# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761119Orig1s000

# OTHER REVIEW(S)

**MEMORANDUM**

**DEPARTMENT OF HEALTH & HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**

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**Division of Neurology Products (HFD-120)**
**Center for Drug Evaluation and Research**

Date: February 18, 2020

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: BLA 761119 (Vyepti, eptinezumab, ALD-430)

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BLA 761119 was submitted by Lundbeck Seattle BioPharmaceuticals, Inc. on February 21, 2019, to support marketing approval of eptinezumab, a calcitonin gene-related peptide (CGRP) receptor antagonist, for the "preventive treatment of migraine in adults." Clinical development of eptinezumab for the proposed indication was conducted by Lundbeck under IND 114647.

Nonclinical studies submitted to the BLA include pharmacology (primary, secondary) and general toxicology (acute IV in rat and monkey; 28-day IV in rat and monkey; 6-month IV in monkey) studies and a standard battery of reproductive and developmental toxicology studies (rat and rabbit). (A chronic toxicity study in a second species (rat) and rodent carcinogenicity studies were not required, primarily because of data demonstrating development of anti-drug antibodies in rat that precluded conduct of meaningful long-term studies.) These studies were reviewed by Dr. Siarey (Pharmacology/Toxicology NDA Review and Evaluation, BLA 761119, Richard Siarey, Ph.D., February 10, 2020). (Dr. Siarey's review references those conducted by Drs. D. Charles Thompson and Edmond Nesti under IND 114647.) Based on the review, Dr. Siarey concludes the nonclinical data are adequate and support approval of the BLA.

Pharmacology

Eptinezumab is a humanized monoclonal $IgG_1$ antibody that targets both α- and β-CGRP. In vitro binding and functional assays demonstrated pharmacological activity in human, rat, rabbit, and cynomolgus monkey. (In vitro binding data were not provided for monkey because of identical amino acid sequences in human and monkey for both CGRP isoforms.)

| SPECIES | BINDING ($K_D$, nM) | | cAMP ACCUMULATION ($EC_{50}$, nM) | |
|---|---|---|---|---|
| | α-CGRP | β-CGRP | α-CGRP | β-CGRP |
| human | 0.015 | 0.057 | 1.43 | 0.91 |
| rat | 0.170 | 0.0084 | 0.55 | 1.05 |
| rabbit | 1.50 | 0.250 | 0.12 | 0.06 |

Eptinezumab demonstrated no cross-reactivity to other members of the gene family (adrenomedullin, adrenomedullin2/intermedin, amylin, or calcitonin).

Safety pharmacology and PK/TK analyses were incorporated into general toxicology studies.

Toxicology

Non-GLP acute IV toxicity studies were conducted in Sprague-Dawley rat (0, 10, 30, and 100 mg/kg) and cynomolgus monkey (0, 5, 10, 30, and 100 mg/kg). No toxicity was observed in either species.

Pivotal (GLP) toxicity studies were conducted in the same species/strain. In rat, only a 28-day IV toxicity study was conducted. Doses of 0, 10, 30, and 100 mg/kg Q2W produced no toxicity; plasma exposures at the high dose were 3429 µg/mL and 272050 µg*hr/mL for $C_{max}$ and $AUC_{(0\text{-}7d)}$, respectively. In monkey, eptinezumab was tested in 28-day (0, 10, 30, and 100 mg/kg IV Q2W) and 6-month (0, 20, 50, and 150 mg/kg Q2W) studies. No product-related toxicity was evident in the 28-day study. In the 6-month study, death of one low-dose female was attributed to AND-mediated anaphylaxis, which was not considered relevant to human. Plasma exposures at the highest doses tested were 4623 µg/mL and 445733 µg*hr/mL for $C_{max}$ and $AUC_{(0\text{-}7d)}$, respectively, in the 28-day study and 12900 µg/mL and 1290000 µg*hr/mL for $C_{max}$ and $AUC_{(0\text{-}14d)}$, respectively, in the 6-month study. The exposures achieved in the 6-month study provide an adequate safety margin compared to that achieved in humans at the maximum proposed human dose of 300 mg/day (114 µg/mL and 69630 µg*hr/mL for $C_{max}$ and $AUC_{(0\text{-}t)}$, respectively; sponsor's Summary of Clinical Pharmacology Studies, Study ALD403-CLIN-005).

Reproductive and developmental toxicology

A standard battery of reproductive and developmental toxicology studies was conducted in Sprague-Dawley rat (fertility and early embryonic development, embryofetal development (EFD), and pre- and postnatal development) and New Zealand White rabbit (EFD).

In the fertility study, eptinezumab (0, 75, and 150 mg/kg IV QW) was administered to male and female rats prior to and during mating and continuing in females to gestation day (GD) 3-4. The same doses were used in the EFD and pre- and postnatal studies in rat and in the EFD study in rabbit. In the EFD studies, eptinezumab was administered IV on GDs 6, 12, and 18 in rat and on GDs 7, 13, and 20 in rabbit. In the pre- and postnatal development study in rat, eptinezumab was administered IV on GDs 6, 12, and 18 and LDs 4, 10, 16, and 20. No adverse effects were observed. The higher dose tested (150 mg/kg) was the NOAEL in dams, fetuses, and offspring. Plasma exposure data at 150 mg/kg (collected in the pivotal EFD studies) were limited to mean concentrations at 5 min postdose: 4473 and 4116 µg/mL in rat and rabbit, respectively. Therefore, safety margins for labeling must rely on interspecies comparisons based on dose (mg/kg).

Recommendation

The nonclinical studies conducted by the sponsor are adequate to support approval of the BLA for the proposed indication. To support clinical studies under PREA, the sponsor planned to conduct a juvenile animal toxicology study (Agreed iPSP Agreement letter, December 21, 2018); however, the study report has not been submitted. The study should be completed as a post-marketing requirement.

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LOIS M FREED
02/18/2020 12:24:31 PM

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: | February 13, 2020 |
| Reviewer/Team Leader: | Catherine Callahan, PhD, MA<br>Division of Epidemiology I |
| Deputy Director: | CAPT. Sukhminder K. Sandhu, PhD, MPH, MS<br>Division of Epidemiology I |
| Subject: | ARIA Sufficiency Memo for Pregnancy Safety Concerns |
| Drug Name: | Vyepti (eptinezumab) |
| Application Type/Number: | BLA 761119 |
| Sponsor: | Alder BioPharmaceuticals, Inc. |
| OSE RCM #: | 2019-512 |

## 1. BACKGROUND INFORMATION

### 1.1. Medical Product

Eptinezumab is a calcitonin-gene related peptide antagonist (new molecular entity) with the proposed indication for the preventive treatment of migraine in adults. The recommended dosage is 100 mg administered by intravenous infusion every 3 months. The adverse reactions most frequently reported were nasopharyngitis and hypersensitivity (Table 1).

Table 1: Adverse Reactions Occurring with an Incidence of at Least 2% for VYEPTI and at Least 2% Greater Than Placebo in Studies 1 and 2

| **Adverse Reactions** | **VYEPTI 100 mg (b) (4) (b) (4) N=579 %** | **VYEPTI 300 mg (b) (4) months N=574 %** | **Placebo N=588 %** |
|---|---|---|---|
| Nasopharyngitis | 6 | 8 | 6 |
| Hypersensitivity reactions* | 1 | 2 | 0 |

*Hypersensitivity reactions includes multiple related adverse event terms, such as hypersensitivity, pruritus, and flushing/hot flush that occurred on the day of dosing.
[a]Source: Eptinezumab draft labelling as of February 5, 2020.

### 1.2. Describe the Safety Concern

The Division of Neurology 2 (DN2) requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for broad-based signal detection studies of eptinezumab during pregnancy.

