notwithstanding the attachment by a hyphen. We also note that (b) (4) have a POCA score of 56% (73% orthographic) and that (b) (4) have a POCA score of 69% (82% orthographic). This suggests that there is moderate to strong similarity between this proposed suffix and the proprietary names of these currently marketed drugs.

Moreover, there are overlapping product characteristics between these products. (b) (4) Galcanezumab-xxxx is proposed to be available as a single strength injection for subcutaneous administration. The product is proposed to be used as a single bolus dose (2 syringes or 2 mL) followed by once monthly (1 syringe or 1 mL) administration. Alternatively, (b) (4)

[a] See Section VI in Guidance for Industry:
Nonproprietary Naming of Biological Products. 2017. Available from

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

Collectively, the data and information we reviewed, suggests that this proposed suffix could be confused with the names (b) (4) and result in medication errors in clinical practice.

FDA finds that this suffix is meaningful (b) (4) Additionally, the proposed suffix, (b) (4) . Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**2. galcanezumab** (b) (4)

We note that the second proposed suffix, (b) (4)

(b) (4)

(b) (4)

FDA finds that this suffix is meaningful (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**3. galcanezumab-** (b) (4)

We note that the third proposed suffix, (b) (4)

FDA finds that this suffix is meaningful (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**4. galcanezumab** (b) (4)

(b) (4)

FDA finds that this suffix is meaningful (b) (4) Thus, we find this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**5. galcanezumab-gnlm**

Eli Lilly's fifth proposed suffix, -gnlm, is comprised of three distinct letters, is not too like any other products' suffix designation, does not look like the names of other currently marketed products, is devoid of meaning, and does not make any misrepresentations with respect to the safety or efficacy of this product.

These findings were shared with the TBBS, ORP, and OPDP. In email correspondence dated January 29, 2018, the workgroup concurred with DMEPA's assessment and conclusion.

## 3 CONCLUSION

FDA conducted an evaluation of Eli Lilly's proposed suffixes, [redacted] (b) (4) and identified concerns that render the suffixes non-viable.

We find that Eli Lilly's proposed suffix, -gnlm, is acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to galcanezumab-gnlm.

### 3.1 COMMENTS FOR THE APPLICANT

We find the nonproprietary name, galcanezumab-gnlm, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, galcanezumab-gnlm will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a Complete Response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your proposal unacceptable upon our re-evaluation, we will inform you of our finding.

We also note that the first five proposed suffix candidates are unacceptable for the following reasons:

**galcanezumab** [redacted] (b) (4)

FDA finds that this suffix is meaningful [redacted] (b) (4) . Additionally, the proposed suffix, [redacted] (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**galcanezumab** [redacted] (b) (4)

FDA finds that this suffix is meaningful [redacted] (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**galcanezumab** [redacted] (b) (4)

FDA finds that this suffix is meaningful [redacted] (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

**galcanezumab** [redacted] (b) (4)

FDA finds that this suffix is meaningful [redacted] (b) (4) Thus, we find that

this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

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/s/

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JOHN C MORRIS
02/16/2018

LUBNA A MERCHANT
02/19/2018

**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**

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DATE: 12/21/2017

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: BLA 761063

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

## Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI), in addition, (b) (4) is permanently closed.

Inspection Sites

| Facility Type | Facility Name | Facility Address |
|---|---|---|
| Clinical | (b) (4) | |
| Clinical | | |

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/s/

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SHILA S NKAH
12/22/2017