

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**761119Orig1s000**

**CLINICAL REVIEW(S)**

Clinical Review  
Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

### CLINICAL REVIEW

|                                                       |                                                                |
|-------------------------------------------------------|----------------------------------------------------------------|
| <b>Application Type</b>                               | Original BLA                                                   |
| <b>Application Number(s)</b>                          | 761119                                                         |
| <b>Priority or Standard</b>                           | Standard                                                       |
| <b>Submit Date(s)</b>                                 | 2/21/2019                                                      |
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| <b>Division/Office</b>                                | Division of Neurology 2 / Office of Neuroscience               |
| <b>Reviewer Name(s)</b>                               | Emily R. Freilich, MD                                          |
| <b>Review Completion Date</b>                         | 1/31/2020                                                      |
| <b>Established/Proper Name</b>                        | Eptinezumab                                                    |
| <b>(Proposed) Trade Name</b>                          | Vyepti                                                         |
| <b>Applicant</b>                                      | Alder Biopharmaceuticals, Inc/Lundbeck                         |
| <b>Dosage Form(s)</b>                                 | 100 mg/mL                                                      |
| <b>Applicant Proposed Dosing Regimen(s)</b>           | 100 mg infusion every 3 months; 300 mg infusion every 3 months |
| <b>Applicant Proposed Indication(s)/Population(s)</b> | Prevention of migraine                                         |
| <b>Recommendation on Regulatory Action</b>            | Approval                                                       |
| <b>Recommended Indication(s)/Population(s)</b>        | For the preventive treatment of migraine in adults             |

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## Glossary

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|         |                                                        |
|---------|--------------------------------------------------------|
| AAN     | American Academy of Neurology                          |
| Ab      | antibody                                               |
| AC      | advisory committee                                     |
| ADA     | anti-drug antibody                                     |
| ADL     | activities of daily living                             |
| AE      | adverse event                                          |
| AESI    | adverse event of special interest                      |
| AHS     | American Headache Society                              |
| ALP     | alkaline phosphatase                                   |
| ALT     | alanine aminotransferase                               |
| AR      | adverse reaction                                       |
| AST     | aspartate aminotransferase                             |
| BLA     | biologics license application                          |
| BPCA    | Best Pharmaceuticals for Children Act                  |
| BRF     | Benefit Risk Framework                                 |
| CBER    | Center for Biologics Evaluation and Research           |
| CDER    | Center for Drug Evaluation and Research                |
| CDRH    | Center for Devices and Radiological Health             |
| CDTL    | Cross-Discipline Team Leader                           |
| CGRP    | calcitonin gene-related peptide                        |
| CFR     | Code of Federal Regulations                            |
| CK      | creatine kinase                                        |
| CM      | chronic migraine                                       |
| CMC     | chemistry, manufacturing, and controls                 |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF     | case report form                                       |
| CRO     | contract research organization                         |
| CRT     | clinical review template                               |
| CSR     | clinical study report                                  |
| CSS     | Controlled Substance Staff                             |
| C-SSRS  | Columbia-Suicide Severity Rating Scale                 |
| CT      | computed tomography                                    |
| CV      | cardiovascular                                         |
| DBP     | diastolic blood pressure                               |
| DM      | diabetes mellitus                                      |
| DMC     | data monitoring committee                              |