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.[1]

In rat and rabbit studies of administration of eptinezumab at 75 or 150 mg/kg/dose, there were no maternal effects or evidence of embryofetal mortality alterations in growth or structural abnormalities for either species.[1]

There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after eptinezumab exposure and a lack of pregnancy studies generally. Eptinezumab has a low plasma clearance, 0.15 L/d, and protracted terminal-elimination half-life of 27 days, which support a sustained duration of effect and once every 3-months, dosing.[2] In eptinezumab clinical studies, there were 24 pregnancies reported after at least one dose of eptinezumab. Of these, 8 patients delivered normal full-term infants; 1 patient delivered a preterm healthy infant (34 gestational weeks) 5 resulted in elective termination (none for medical reasons); and three in spontaneous

[1] Alder BioPharmaceuticals, Inc. Pharmaceuticals Toxicology Written Summary Eptinezumab (ALD403)
[2] Alder BioPharmaceuticals, Inc.Eptinezumab (ALD403) Clinical Overview

abortion (gestational age of 14 weeks, 4 weeks, and not reported) and 7 were lost to follow-up.[3] Overall, the data on pregnancy exposure during clinical trials are insufficient to inform the risk associated with eptinezumab.

In the proposed labeling, as of February 5, 2020 the Risk Summary in Section 8.1 states:

8.1 Pregnancy

Risk Summary

There are no adequate data on developmental risks associated with the use of VYEPTI in pregnant women.

No adverse developmental effects were observed following administration of eptinezumab-jjmr to pregnant animals at doses greater than those used clinically *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively. The estimated rate of major birth defects (2.2%-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

*Animal Data*

When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats and rabbits by intravenous injection throughout organogenesis, no adverse effects on embryofetal development were observed. The higher dose tested (150 mg/kg) is 30 times the maximum recommended human dose (MRHD) of 300 mg, on a body weight basis (mg/kg).

When eptinezumab-jjmr (0, 75, or 150 mg/kg) was administered weekly to female rats throughout pregnancy and lactation, no adverse effects on pre- and postnatal development were observed. The higher dose tested (150 mg/kg) is 30 times the MRHD, on mg/kg basis.

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 |

[3] Alder BioPharmaceuticals, Inc.Eptinezumab (ALD403) Eptinezumab – Safety Narratives, Case Report Forms, and Subject Profiles

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: alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data or a case control study

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

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

*For any checked boxes above, please describe briefly:*

| |
|---|
| Analytical Tools: 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. |

Because broad-based signal detection is not currently available, other parameters were not assessed.

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

The Division of Neurology 2 requests two PMRs related to pregnancy outcomes. As of February 3, 2020, the proposed PMR language for these are:

PMR-4 A prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Vyepti during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Vyepti 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.

| | |
|---|---|
| Draft Protocol Submission: | May 2020 |
| Final Protocol Submission: | December 2020 |
| Annual Interim Report Submissions: | December 2021 |
| | December 2022 |
| | December 2023 |
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| | December 2025 |
| | December 2026 |
| | December 2027 |
| | December 2028 |
| | December 2029 |
| | December 2030 |
| | December 2031 |
| | December 2032 |
| Study Completion: | December 2033 |
| Final Report Submission: | December 2034 |

PMR-5 A pregnancy outcomes study using a different study design than provided for in PMR-4 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions,

stillbirths, and small-for-gestational-age births in women exposed to Vyepti during pregnancy compared to an unexposed control population.

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|---|---|
| Draft Protocol Submission: | May 2020 |
| Final Protocol Submission: | December 2020 |
| Annual Interim Report Submissions: | December 2021 |
| | December 2022 |
| | December 2023 |
| | December 2024 |
| | December 2025 |
| | December 2026 |
| Study Completion: | December 2027 |
| Final Report Submission: | December 2028 |

## 3. References

1. 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 October 11, 2018.

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CATHERINE L CALLAHAN
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MICHAEL D NGUYEN
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ROBERT BALL
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**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | February 6, 2020 |
| To: | Lana Chen<br>Regulatory Project Manager<br>**Division of Neurology II (DN2)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Aman Sarai, BSN, RN<br>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) |
| Drug Name (established name): | VYEPTI (eptinezumab-jjmr) |
| Dosage Form and Route: | injection, for intravenous use |
| Application Type/Number: | BLA 761119 |
| Applicant: | Lundbeck Seattle BioPharmaceuticals, Inc. |

## 1 INTRODUCTION

On February 21, 2019, Alder BioPharmaceuticals, Inc. submitted for the Agency's review an original Biologics Licence Application (BLA) for VYEPTI (eptinezumab) injection, for intravenous use. On November 1, 2019, Alder BioPharmaceuticals, Inc. was acquired by Lundbeck Seattle BioPharmaceuticals, Inc. VYEPTI (eptinezumab) is a calcitonin gene-related peptide antagonist indicated for the 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 II (DN2) on May 1, 2019 and April 30, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VYEPTI (eptinezumab) injection, for intravenous use.

## 2 MATERIAL REVIEWED

- Draft VYEPTI (eptinezumab) PPI received on February 21, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 21, 2020.
- Draft VYEPTI (eptinezumab) Prescribing Information (PI) received on February 21, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 21, 2020.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level. In our review of the PPI the target reading level is at or below an 8$^{th}$ grade level.

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

In our collaborative review of the PPI we:

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

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The PPI is 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 PPI 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 PPI.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
02/06/2020 03:28:30 PM

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

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

## Memorandum

**Date:** January 30, 2020

**To:** Heather Fitter, M.D.
Division of Neurology II (DN II)

Lana Chen, 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 VYEPTI (eptinezumab-jjmr) injection, for intravenous use

**BLA:** 761119

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In response to the DN II consult request dated April 30, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original BLA submission for VYEPTI (eptinezumab-jjmr) injection, for intravenous use.

**PI and PPI**: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Lana Chen) on January 21, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 25, 2019, 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
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**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: December 18, 2019

TO: Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
(DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: (b) (4)

## 1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of study ALD403-CLIN-014 (BLA 761119) conducted at (b) (4) (b) (4)

We observed objectionable conditions and issued Form FDA 483 at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

### 1.1. Recommendation

Objectionable conditions observed during the inspection impacted reliability of some pharmacokinetic data in the study ((b) (4) #00997061). (b) (4) (b) (4) are not reliable to support a regulatory decision. Additional items were discussed with (b) (4) during the inspection pertaining to the (b) (4) (b) (4) (b) (4) #00997062). However, data from study #00997062 are reliable to support a regulatory decision.

## 2. Inspected Studies

**Study ALD403-CLIN-014 (BLA 761119)**
"A Randomized, Double-Blind, Single-Dose, Parallel Group Phase 1 Comparative Pharmacokinetic Trial to Support the Comparability Evaluation of Manufacturing Sites for Commercial Eptinezumab"

***Study 00997601***: "Quantification of ALD403 in Human K2EDTA Plasma Samples from a Randomized, Double-Blind, Single-Dose, Parallel Group Phase 1 Comparative Pharmacokinetic Trial to Support the Comparability Evaluation of Manufacturing Sites for Commercial Eptinezumab"
Sample Analysis Period: 05/30/2018 – 08/20/2018

***Study 00997062***: "Assessment of Anti-ALD403 Antibodies in Human Serum Samples from a Randomized, Double-Blind, Single-Dose, Parallel Group Phase 1 Comparative Pharmacokinetic Trial to Support the Comparability Evaluation of Manufacturing Sites for Commercial Eptinezumab"
Sample Analysis Period: 07/03/2018 – 08/02/2018

## 3. Scope of Inspection

OSIS pharmacologist Kara A. Scheibner and ORA investigator Jeanne J. Thai, audited the analytical portion of the studies above at [redacted] from [redacted]

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, training records, and sample analysis, including data verification. The inspection also included interviews with the firm's management and staff.

## 4. Inspectional Findings

At the conclusion of the inspection, we observed objectionable conditions and issued Form FDA 483 to [redacted] My evaluation of the Form FDA 483 observations (**Attachment 1**) and the firm's response dated 08/14/2019 (**Attachment 2**) is presented below.

[redacted]

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(b) (4)

(b) (4)

**5. Conclusion**

Based on my review, I conclude that a portion of data from study ALD403-CLIN-014 (BLA 761119) is not reliable to support a regulatory decision. (b) (4)

(b) (4)

study 00997601 are not reliable. Data affected are (b) (4)

(b) (4)

(b) (4) However, the remaining data from study 00997061 and data from study 00997062 are acceptable for regulatory review. Of note, we recommend that the Review Division consider the impact of discussion items 3 and 4 on data in studies 00997601 and 00997602, and in additional ADL403 studies under Agency review.

**Final Classification:**

**VAI**- (b) (4)

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Scheibner
ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: KAS 12/17/2019
Edit: MFS 12/17/2019; JAK 12/18/2019

ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a1c94b
OSIS File #: BE8490

FACTS: (b) (4)

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KARA A SCHEIBNER
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MICHAEL F SKELLY
12/18/2019 04:28:04 PM

JOHN A KADAVIL
12/18/2019 07:01:43 PM

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | 12/17/2019 |
| **From** | Cara Alfaro, Pharm.D., Clinical Analyst<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Lana Chen, Regulatory Project Manager<br>Emily Frelich, M.D., Medical Officer<br>Division of Neurology 2<br>Office of Neuroscience |
| **BLA #** | 761119 |
| **Applicant** | Alder BioPharmaceuticals, Inc. |
| **Drug** | Eptinezumab |
| **NME** | Yes |
| **Proposed Indication** | Preventive treatment of migraine |
| **Consultation Request Date** | 4/10/2019 |
| **Summary Goal Date** | 12/20/2019 |
| **Action Goal Date** | 2/21/2020 |
| **PDUFA Date** | 2/21/2020 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Eldeeb, Khan, and Smith were inspected in support of this NDA and covered Protocols ALD403-CLIN-006 and ALD403-CLIN-011. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

While no significant inspectional findings were noted during these clinical investigator inspections, several observations prompted information requests to the sponsor. At the Eldeeb site, it was noted that approximately 14% of subjects enrolled in one of the studies had been randomized to the incorrect migraine severity stratum. The sponsor indicated that the strata randomization errors could have been due to human error, however, they were unable to confirm this as the root cause. The sponsor has submitted revised datasets with corrected strata randomization.

At the Khan site, a potential unblinding event was identified during the inspection. Based on this inspectional finding, the sponsor was asked to provide a list of all unblinding and potential unblinding events occurring during the conduct of both protocols. The sponsor identified 2 unblinding events involving 6 subjects and 13 potential unblinding events occurring for Protocol ALD403-CLIN-006 and 4 unblinding events involving 6 subjects and 8 potential unblinding events occurring for Protocol ALD403-CLIN-011. These events were reviewed by this reviewer, and, based on the information provided, the sponsor's characterization of the unblinding and potential unblinding events appeared appropriate.

The review division should consider conducting sensitivity analyses using the datasets submitted by the sponsor with randomization to the correct migraine severity stratum. We also recommend that the review division perform a sensitivity analysis excluding the 12 subjects for whom an unblinding event was identified by the sponsor.

## II. BACKGROUND

Eptinezumab injection is a human monoclonal antibody being developed for the preventive treatment of migraine under BLA 761119 (IND 114647). The sponsor has submitted two Phase 3 studies, Protocol ALD403-CLIN-006 (episodic migraine) and Protocol ALD403-CLIN-011 (chronic migraine) to support the efficacy and safety of eptinezumab for the preventive treatment migraine.

Protocol ALD403-CLIN-006

*Title*: "A parallel group, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of ALD403 [eptinezumab] administered intravenously in patients with frequent episodic migraines"

*Subjects*: 888 enrolled subjects

*Sites*: 84 sites; United States (79 sites) and the Republic of Georgia (5 sites)

*Study Initiation and Completion Dates*: 9/30/2015 to 12/14/2017

This was a double-blind, randomized, placebo-controlled, Phase 3 study in subjects with episodic migraines. The study was comprised of 3 phases, Screening Phase, Primary Efficacy/Safety Phase (Weeks 1-24), and Long-Term Safety Phase (Weeks 28-56). During the 28 days following the screening visit, subjects had to experience <14 headache days, of which at least 4 were migraine days as recorded in the e-diary, to be eligible for randomization. Subjects entered data into an electronic diary (e-diary) on a daily basis throughout the study.

Eligible subjects were randomized to one of four treatment groups:

- Eptinezumab 30 mg IV every 3 months
- Eptinezumab 100 mg IV every 3 months
- Eptinezumab 300 mg IV every 3 months
- Placebo IV every 3 months

Randomization was stratified by the number of migraine days (≤9, >9) during the screening period. Investigational product was administered by IV infusion over one hour (± 15 minutes). Subjects were to be monitored for 4 hours after completion of the infusion. Although the duration of the study was 56 weeks, the primary efficacy endpoint was from baseline to Week 12.

The *primary efficacy endpoint* was the mean change from Weeks 1 to 12 in the frequency of migraine days. This endpoint was calculated as the number of migraine days within 4-week

intervals that were then averaged up to Week 12.

Migraine day was defined as:

- lasting 4 to 72 hours
- having at least 2 of the following: unilateral location, pulsating quality, moderate or severe pain, aggravation by or causing avoidance of routine physical activity
- having at least one of the following: nausea and/or vomiting, photophobia and phonophobia

Protocol ALD403-CLIN-011

*Title*: "A parallel group, double-blind, randomized, placebo-controlled Phase 3 trial to evaluate the efficacy and safety of ALD403 [eptinezumab] administered intravenously in patients with chronic migraine"

*Subjects*: 1072 enrolled subjects

*Sites*: 124 sites; United States (66 sites), Eastern Europe (28 sites), Western Europe (26 sites), Middle East/Central Asia (4 sites)

*Study Initiation and Completion Dates*: 11/30/2016 to 4/20/2018

This was a double-blind, randomized, placebo-controlled, Phase 3 study in subjects with chronic migraines. The study was comprised of a Screening Phase, a Double-Blind Treatment Phase (Weeks 1 to 12), and a Follow-Up Phase (Weeks 16 to 32). During the 28 days following the screening visit, subjects had to experience headaches occurring on $\geq$15 to $\leq$26 days of which at least 8 must be migraine days to be eligible for randomization. Subjects entered data into an electronic diary (e-diary) on a daily basis throughout the study.

Eligible subjects were randomized to one of three treatment groups:

- Eptinezumab 100 mg IV on Day 0 and Day 84 (Week 12)
- Eptinezumab 300 mg IV on Day 0 and Day 84 (Week 12)
- Placebo IV on Day 0 and Day 84 (Week 12)

Randomization was stratified by the number of migraine days (<17, >17) during the screening period and prophylactic medication use (yes/no) during the 3 months prior to screening.

The *primary efficacy endpoint* was the mean change from Weeks 1 to 12 in the frequency of migraine days. This endpoint was calculated as the number of migraine days within 4-week intervals that were then averaged up to Week 12.

**Rationale for Site Selection**

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, and prior inspectional history.

## III. RESULTS

**1. Mohammad Eldeeb, M.D.**
500 East Central Avenue
Research Department
Winter Haven, FL 33880

At this site for Protocol ALD403-CLIN-006 (Site #136), 82 subjects were screened, 32 were randomized, and 20 subjects completed the study. Twelve subjects discontinued the study due to the following: loss to follow-up (n = 4), withdrawal of consent (n = 5), and adverse events (n = 3). The discontinuations due to adverse events included Subject (b) (6) randomized to eptinezumab 100 mg, who experienced cholelithiasis; Subject (b) (6) randomized to eptinezumab 30 mg, who experienced an allergic reaction (cough lasting 10 minutes) approximately four minutes into the infusion; and Subject (b) (6) randomized to eptinezumab 30 mg, who experienced the serious adverse event (SAE) stomal hernia. The narrative for this SAE is included in the NDA submission.

At this site for Protocol ALD403-CLIN-011 (Site #411), 64 subjects were screened, 22 were enrolled and randomized, and 19 subjects completed the study. Three subjects discontinued the study due to withdrawal of consent (n = 2) and adverse event (n = 1). The discontinuation due to adverse event occurred in Subject (b) (6) randomized to eptinezumab 300 mg, who experienced worsening headache.

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 (62%) subjects enrolled in Protocol ALD403-CLIN-006 and all subjects enrolled in Protocol ALD403-CLIN-011 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint data, migraine days, were obtained from electronic diaries in which subjects entered data on a daily basis. During the inspection, electronic diary data was available for review via an archival CD of the subjects' e-diary data at the site. These data were verified against sponsor data listings for 20 (62%) subjects enrolled in Protocol ALD403-CLIN-006 and all subjects enrolled in Protocol ALD403-CLIN-01; no discrepancies were identified.