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|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| DME       | designated medical event                                                |
| ECG       | electrocardiogram                                                       |
| eCTD      | electronic common technical document                                    |
| EEG       | electroencephalogram                                                    |
| EGA       | estimated gestational age                                               |
| EM        | episodic migraine                                                       |
| ET        | elective termination                                                    |
| ETASU     | elements to assure safe use                                             |
| FAS       | full analysis set                                                       |
| FDA       | Food and Drug Administration                                            |
| FDAAA     | Food and Drug Administration Amendments Act of 2007                     |
| FDASIA    | Food and Drug Administration Safety and Innovation Act                  |
| FT        | full-term                                                               |
| GCP       | good clinical practice                                                  |
| GI        | gastrointestinal                                                        |
| GRMP      | good review management practice                                         |
| HIT       | headache impact test                                                    |
| ICH       | International Council for Harmonization                                 |
| ICHHD     | International Classification of Headache Disorders                      |
| IHS       | International Headache Society                                          |
| IND       | Investigational New Drug Application                                    |
| IM        | intramuscular                                                           |
| iPSP      | initial Pediatric Study Plan                                            |
| ISE       | integrated summary of effectiveness                                     |
| ISS       | integrated summary of safety                                            |
| ITT       | intent to treat                                                         |
| IV        | intravenous                                                             |
| mAb       | monoclonal antibody                                                     |
| MBS       | most bothersome symptom                                                 |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| MRI/MRA   | magnetic resonance imaging/magnetic resonance angiogram                 |
| mITT      | modified intent to treat                                                |
| Nab       | neutralizing antibody                                                   |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application                                                    |
| NME       | new molecular entity                                                    |
| NSAID     | non-steroidal anti-inflammatory drug                                    |
| OCS       | Office of Computational Science                                         |
| OCP       | Office of Clinical Pharmacology                                         |
| OE        | overall eptinezumab population                                          |
| OPQ       | Office of Pharmaceutical Quality                                        |

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|       |                                           |
|-------|-------------------------------------------|
| OSE   | Office of Surveillance and Epidemiology   |
| OSI   | Office of Scientific Investigation        |
| PBRER | Periodic Benefit-Risk Evaluation Report   |
| PC    | placebo-controlled pool                   |
| PD    | pharmacodynamics                          |
| PI    | prescribing information or package insert |
| PK    | pharmacokinetics                          |
| PMC   | postmarketing commitment                  |
| PMR   | postmarketing requirement                 |
| PP    | per protocol                              |
| PPI   | patient package insert                    |
| PREA  | Pediatric Research Equity Act             |
| PRO   | patient reported outcome                  |
| PSS   | pivotal study population                  |
| PSUR  | Periodic Safety Update report             |
| PT    | preferred term                            |
| PTSD  | post-traumatic stress disorder            |
| REMS  | risk evaluation and mitigation strategy   |
| SA    | spontaneous abortion                      |
| SAE   | serious adverse event                     |
| SAP   | statistical analysis plan                 |
| SBP   | systolic blood pressure                   |
| SGE   | special government employee               |
| SOC   | system organ class                        |
| TEAE  | treatment emergent adverse event          |
| TIA   | transient ischemic attack                 |
| ULN   | upper limit of normal                     |

## 1. Executive Summary

---

### 1.1. Product Introduction

Eptinezumab (ALD403) is a humanized anti-calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) that antagonizes the CGRP ligand and prevents interaction with CGRP receptors and other effector receptors, inhibiting the CGRP-related cascade of physiological events that is proposed to initiate migraine attacks. CGRP has been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP has been shown to induce migraine-like attacks in susceptible individuals<sup>1</sup>. CGRP is a potent vasodilator in the cerebral, coronary, and renal vascular beds<sup>2</sup>. Vasodilation is a known contributor to the pathophysiology of migraine; CGRP inhibition in other organs can potentially lead to off-target effects as well.

Eptinezumab is a new biological product. The applicant is seeking an indication for the preventive treatment of migraine, and proposes a dose of 100 mg administered as an intravenous (IV) infusion every 3 months, with an option for 300 mg IV every 3 months as well.

The FDA recently approved three other biologics in the same class that also work on the CGRP pathway for the preventive treatment of migraine (see Section 2.2). Eptinezumab is proposed for intravenous infusion; the other recently approved products are administered via subcutaneous injection.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for eptinezumab is based on the positive results of two randomized, double-blind, placebo-controlled efficacy studies in adult patients with migraine. One study evaluated patients with frequent, episodic migraine, and the other study evaluated patients with chronic migraine.

The level of evidence provided is adequate to support the conclusion that eptinezumab is effective for the preventive treatment of migraine.

### 1.3. Benefit-Risk Assessment

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<sup>1</sup> Hansen J, Hauge A, Olesen J, and M Ashina. Calcitonin Gene-Related Peptide Triggers Migraine-Like Attacks in Patients with Migraine with Aura. *Cephalalgia*. 2010 Oct; 30(10): 1179-1186.

<sup>2</sup> Russell F, King R, Smillie S, Kodji X, and S Brain. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. *Physiol Rev*. 2014 Oct; 94(4): 1099-1142.

### Benefit-Risk Integrated Assessment

The overall benefit-risk analysis of eptinezumab in patients with episodic and chronic migraine is acceptable. Migraine is a common, chronic, and often debilitating neurologic disease that may have significant impact on a patient's quality of life. Migraine is characterized by recurrent attacks of headache which are typically moderate to severe in intensity, and characterized by unilateral pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. They typically occur on a recurrent, episodic basis but often occur with sufficient frequency and severity to warrant preventive treatment to minimize the impact on quality of life. Patients who suffer from chronic migraine may experience moderate to severe headaches on 15 or more days per month. Recent approvals of new therapies with the same class for the preventive treatment of migraine are an improvement over previous options which were daily, oral medications that had significant side effects. However, the recently approved CGRP therapies are self-administered as subcutaneous injections, sometimes with multiple doses required simultaneously on a monthly or every 3 month basis.

Eptinezumab is a new biological product administered via intravenous infusion for the preventive treatment of migraine. It binds to the CGRP ligand, and prevents the interaction with the CGRP receptor, inhibiting the CGRP-related cascade of physiological events that is proposed to initiate migraine attacks. It is administered intravenously every 3 months. The applicant has studied the safety and efficacy of eptinezumab in two randomized, double-blind, placebo-controlled clinical trials in migraine patients. A study in patients with episodic migraine (Study ALD403-CLIN-006) demonstrated effectiveness of eptinezumab in the reduction of monthly migraine days, based on the primary efficacy endpoint of change from baseline in frequency of migraine days over Weeks 1-12. The primary endpoint was statistically significant at the 100 mg and 300 mg doses, and reduced migraine days by a mean of 3.9 and 4.3 days, respectively, compared to 3.2 days in the placebo arm, for a mean treatment effect of -0.7 and -1.1 migraine days. A study in patients with chronic migraine (Study ALD403-CLIN-011) demonstrated effectiveness of eptinezumab in the reduction of monthly migraine days, based on the primary efficacy endpoint of change from baseline in frequency of migraine days over Weeks 1-12. The primary endpoint was statistically significant at the 100 mg and 300 mg doses, and reduced monthly migraine days by a mean of 7.7 and 8.2 days, respectively, compared to 5.6 days in the placebo group, for a mean treatment effect of -2.0 and -2.6 migraine days. Key secondary endpoints of 50% and 75% migraine responders and reduction in acute migraine medication days were supportive of the primary endpoint. Administration will be in a doctor's office or infusion center every 3 months, which may increase compliance compared to daily oral therapies, monthly therapy, or in patients reluctant to self-administer injections.

The safety profile of eptinezumab was characterized in two pivotal studies, two dose-ranging studies, and an open-label extension study. There were no serious safety signals identified in these studies, and no common adverse events that appeared drug-related. There were no common

adverse events that appeared drug-related and occurred in  $\geq 2\%$  of the population and  $> 2\%$  more than placebo. There were also a number of patients who discontinued from the studies due to mild or moderate hypersensitivity reactions which appeared to be drug-related. There were no serious or severe hypersensitivity reactions; however, it is possible that more serious hypersensitivity reactions may have occurred if these discontinued patients had received subsequent doses of the study treatment. Hypersensitivity is also a known risk with other monoclonal antibodies and specifically other anti-CGRP antibodies indicated for preventive treatment of migraine.

The studies also demonstrated a slight imbalance compared to placebo in patients reporting suicidal behaviors and constipation. These adverse events did not occur with sufficient frequency to be reported in patient labeling, but are recommended for enhanced pharmacovigilance. The pivotal studies were conducted in primarily young, healthy patients and those with cardiovascular risk factors were excluded from the studies. Only a very small number of patients over 65 years of age were studied. There may be a higher incidence of adverse events noted in the postmarketing setting when administered to an older population, or those with comorbid conditions.

Eptinezumab is recommended for approval of both the 100 mg and 300 mg doses. Eptinezumab provides an additional treatment option for patients suffering from frequent migraine headaches. The efficacy is similar to other products that have been approved for preventive treatment of migraine. It is very well tolerated and is only administered once every 3 months which may improve compliance over treatments that need to be taken daily or monthly.