There was no evidence of under-reporting of adverse events. One SAE occurring in Protocol ALD403-CLIN-006, as noted above, occurred at this site and was reported to the IRB and sponsor in the appropriate time frame.

(b) (4) was the CRO responsible for clinical monitoring of both protocols. For Protocol ALD403-CLIN-011, one of the randomization strata was the number of migraine days ($< 17$ or $\geq 17$) during the screening period. A monitoring report reviewed during the inspection noted three subjects who were randomized to the wrong migraine frequency stratum (*see Reviewer's*

*Comments*).

*Reviewer's comment: According to a monitor report, some subjects were randomized to an incorrect stratification of < 17 or ≥ 17 migraines during screening. This information was shared with the review division, and an information request was sent to the sponsor asking them to provide the numbers of subjects randomized to incorrect strata for both studies as well as corrected datasets and identification of the root cause of this error in stratification.*

*The sponsor submitted a response on 10/24/2019. For Protocol ALD403-CLIN-006, the sponsor identified 37/888 (4.2%) subjects who had been randomized to the incorrect migraine frequency stratum (≤9, >9 migraines during screening). For Protocol ALD403-CLIN-011, the sponsor identified 56/1072 (5.2%) subjects who had been randomized to the incorrect migraine frequency stratum (<17, ≥ 17 migraines during screening) and 28/1072 (2.6%) subjects who were randomized to the incorrect prophylactic medication use (yes/no) stratum. The sponsor explained that the clinical investigator selected the stratification levels and entered them into the Interactive Voice Response System (IVRS) on the basis of data collected in the electronic diary. The sponsor indicated that the strata randomization errors could have been due to human error, although they were unable to confirm that as the source of the errors.*

*The sponsor has submitted revised datasets with corrected strata randomization. The review division should consider additional sensitivity analyses using these corrected datasets.*

**2. Arifulla Khan, M.D.**
1951 152nd Place Northeast, Suite 200
Bellevue, WA 98007

At this site for Protocol ALD403-CLIN-006 (Site #157), 52 subjects were screened, 20 were randomized, and 15 subjects completed the study. Five subjects discontinued the study due to withdrawal of consent (n = 4) and adverse event (n = 1). The discontinuation due to adverse event occurred in Subject (b) (6) randomized to eptinezumab 100 mg, who experienced tinnitus.

At this site for Protocol ALD403-CLIN-011 (Site #418), 76 subjects were screened, 43 were randomized, and 41 subjects completed the study. Two subjects discontinued the study due to withdrawal of consent.

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 subjects enrolled in Protocol ALD403-CLIN-006 and 22 (51%) subjects enrolled in Protocol ALD403-CLIN-011 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations and primary efficacy endpoint data.

The primary efficacy endpoint data, migraine days, were obtained from electronic diaries in which subjects entered data on a daily basis. During the inspection, electronic diary data was

available for review via an archival CD of the subjects' e-diary data at the site. These data were verified against sponsor data listings for all subjects enrolled in Protocol ALD403-CLIN-006 and 22 (51%) subjects enrolled in Protocol ALD403-CLIN-011; no discrepancies were identified.

There was no evidence of under-reporting of adverse events. Two SAEs occurred in two subjects enrolled in Protocol ALD403-CLIN-011:

- Nephrolithiasis/hospitalization (Subject (b) (6) placebo)
- Suicide attempt/hospitalization (Subject (b) (6) eptinezumab 300 mg). The suicide attempt occurred approximately 6 weeks after the last IV infusion when the subject was in the follow-up phase (no study drug administration).

Narratives for these SAEs are included in the BLA submission.

During the inspection, Dr. Khan reported one instance of potential unblinding when an unblinded pharmacist accidentally copied Dr. Khan and one other blinded study staff member on an email containing unblinding information. The study coordinator stated Dr. Khan and the study staff member deleted the email before it was read (*see Reviewer Comments*). The FDA field investigator did not provide any further details about this potential unblinding incident, including to which study this event pertained.

*Reviewer comments: Due to the potential unblinding event at this site, an information request was sent to the sponsor asking for a list of all unblinding events and potential unblinding events occurring during both protocols. Of note, the Clinical Study Reports did not contain information on the presence or absence of unblinding events occurring for either study.*

*The sponsor submitted a response on 10/16/2019 identifying 2 unblinding events involving 6 subjects and 13 potential unblinding events occurring for Protocol ALD403-CLIN-006 as well as 4 unblinding events involving 6 subjects and 8 potential unblinding events occurring for Protocol ALD403-CLIN-011. This reviewer reviewed the sponsor's response and found that the sponsor's characterization and classification of the unblinding and potential unblinding events for both protocols appeared appropriate.*

*The most serious unblinding event appeared to be for Protocol ALD403-CLIN-011. This event involved 5 subjects at one site in which unblinding information was inadvertently entered on saline bags given to the blinded staff for infusion. For this event, both blinded staff and blinded subjects could have been unblinded. Since the primary endpoint data, migraines, was derived from subject reported data, unblinding subjects could impact this endpoint.*

*We recommend that the review division perform a sensitivity analysis excluding the 12 subjects for whom an unblinding event was identified by the sponsor. For Protocol ALD403-CLIN-006, unblinding events were noted at two sites involving 6 subjects (Subject #s* (b) (6) (b) (6) *For Protocol ALD403-CLIN-011, unblinding events were noted at four sites involving 6 subjects* (b) (6) (b) (6)

**3. Timothy Smith, M.D.**
3862 Mexico Road
St. Peters, MO 63303

At this site for Protocol ALD403-CLIN-006 (Site #193), 16 subjects were screened, 11 were randomized, and 10 subjects completed the study. One subject discontinued the study due to "loss to follow-up." At this site for Protocol ALD403-CLIN-011 (Site #479), 28 subjects were screened, 19 were randomized, and 19 subjects completed 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 all subjects for Protocol ALD403-CLIN-006 and Protocol ALD403-CLIN-011 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations and primary efficacy endpoint data.

The primary efficacy endpoint data, migraine days, were obtained from electronic diaries in which subjects entered data on a daily basis. During the inspection, electronic diary data was available for review via an archival CD of the subjects' e-diary data at the site. These data were verified against sponsor data listings for all subjects enrolled at the site for Protocol ALD403-CLIN-006 and Protocol ALD403-CLIN-011; no discrepancies were identified.

There was no evidence of under-reporting of adverse events. There were three SAEs reported in Subject (b) (6) who participated in Protocol ALD403-CLIN-006, was randomized to eptinezumab 300 mg, and experienced a benign right breast lump, postsurgical abdominal wound dehiscence secondary to double mastectomy, and skin ischemia of left breast secondary to surgical complication. The SAEs were reported to the IRB and sponsor in the appropriate time frame. The narrative for the SAEs are included in the NDA submission.

Complaint Follow-up
OSI received a complaint in 2017 for this clinical investigator pertaining to IND 114647 (eptinezumab) and referencing Protocols ALD403-CLIN-006, ALD403-CLIN-011. The complainant alleged that Dr. Smith was "rarely" at the site (1 or 2 days/week) and that the nurse practitioners ran the studies. The complainant did not provide details of any tasks that might have been inappropriately delegated. At the time the complaint was received, there were insufficient details to warrant an inspection. However, since this complaint pertained to protocols submitted for this BLA, the complaint was evaluated during this clinical investigator inspection.

According to the Form FDA 1572s submitted by the sponsor, Dr. Smith was the clinical investigator at this site for Protocols ALD403-CLIN-006 and ALD403-CLIN-011. The sponsor identified two different sites where Dr. Smith was a clinical investigator for these protocols, one site located in St. Peters, MO (StudyMetrix Research) and the other in Springfield, MO (Clinvest Research; separate Form FDA 1572s submitted). Subjects were enrolled at both sites for both studies, and these sites are approximately 250 miles apart. For Protocol ALD403-

CLIN-006, 11 subjects were enrolled at the St. Peters site, and one subject was enrolled at the Springfield site. For Protocol ALD403-CLIN-011, 19 subjects were enrolled at the St. Peters site, and 17 subjects were enrolled at the Springfield site.