#### Benefit-Risk Dimensions

| Dimension                             | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                               | Conclusions and Reasons                                                                                                                                                                                                                                                       |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Analysis of Condition</a> | <ul style="list-style-type: none"> <li>Migraine is a very common, chronic, neurologic disease with a broad spectrum of frequency and severity.</li> <li>Migraine is characterized by recurrent attacks of headache which are typically moderate to severe in intensity, unilateral, and associated with other symptoms such as nausea, vomiting, phonophobia, or photophobia. They typically last anywhere from 4 hours to 72</li> </ul> | <p>Migraine is a common, chronic disease which can be serious and debilitating with significant impact on quality of life.</p> <p>Migraine can range in severity and frequency, but patients who suffer from chronic migraines may experience headaches more than half of</p> |

| Dimension                               | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Conclusions and Reasons                                                                                                                                                                                                                                                    |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         | <p>hours, and may be preceded by an aura 30 minutes to 1 hour prior to the onset of the headache.</p> <ul style="list-style-type: none"> <li>• Migraine typically occur on a recurrent, episodic basis. However, some patients meet the International Headache Society (IHS) definition for chronic migraine, defined by having headaches on 15 or more days per month, of which 8 have the features of migraine.</li> <li>• Migraine is more frequent in females than males, and peaks in the 4<sup>th</sup> decade of life for both males and females.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p>the days in a month. Even when episodic, frequent migraines are disruptive and may benefit from medications which decrease the frequency of the headaches.</p>                                                                                                          |
| <p><u>Current Treatment Options</u></p> | <ul style="list-style-type: none"> <li>• There are several FDA-approved treatments for the preventive treatment of migraine, as well as many treatments used off-label.</li> <li>• Approved therapies include CGRP antagonists erenumab, fremanezumab, and galcanezumab which were approved in 2018.</li> <li>• Previous approved therapies include propranolol, timolol, divalproex/sodium valproate, and onabotulinumtoxin A.</li> <li>• The three previously approved CGRP antagonists are self-administered by subcutaneous injection monthly, or up to every 3 months.</li> <li>• Prior therapies were mainly oral therapies that were taken at least daily, and up to three times daily. OnabotulinumtoxinA requires 31 injections in the head and neck, given every 3 months.</li> <li>• All of the approved therapies have similar modest effects at reducing the frequency of migraine headaches by 1-2.5 days monthly compared to placebo.</li> <li>• There are no currently available therapies that are able to completely or nearly completely prevent the condition.</li> <li>• Many available therapies have intolerable or dose-limiting side effects</li> </ul> | <p>Alternative options are needed to improve compliance over daily or monthly treatments, or for those patients who are reluctant to self-administer injections. Therapies that are available orally have significant adverse events and are often not well tolerated.</p> |

| Dimension      | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | that are hard to justify daily therapy for limited benefit.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Benefit</b> | <ul style="list-style-type: none"> <li>Eptinezumab administered intravenously every 3 months demonstrated efficacy in reducing monthly migraine days when compared to placebo in two randomized, double-blind, placebo-controlled studies.</li> <li>In patients with episodic migraine, eptinezumab demonstrated statistically significant benefit in the primary efficacy endpoint of change from baseline in frequency of monthly migraine days over Weeks 1-12. At doses of 100 mg and 300 mg, eptinezumab reduced monthly migraine days by a mean of 3.9 and 4.3 days, compared to 3.2 days in the placebo arm. This results in a treatment effect of 0.7-1.1 mean reduction in migraine days.</li> <li>In patients with chronic migraine, eptinezumab demonstrated statistically significant benefit in the same primary efficacy endpoint. At doses of 100 mg and 300 mg, eptinezumab reduced monthly migraine days by a mean of 7.7 and 8.2 days, respectively, compared to 5.6 days in the placebo arm. This results in a treatment effect of 2.0-2.6 mean reduction in migraine days.</li> <li>Key secondary endpoints of 50% and 75% responder rates over Weeks 1-12, 75% responder rates over Weeks 1-4, and use of acute migraine medication were also analyzed and supportive of the primary endpoints.</li> <li>It was demonstrated that the percentage of patients with a migraine</li> </ul> | <p>Eptinezumab 100 mg and 300 mg were both found to be effective in reducing monthly migraine days in patients with either episodic migraine or chronic migraine. The treatment effect is similar to that seen in clinical trials of other approved products for migraine prevention.</p> <p>Fewer monthly migraine days may translate into fewer days of disability and improvements in quality of life. The reduction in acute migraine medication use may lead to reduced risks of medication overuse headache and reduced risk of side effects related to the use of acute medications.</p> <p>Eptinezumab is convenient, as it is only given every 3 months, and is administered by a provider, which may improve compliance over daily or monthly medications. There is no need for self-injection which will be a benefit for some patients.</p> <p>The more rapid onset of efficacy may provide benefit over older treatments that required</p> |