The inspection did not find any evidence of lack of Dr. Smith's oversight of these studies for either site. Of note, Dr. Smith stated that he had been driving to Springfield weekly for the duration of these studies. He stated that he reviewed laboratory reports and study records for the Springfield site when he was there and tried to schedule subject visits when he was at that site. At the time of this inspection, Dr. Smith was no longer affiliated with the Springfield (Clinvest) site. He is currently only affiliated with the site in St. Peters (StudyMetrix).

*{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}*

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**cc:**

Central Document Room/BLA #761119
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Division of Neurology 2/Medical Team Leader/Heather Fitter
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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

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/s/

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CARA L ALFARO
12/17/2019 01:58:29 PM

PHILLIP D KRONSTEIN
12/17/2019 02:23:08 PM

KASSA AYALEW
12/17/2019 03:13:42 PM

# 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: | November 26, 2019 |
| Requesting Office or Division: | Division of Neurology 2 (DN 2) |
| Application Type and Number: | BLA 761119 |
| Product Name and Strength: | Vyepti (eptinezumab-jjmr) injection, 100 mg/mL |
| Applicant/Sponsor Name: | Lundbeck Seattle BioPharmaceuticals, Inc. (Lundbeck) |
| OSE RCM #: | 2019-514-2 |
| DMEPA Safety Evaluator: | Chad Morris, PharmD, MPH |
| DMEPA Team Leader: | Briana Rider, PharmD, CPPS |

## 1 PURPOSE OF MEMORANDUM

Lundbeck submitted revised container label and carton labeling received on November 25, 2019 for Vyepti. The Division of Neurology 2 (DN 2) requested we review the revised carton labeling and container label for Vyepti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review[a], as well as updates due to transfer of obligation, and our General Advice Letter regarding the non-proprietary name suffix[b].

## 2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations.

[a] Morris, C. Label and Labeling Review MEMO for Vyepti (BLA 761119). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 16. RCM No.: 2019-514-1.
[b] Non-proprietary name suffix General Advice letter available at: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80522582&_afrRedirect=2741838461311009

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 25, 2019

Container label

Carton labeling

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JOHN C MORRIS
11/27/2019 11:44:03 AM

BRIANA B RIDER
11/30/2019 02:02:42 PM

**COA Tracking ID:** C2019111
**BLA Number:** BLA 761119

# CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

| | |
|---|---|
| **COA Tracking ID:** | C2019111 |
| **NDA/BLA Number/Referenced IND**: | BLA 761119 / IND 114647 |
| **Applicant**: | Lundbeck |
| **Established Name/Trade Name**: | Vyepti (eptinezumab) |
| **Indication**: | Preventive treatment of migraine in adults |
| **Meeting Type/Deliverable**: | BLA review |
| **Review Division**: | Division of Neurology Products (DNP) |
| **Clinical Reviewer** | Emily Freilich |
| **Clinical Team Leader (TL)** | Heather Fitter |
| **Review Division Project Manager**: | Lana Chen |
| **COA Reviewer**: | Christopher St. Clair |
| **COA TL**: | Sarrit Kovacs |
| **COA Associate Director**: | Elektra Papadopoulos |
| **Date Consult Request Received:** | April 1, 2019 |
| **Date COA Review Completed**: | November 21, 2019 |

***Please check all that apply:*** ☐Rare Disease/Orphan Designation
☐Pediatric

## A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is in response to a consult request by the Division of Neurology Products (DNP) related to BLA 761119 for eptinezumab. The Applicant has completed phase 3 of their drug development program and has submitted a BLA. The proposed indication is for preventive treatment of migraine in adults.

The Applicant used the patient-reported outcome (PRO) assessments listed in Table 1 in their randomized, double-blind, placebo-controlled phase 3 clinical trial (ALD403-CLIN-011, a.k.a. PROMISE-2) in adults with chronic migraine. During both the investigational new drug (IND) phase and during the BLA review, COA Staff were consulted by DNP (b) (4) (b) (4) (b) (4)

**Table 1.** COAs Included in Study PROMISE-2

| COA Name (COA Type) | Concept(s) | Endpoint Position[1] | Copy of COA |
|---|---|---|---|
| Daily headache e-diary (PRO) | Migraine frequency and severity | Primary | Not submitted by Applicant |
| Patient Global Impression of Change (PGIC; PRO) | Change in migraine symptom severity | Secondary | Appendix A |
| SF-36 v2.0 (PRO) | Health-related quality of life | Secondary | Not applicable |

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

| | | | |
|---|---|---|---|
| EQ-5D-5L (PRO) | Health-related quality of life | Secondary | Not applicable |
| Headache Impact Test-6 (HIT-6; PRO) | Headache severity and impacts | Secondary | Appendix B |

This submission included a briefing package with a study protocol and COA evidence dossier for the HIT-6. (b) (4)

The review concludes that there is no evidence to demonstrate that the (b) (4) (see Table 2). The HIT-6 instructions and items ask only about headaches and do not focus specifically on migraines. Therefore, the HIT-6 does not assess impacts of migraines on functioning, but rather it assesses pain severity of headaches in particular and only the impact of headaches on patients' daily functioning, desire to lie down, feelings of tiredness, irritability, and ability to concentrate. (b) (4)

(b) (4)

Please refer to Section B for detailed comments and additional advice to the Division, as well as Section C2 (b) (4) Summary) for reviewer's comments.

## B. COMMENTS TO THE DIVISION

No COA-related questions were submitted by the Applicant. COA Staff were consulted by DNP (b) (4) (b) (4) In completion of our COA Review, we have the following comments for DNP regarding the HIT-6:

1. HIT-6 instructions and items ask only about headaches and do not focus specifically on migraines. Therefore, the HIT-6 does not assess impacts of migraines on functioning, but rather it assesses pain severity of headaches in particular and only the impact of headaches on patients' daily functioning, desire to lie down, feelings of tiredness, irritability, and ability to concentrate.

(b) (4)

2. The HIT-6 was developed in the general headache population. (b) (4) (b) (4)

3. The impacts of headache that are being assessed by the HIT-6 likely do not sufficiently capture the impact of migraine on patient's functioning. This is further supported by an article by Mannix and colleagues (2016)[3] referenced in the Applicant's HIT-6 dossier submitted under this BLA, which stated the following:

    a. "The HIT-6 was designed to measure impact of headaches; it is not migraine-specific and also did not involve patient input during its development..." (page 8).

    b. With regard to the HIT-6 and two other instruments: "None of these three instruments were designed to capture the impact of migraine on physical functioning and the day-to-day variability of the experience as reported by patients in the concept elicitation research" (page 8).

    c. "Although the existing instruments are useful in establishing the impact of migraine and its treatment on patients' quality of life, the lack of complete coverage of the immediate impacts of migraine, the inability to capture the day-to-day variability of ictal and inter-ictal experiences of migraine patients and the lack of evidence of content validity to meet the FDA guidelines of development of PRO tools demonstrates the need for a new instrument to measure the benefit of prophylactic treatment of migraines" (page 9).

# C. CLINICAL OUTCOME ASSESSMENT REVIEW

## 1 BACKGROUND AND MATERIALS REVIEWED

Previous COA Reviews:

- IND 114647 - Eptinezumab for (b) (4) migraine (b) (4) in adult patients: Type B Pre-BLA Meeting (Susan Pretko; dated April 16, 2019)

Background:

- COA Staff have previously commented on the (b) (4) The Sponsor stated that they would submit additional evidence with their BLA package.

[3] Mannix S, Skalicky A, Buse DC, Desai P, Sapra S, Ortmeier B, Widnell K, Hareendran A. Measuring the impact of migraine for evaluating outcomes of preventive treatments for migraine headaches. Health Qual Life Outcomes. 2016 Oct 6;14(1):143.

- (b) (4)

Other materials reviewed:

- (b) (4)

## 2 (b) (4) SUMMARY

**Table 2.** (b) (4) assessment (based on available evidence)

| COA Name(s) | Attribute sufficiently established[4] | Supported by: | Location of Supporting Materials |
|---|---|---|---|
| HIT-6 | ☐ Yes<br>☐ Potentially - insufficient evidence available; additional information is needed<br>☒ No | ☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment)<br>☐ Evidence of content validity<br>☐ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.)<br>☐ COA well-defined and concept is able to be accurately communicated<br>☐ COA is sensitive to detect change<br>☐ COA is culturally adapted and adequately translated, if appropriate | See reviewer's comments |

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

*The following inconsistencies were found in the BLA 761119 HIT-6 dossier:*

- *The American Headache Society 2018 migraine position statement[5] cited Coeytaux et al. (2006)[6] in reference to their statement saying that "a clinically meaningful improvement in a validated migraine-specific patient-reported outcome measure, including but not limited to:*
  - *A reduction of at least 5 points or more in Migraine Disability Assessment (MIDAS) score for those whose baseline score was between 11 and 20*
  - *A 30% reduction in MIDAS score for those with baseline scores above 20*

[4] See Sections 5 and 6 of this COA review for more detailed information.
[5] American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache. 2019 Jan;59(1):1-18. doi: 10.1111/head.13456. Epub 2018 Dec 10.
[6] Coeytaux RR, Kaufman JS, Chao R, Mann JD, Devellis RF. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. J Clin Epidemiol. 2006 Apr;59(4):374-80.

- *Reduction of 5 or more points on the Migraine Physical Function Impact Diary (MPFID)*
- *Reduction in scores on the 6-item Headache Impact Test (HIT-6) of at least 5 points (Coeytaux et al., 2006)"*

*However, the Coeytaux et al. (2006) paper did not establish that the HIT-6 is a validated migraine-specific PRO measure; the term "migraine" is not mentioned even once throughout the entire manuscript. Rather, Coeytaux et al. (2006) focused on use of the HIT-6 in patients with chronic daily headache.*

- *The HIT-6 dossier stated, "the HIT-6 was developed with clinical relevance to migraine patients in mind. For example, as outlined in Kosinski et al (2003) the development of the HIT-6 specifically included items that were "clinically useful in gauging the severity of migraine" (p. 965)." However, the exact quote from Kosinski et al. (2003)[7] is,*

  > *"The next phase of development consisted of an independent review of the 10 candidate items by a 964 panel of clinicians involved in the treatment of migraine headaches. The panel of clinicians recommended 35 newly developed items to be considered for the short form. Many of these suggested items covered similar content areas as captured by the original 10 candidate items, except that they were worded differently. Some of the suggested items covered content areas not captured by the original 10 candidate items and were regarded as clinically useful in gauging the severity of migraine during a typical physician patient interview."*

  *While some items may have been determined by clinicians to be clinically useful in gauging the severity of migraine, this does not relate to use of the total score to measure impact of migraine on functioning. Kosinski et al. (2003) stated that the HIT-6 was significantly predictive of probability of a migraine diagnosis, but this does not indicate that headache is the sole symptom, or even the most important symptom, that affects functioning in patients with migraine.*

- *The HIT-6 dossier stated: "Mannix et al. (2016) reported that migraine intensity (such as assessed in the HIT-6 pain severity item) had a "direct and immediate impact" on patients' ability to function (pg. 5)." However, Mannix et al. (2016)[3] actually stated, on page 5 of their paper, that "the intensity of the migraine often had a direct and immediate impact on their ability to function during and after the episode." The Mannix*

[7] Kosinski M, Bayliss MS, Bjorner JB, Ware JE Jr, Garber WH, Batenhorst A, Cady R, Dahlöf CG, Dowson A, Tepper S. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003 Dec;12(8):963-74.

*et al. paper concluded that the HIT-6 is not appropriate for measuring impact of migraine:*

- *On page 8, Mannix et al. stated, "the HIT-6 was designed to measure impact of headaches; it is not migraine-specific and also did not involve patient input during its development [41] it aims to collect data on the impact of headaches have on the ability to function on the job, at school, at home and in social situations in the past 4 weeks."*

- *On page 8, Mannix et al. stated, regarding the HIT-6, MIDAS, MSQ, "none of these three instruments were designed to capture the impact of migraine on physical functioning and the day-to-day variability of the experience as reported by patients in the concept elicitation research."*

- *On page 9, Mannix et al. stated, "although the existing instruments are useful in establishing the impact of migraine and its treatment on patients' quality of life, the lack of complete coverage of the immediate impacts of migraine, the inability to capture the day-to-day variability of ictal and inter-ictal experiences of migraine patients and the lack of evidence of content validity to meet the FDA guidelines of development of PRO tools demonstrates the need for a new instrument to measure the benefit of prophylactic treatment of migraines."*

- (b) (4)

# 3 CONTEXT OF USE

## 3.1 Clinical Trial Population

The target population for Study PROMISE-2 were adults (age 18-65 years) who were diagnosed with migraines at ≤ 50 years of age, and had a history of chronic migraine for ≥ 12 months before screening.

A complete list of the inclusion and exclusion criteria is summarized in the clinical trial protocol for PROMISE-2.

## 3.2 Clinical Trial Design

Table 3 describes the clinical trial design of Study PROMISE-2 (Protocol Number: ALD403-CLIN-011).

**Table 3.** Clinical Trial Design for Study PROMISE-2

| Trial Phase | Trial Design | Trial Duration | Registration Intent |
|---|---|---|---|
| Phase 3 | ☐ Single arm<br>☐ Open label<br>☒ Double-blind<br>☒ Randomized<br>☒ Placebo-/Vehicle-controlled<br>☐ Active comparator-controlled<br>☐ Cross-over<br>☒ Multinational<br>☐ Non-inferiority | 32 weeks | Yes |

Refer to the clinical trial protocol for more details on the clinical trial design.

## 3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the HIT-6 in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study PROMISE-2.

**Table 4.** Endpoint Position, Definition, and Assessment Schedule for Study PROMISE-2

| Endpoint Position | Assessment | Concept | Endpoint Definition | Assessment Frequency |
|---|---|---|---|---|
| Primary | Daily headache e-diary (PRO) | Migraine frequency | Change in frequency of migraine days (Weeks 1-12) | ☒ Daily<br>☐ Weekly<br>☐ Monthly<br>☐ Other:<br>☐ Assessment at cross-over or early discontinuation |
| Secondary | Patient Global Impression of Change (PGIC; PRO) | Change in disease status | Change in score | ☐ Daily<br>☐ Weekly<br>☐ Monthly<br>☒ Other: Weeks 4, 8, 12, 16, 20, 24, 43<br>☒ Assessment at cross-over or early discontinuation |

| Endpoint Position | Assessment | Concept | Endpoint Definition | Assessment Frequency |
|---|---|---|---|---|
| Secondary | SF-36 v2.0 (PRO) | Health-related quality of life | Change in score | ☐ Daily<br>☐ Weekly<br>☐ Monthly<br>☒ Other: Screening, Baseline, Weeks 4, 12, 16, 24, 32<br>☒ Assessment at cross-over or early discontinuation |
| Secondary | EQ-5D-5L (PRO) | Health-related quality of life | Change in score | ☐ Daily<br>☐ Weekly<br>☐ Monthly<br>☒ Other: Screening, Baseline, Weeks 4, 12, 16, 24, 32<br>☒ Assessment at cross-over or early discontinuation |
| Secondary | Headache Impact Test-6 (HIT-6; PRO) | Migraine severity and impacts | Change in HIT-6 total score (Weeks 1-12) | ☐ Daily<br>☐ Weekly<br>☐ Monthly<br>☒ Other: Screening, Baseline, Weeks 4, 12, 16, 24, 32<br>☒ Assessment at cross-over or early discontinuation |

## 3.4 Labeling or promotional claim(s) based on the COA

The Applicant has proposed specific targeted COA-related labeling claims in Section 14 (Clinical Studies).