| Dimension                              | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        | <p>on the day after dosing was higher in patients who received placebo compared to those who received treatment for both studies, and this benefit continued for most individual days of the first month following infusion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>long titration periods or had delayed onset of efficacy.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><u>Risk and Risk Management</u></p> | <ul style="list-style-type: none"> <li>• No serious safety signals were identified in this review. There were no deaths.</li> <li>• There were several patients who had hypersensitivity reactions, compared to zero patients in placebo. The reactions were mild or moderate and none were serious or severe. However, they all led to discontinuation from the study.</li> <li>• There were no adverse events that occurred frequently enough to be considered common adverse events.</li> <li>• Potential safety issues related to the use of CGRP antagonists and those seen in previously approved CGRP antagonists were reviewed in detail:</li> <li>• Hypertension: There were two patients who withdrew from the study for moderate hypertension; however, they both had elevated blood pressure prior to treatment.</li> <li>• GI: constipation may result from blockage of CGRP. There were slightly increased cases of constipation in the treatment group compared to placebo, but the incidence was still less than 1% of the treatment arm and there were no serious or severe cases, or any cases that resulted in study discontinuation.</li> <li>• Suicidality – There were an increased number of reports of suicidal ideation and suicidal attempts in the treatment group compared to</li> </ul> | <p>Eptinezumab is generally very well tolerated and had an acceptable safety profile with minimal adverse events noted in the migraine population.</p> <p>Eptinezumab has not been adequately evaluated in the elderly or those with cardiovascular disease.</p> <p>There is a potential for hypersensitivity reactions, which could be severe given the risk for immunogenicity and the infusion-related hypersensitivity reactions that were noted during the clinical trials. More serious hypersensitivity reactions may have been noted upon further exposure to the drug if patients had not been discontinued from the study.</p> <p>Hypersensitivity is recommended for inclusion as a warning in the prescribing information. Enhanced pharmacovigilance is recommended for other adverse events that occurred at rates higher than placebo, but not with frequency</p> |

| Dimension | Evidence and Uncertainties                                                                                                               | Conclusions and Reasons                                                                              |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
|           | placebo. They were mostly mild or moderate and occurred primarily in chronic migraine patients with a history of anxiety and depression. | sufficient for inclusion in the label, including hypertension, suicidal behaviors, and constipation. |

## 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

|                                     |                                                                                                                                    |                                        |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| <input type="checkbox"/>            | The patient experience data that was submitted as part of the application include:                                                 | Section where discussed, if applicable |
| <input type="checkbox"/>            | Clinical outcome assessment (COA) data, such as                                                                                    | [e.g., Sec 6.1 Study endpoints]        |
| <input checked="" type="checkbox"/> | Patient reported outcome (PRO)                                                                                                     |                                        |
| <input type="checkbox"/>            | Observer reported outcome (ObsRO)                                                                                                  |                                        |
| <input type="checkbox"/>            | Clinician reported outcome (ClinRO)                                                                                                |                                        |
| <input type="checkbox"/>            | Performance outcome (PerfO)                                                                                                        |                                        |
| <input type="checkbox"/>            | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                        |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      | [e.g., Sec 2.1 Analysis of Condition]  |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                        |
| <input type="checkbox"/>            | Natural history studies                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                        |
| <input type="checkbox"/>            | Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient experience data that were not submitted in the application, but were considered in this review:                            |                                        |
| <input type="checkbox"/>            | Input informed from participation in meetings with patient stakeholders                                                            |                                        |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      | [e.g., Current Treatment Options]      |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                        |
| <input type="checkbox"/>            | Other: (Please specify)                                                                                                            |                                        |
| <input type="checkbox"/>            | Patient experience data was not submitted as part of this application.                                                             |                                        |

## 2. Therapeutic Context

## 2.1. Analysis of Condition

Migraine is a very common, chronic neurological disease with a broad spectrum of frequency and severity. Migraine can be a serious, and at times disabling, condition that can impact the quality of patients' lives.