The targeted labeling claims are:

(b) (4) **2: Chronic Migraine**

[…] The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1 - 3. Secondary endpoints included (b) (4) reduction from baseline in monthly migraine days over Months 1 – 3, (b) (4)
(b) (4)

(b) (4)

***Reviewer's comment(s):***

(b) (4)

# 4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

**Table 5.** Concepts of Interest for COAs Included in Study PROMISE-2

| COA name | Concept(s) |
|---|---|
| Daily headache e-diary (PRO) | Not provided by Applicant |
| Patient Global Impression of Change (PGIC; PRO) | Change in different aspects of the patient's life related to their migraine |
| SF-36 v2.0 (PRO) | General health status |
| EQ-5D-5L (PRO) | Health-related quality of life |
| Headache Impact Test-6 (HIT-6; PRO) | Headache severity and impacts |

The conceptual framework for HIT-6 is shown in Table 6.

**Table 6.** Conceptual Framework for HIT-6

| Item | Domain | General Concept |
|---|---|---|
| When you have headaches, how often is the pain severe? | Pain severity | Headache Impact |
| How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities? | Daily activities | |
| When you have a headache, how often do you wish you could lie down? | Lying down | |
| In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches? | Fatigue | |
| In the past 4 weeks, how often have you felt fed up or irritated because of your headache? | Irritability | |
| In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities? | Concentration | |

***Reviewer's comment(s):***
*HIT-6 asks about headaches, not migraines. Headache and migraine are not synonymous or interchangeable concepts.*

# 5 CLINICAL OUTCOME ASSESSMENT(S)

**Headache Impact Test-6 (HIT-6)**
HIT-6 is a 6-item PRO instrument for assessing headache severity and impacts on functioning. Each item is rated on a 5-point scale with check boxes indicating the following response options: Never, Rarely, Sometimes, Very Often, and Always. Respondents are instructed to check one box for each question. Items 1-3 do not have an explicitly specified recall period, whereas items 4-6 specify "in the past 4 weeks."

***Reviewer's comment(s):***
*HIT-6 items 1-3 ask about "how often" something occurs, but do not state a reference time period (i.e., recall period). This leaves significant room for interpretation. While items 4-6 have a more clearly-defined recall period of the past 4 weeks, we recommend shorter recall periods to minimize the risk of patient recall error.*

# 6 SCORING ALGORITHM

**Headache Impact Test-6 (HIT-6)**
HIT-6 is scored by summing the weighted responses to all 6 items. Response options are weighted as follows:

- Never: 6 points
- Rarely: 8 points
- Sometimes: 10 points
- Very Often: 11 points
- Always: 13 points

Total scores range from 36 to 78, and are interpreted as having the following life impact:

- ≥ 60: Very severe impact
- 56-59: Substantial impact
- 50-55: Some impact
- ≤ 49: Little to no impact

***Reviewer's comment(s):***
1. *Scoring (and item weighting) was developed by Kosinski et al. (2003).*[7]

# 7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

☒ Copy of instrument
☒ Literature review and/or publications
☐ Documentation of expert input
☐ Qualitative study protocols and interview guides for focus group or patient interviews
☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
☐ Synopsis of qualitative findings

- ☐ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Table 7 documents the adequacy of the content of the HIT-6.

**Table 7.** Review of Content Validity for HIT-6

| COA Attribute | Attribute sufficiently established | Supported by: | Location of Supporting Materials |
|---|---|---|---|
| Face validity | ☐ Yes<br>☒ No | ☐ Literature<br>☒ Clinical input e.g. discussion with clinical reviewer | |
| Content validity | ☐ Yes<br>☐ Potentially – insufficient evidence available; additional information is needed<br>☒ No | ☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives<br>☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content)<br>☐ Target sample for qualitative research is appropriate.<br>☐ Studied sample for qualitative research adequately represents the target patient population<br>☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives<br>☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity)<br>☐ COA is culturally adapted and adequately translated<br>☐ Descriptive statistics (if available) support content relevance<br>☒ Other (see Reviewer's comments) | HIT-6 evidence dossier section 5.2 |

***Reviewer's comment(s):***

*The HIT-6 was developed in the general headache population.* (b) (4)

a. *The Applicant provided literature sources* [redacted] *See reviewer's comments under Section C2 of this review (* [redacted] *Summary).*

b. *The Applicant did not conduct additional qualitative research* [redacted]

# 8 OTHER MEASUREMENT PROPERTIES

Not applicable.

***Reviewer's comments:*** [redacted]

# 9 INTERPRETATION OF SCORES

Not applicable.

***Reviewer's comments:*** [redacted]

# D. APPENDICES

Appendix A: Patient Global Impression of Change (PGIC)
Appendix B: Headache Impact Test-6 (HIT-6)



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ELEKTRA J PAPADOPOULOS
11/26/2019 08:36:37 PM

# 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 16, 2019 |
| Requesting Office or Division: | Division of Neurology Products (DNP) |
| Application Type and Number: | BLA 761119 |
| Product Name and Strength: | Vyepti (eptinezumab-xxxx)[a] injection, 100 mg/mL |
| Applicant/Sponsor Name: | Alder BioPharmaceuticals, Inc. |
| OSE RCM #: | 2019-514-1 |
| DMEPA Safety Evaluator: | Chad Morris, PharmD, MPH |
| DMEPA Team Leader (Acting): | Briana Rider, PharmD, CPPS |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling and container label received on September 11, 2019 for Vyepti. The Division of Neurology Products (DNP) requested that we review the revised carton labeling and container label for Vyepti (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

## 2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. We provide recommendation for Alder Biopharmaceuticals, Inc. in Section 3, Table 1.

[a] The proper name for Vyepti has not yet been determined; therefore, "eptinezumab-xxxx" is used throughout this review as the proper name for this product.
[b] Morris, C. Label and Labeling Review for Vyepti (BLA 761119). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 22. RCM No.: 2019-514.

## 3 RECOMMENDATIONS FOR ALDER BIOPHARMACEUTICALS, INC.

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

Table 1. Identified Issues and Recommendations for Alder BioPharmaceuticals, Inc. (entire table to be conveyed to Applicant)

| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
|---|---|---|---|
| 1. | The histidine contents statement contains a trailing zero. | Can be improved to reduce the risk of ten-fold misinterpretation. | We recommend you remove the trailing zero from the statement of histidine content (that is, revise from 1.0 mg to 1 mg). |

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON SEPTEMBER 11, 2019

Container label

(b) (4)

Carton labeling

(b) (4)



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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: | August 22, 2019 |
| Requesting Office or Division: | Division of Neurology Products (DNP) |
| Application Type and Number: | BLA 761119 |
| Product Name and Strength: | Vyepti (eptinezumab-xxxx)[a] injection, 100 mg/mL |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Alder BioPharmaceuticals, Inc. |
| FDA Received Date: | 02/21/2019 Prescribing Information<br>05/10/2019 Patient Package Insert<br>06/03/2019 Container label and carton labeling |
| OSE RCM #: | 2019-514 |
| DMEPA Safety Evaluator: | Chad Morris, PharmD, MPH |
| DMEPA Team Leader (Acting): | Briana Rider, PharmD |

[a] The proper name for Vyepti has not yet been determined; therefore, "eptinezumab-xxxx" is used throughout this review as the proper name for this product.

## 1 REASON FOR REVIEW

As part of the approval process for Vyepti (eptinezumab-xxxx) injection, the Division of Neurology Products (DNP) requested that we review the proposed Vyepti Prescribing Information (PI), Patient Package Insert (PPI), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS 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 |
| ISMP Newsletters* | C (N/A) |
| FDA Adverse Event Reporting System (FAERS)* | D (N/A) |
| Other | E (N/A) |
| Labels and Labeling | F |

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 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), Patient Package Insert (PPI), carton labeling, and container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)

| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
|---|---|---|---|
| Prescribing Information – General Issues | | | |
| 1. | The route of administration statement is incomplete. | Can be improved for clarity. | We recommend changing the statement (b) (4) to "for intravenous infusion" throughout the labeling to reduce the risk for IV bolus administration. |
| 2. | Sections 2 and 16 contain trailing zeros. | Can be improved for clarify. | Remove all trailing zeros to reduce the risk for 10-fold misinterpretations. |

| Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 3. | Not all temperatures in Section 2 and 16 are followed by its unit of measure. | Can be improved for readability. | Include the unit of measure for each temperature (for example, change "2 to 8°C" to "2°C to 8°C"). |
| 4. | The package type is listed as (b) (4) | (b) (4) is not the correct package type. | Update the package type from (b) (4) to single-dose vial. |
| Highlights of Prescribing Information | | | |
| 1. | Important dilution warning and route of administration statement can be made more prominent. | Can be improved for clarity. | We recommend using the following statements as the first bullet "Must dilute before use. For intravenous infusion only." |
| Full Prescribing Information – Section 2 Dosage and Administration | | | |
| 1. | Section 2.2 contains the statement "(b) (4) contains no preservative," which may be interpreted as "contains preservative." | Can be improved for clarity and to reduce the risk for degraded drug medication errors. | Revise the statement to read "(b) (4) does not contain preservative" |
| Full Prescribing Information – Section 3 Dosage Forms and Strengths | | | |
| 1. | Important dosage form identification information is not present. | Per CFR 201.57(c)(4)(ii). | Important informative to facilitate identification of the dosage form (i.e., sterile, clear to slightly opalescent, colorless to brownish-yellow solution) should be added to Section 3 of the PI. |
| Full Prescribing Information – Section 16 How Supplied/Storage and Handling | | | |
| 1. | The NDC is denoted by the placeholder XXXXX-XXX-XX. | Should reflect the NDC number on the container labeling and carton label. | Add the proposed NDC number. |

| Table 3. Identified Issues and Recommendations for Alder BioPharmaceuticals, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Label(s) | | | |
| 1. | A linear barcode is not present, nor is its specific | The drug barcode is often used as an additional verification before drug | We request you add the product's linear barcode to each individual vial as required per 21 |

| Table 3. Identified Issues and Recommendations for Alder BioPharmaceuticals, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| | position denoted by a placeholder. | administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.<br><br>Not in alignment with 21 CFR 201.25 and 21 CFR 610.67. | CFR 201.25(c)(2) and 21 CFR 610.67.<br><br>Please note, there should be enough white space surrounding the linear barcode to allow scanners to read the barcode properly per 21CFR 201.25(c)(2).<br><br>Lastly, since your container label is small, we recommend you place the linear barcode in a vertical orientation to maximize the scanability of the linear barcode. |
| Carton Labeling | | | |
| 1. | The proposed format for the expiration date (MM/YYYY) can be improved. | Can be improved for clarity. | FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.<br><br>Additionally, we request you add a placeholder for the expiration date to the container label. |

| Table 3. Identified Issues and Recommendations for Alder BioPharmaceuticals, Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| 2. | The usual dose statement can be improved. | Not in alignment with 21 CFR 201.55 | We recommend you revise the statement (b) (4) to read "Recommended Dosage: See prescribing information for dosage, dilution and administration instructions". |

## 4 CONCLUSION

Our evaluation of the proposed Vyepti Prescribing Information (PI), Patient Package Insert (PPI), carton labeling, and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vyepti that Alder BioPharmaceuticals, Inc. submitted on February 21, 2019.

| Table 4. Relevant Product Information for Vyepti | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | eptinezumab |
| Indication | preventive treatment of migraine in adults |
| Route of Administration | intravenous infusion |
| Dosage Form | Injection |
| Strength | 100 mg/mL |
| Dose and Frequency | 100 mg or 300 mg every 3 months |
| How Supplied | 100 mg/mL single-dose vial |
| Storage | Store refrigerated at 2°C to 8 °C (36 °F to 46 °F) in original outer carton to protect from light until time of use. Do not freeze or shake. |
| Container Closure | (b) (4) glass vial |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 22, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Vyepti and eptinezumab. Our search did not identify any previous labels and labeling reviews.

## APPENDIX F. LABELS AND LABELING

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

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Vyepti labels and labeling submitted by Alder BioPharmaceuticals, Inc..

- Container label received on 06/03/19
- Carton labeling received on 06/03/19
- Patient Package Insert (Image not shown) 05/10/19
- Prescribing Information (Image not shown) received on 02/21/19

### F.2 Label and Labeling Images

Container label


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

Carton labeling

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**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: August 15, 2019

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

Mary T. Thanh Hai, M.D.
Director (Acting)
Division of Anesthesia, Analgesia, & Addiction Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

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

SUBJECT: Routine inspection of Covance Clinical Research Unit, Inc., Dallas, TX

## 1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of studies ALD403-CLIN-014 (BLA 761119) and NON-RESPONSIVE conducted at Covance Clinical Research Unit (Covance), Inc., Dallas, TX.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

### 1.1. Recommendation

An objectionable condition was observed during this inspection for study ALD403-CLIN-014. However, the inspectional finding did not impact the reliability of the clinical data from the study. Thus, the clinical data from studies ALD403-CLIN-014 (BLA

761119) and NON-RESPONSIVE and other studies of similar design are reliable to support a regulatory decision.

**2 Inspected Studies:**

**BLA 761119**

**Study Number:** ALD403-CLIN-014
**Study Title:** "A Randomized, Double-Blind, Single-Dose, Parallel Group Phase 1 Comparative Pharmacokinetic Trial to Support the Comparability Evaluation of Manufacturing Sites for Commercial Eptinezumab"
**Dates of conduct:** 12/12/2017 – 07/03/2018

NON-RESPONSIVE

**Clinical site:** Covance Clinical Research Unit, Inc.
1341 W Mockingbird Ln Ste 200E
Dallas, TX 75247

ORA investigators Andrace Deyampert and Travis M Beard inspected Covance, Dallas, TX from June 03-07, 2019.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

**3 Inspectional Findings**
At the conclusion of the inspection, investigators Deyampert and Beard observed an objectionable condition and Form FDA 483 was issued to the clinical site. Investigators also discussed two items with the site. The Form FDA 483 observation (**Attachment 1**), the firm's response dated 06/21/2019 (**Attachment 2**), discussion items, and my evaluation are presented below.

**3.1 FDA 483 Observation**

**3.1.1 Observation 1:**
**Records and reports were not retained for two years after marketing application approval and discontinuance of the investigation and notification of FDA. Specifically, The individual blinding codes for protocol ALD403-CLIN-014, a randomized, double-blind, single dose trial for IND 114647 were not maintained at the site. The 160 individual blinding codes were destroyed on July 10, 2018. The close-out visit for the trial occurred on March 27, 2018 and the database lock was approved for July 17, 2018.**

**Firm's Response**: Covance acknowledged this observation. As corrective actions, (b) (4)

**OSIS Evaluation**: Covance's corrective and preventative actions are acceptable. Based on the study protocol of ALD403-CLIN-014, the site's unblinded pharmacist obtained the randomization assignment and dispensed the study drug according to the randomization information. During inspection, the ORA investigators confirmed the treatment received for each subject against the randomization schedule on-site and did not note any discrepancy. In addition, although the site destroyed individual blinding codes before the FDA inspection, the ORA investigators did not note any finding that suggests inappropriate unblinding. Therefore, this observation has minimal impact to the data reliability.

**3.2 Discussion Items**

**3.2.1 Discussion Item 1: The firm should ensure the source records are attributable, legible, contemporaneous, original, and accurate. Specifically, in some cases the study stickers covered data on some source records. In addition,** NON-RESPONSIVE

**OSIS Evaluation**: This item does not impact the clinical data reliability or subject safety. The collected exhibits showed that the covered area in source records by study sticker did not affect clinical data evaluation or reporting (**Attachment 3**). For NON-RESPONSIVE

NON-RESPONSIVE

**4. Conclusion:**

An objectionable condition was observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable condition did not impact the reliability of the data from the audited studies. In addition, the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies of similar design.

I conclude the clinical data from studies ALD403-CLIN-014 (BLA 761119) and NON-RESPONSIVE are reliable. In addition, studies of similar design conducted between the previous inspection (Feb 2017) and the end of the current surveillance interval should also be considered reliable without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

**Final Classification:**

**VAI**- Covance Clinical Research Unit, Inc.
Dallas, TX
FEI#: 3007024261

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

ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XHC 08/14/2019; 08/15/19
Edit: JC 08/15/2019

ECMS: Cabinets/CDER/OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Covance Clinical Research Unit, Inc., Dallas, TX, USA

OSIS File #: NON-RESPONSIVE and 8459 (BLA 761119)

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