Migraine is a disease characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last from 4 to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache.

Typically, migraine is experienced on an episodic basis, however, some patients experience migraines with sufficient frequency to benefit from the use of a preventive treatment, rather than relying solely on abortive migraine medications (i.e., triptans or NSAIDs). The International Classification of Headache Disorders (ICHD) published by the International Headache Society (IHS) also recognizes a type of migraine called chronic migraine. Patients with chronic migraine have headaches on 15 or more days per month, at least 8 of which have the features of migraine.

Migraine is more frequent in females than in males. In a large U.S. population based study, the one-year prevalence of migraine was 18% in females, 7% in males, and 12% overall<sup>3</sup>. Migraine prevalence peaks in the 4<sup>th</sup> decade of life for both males and females<sup>4</sup>. Although the prevalence of migraine declines with age, prevalence estimates in the population age 60+ is about 5% for females, and 1.6% for males<sup>4</sup>. Another estimate by Bigal and Lipton<sup>5</sup> shows that the prevalence of migraine in the age 70+ population is about 4% with a 2% prevalence for males, and 5% prevalence for females.

## 2.2. Analysis of Current Treatment Options

There are several FDA-approved therapies for preventive treatment of migraine, as well as many other drugs that are used off-label. In 2018, the FDA approved three new biologics that also work as antagonists on the CGRP pathway for the preventive treatment of migraine:

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<sup>3</sup> Lipton R, Stewart W, Diamond S, Diamond M, and M Reed. Prevalence and Burden of Migraine in the United States: Data from the American Migraine Study II. *Headache*. 2001 Jul-Aug; 41(7):646-657.

<sup>4</sup> Lipton R, Bigal M, Diamond M, Freitag F, Reed M, and W Stewart. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. *Neurology*. 2007 Jan 30; 68(5):343-349.

<sup>5</sup> Bigal M, and R Lipton. Migraine at All Ages. *Current Pain and Headache Reports*. 2006 June; 10(3): 207-213.

erenumab, fremanezumab, and galcanezumab. Erenumab binds to the CGRP receptor, and fremanezumab and galcanezumab bind to the CGRP ligand. The three drugs demonstrated similar efficacy and safety in the preventive treatment of both episodic and chronic migraine. They are each administered monthly via subcutaneous injection, with a loading dose recommended for galcanezumab. Fremanezumab also has an alternate dosing regimen of 3 injections given together once every 3 months.

Prior to those approvals, there were more limited therapies for the preventive treatment of migraine. The American Headache Society (AHS) in conjunction with the American Academy of Neurology (AAN) published two guidelines in 2012 with recommendations for use of certain drugs and complementary therapies in the prevention of episodic migraine<sup>6</sup>. These guidelines include both therapies that are FDA-approved and those that are used off-label. The guidelines are limited to preventive treatment for episodic migraine, and do not address preventive treatment of chronic migraine. The guidelines recommend the following drugs as having Level A evidence (established as effective): divalproex/sodium valproate, metoprolol, butterbur, propranolol, timolol, and topiramate. The following drugs are considered by this guideline to have Level B evidence (probably effective): amitriptyline, fenoprofen, feverfew, histamine, ibuprofen, ketoprofen, magnesium, naproxen, riboflavin, venlafaxine, and atenolol. The following drugs are considered to have Level C evidence (possibly effective): candesartan, carbamazepine, clonidine, guanfacine, lisinopril, nebivolol, pindolol, flurbiprofen, mefenamic acid, coenzyme Q10, and cyproheptadine. See Table 1 for further details.

**Table 1 Summary of Current FDA-Approved Treatments for Migraine Prophylaxis**

| Product Name | Year of Approval for Migraine | Dosing/ Administration  | Efficacy Information                                                                                                   | Important Safety and Tolerability Issues | Other Comments                                   |
|--------------|-------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------------|
| Erenumab     | 2018                          | 70 or 140 mg SC monthly | Treatment effect: 1.0-1.9 day reduction in monthly migraine days (EM), 2.5 day reduction in monthly migraine days (CM) | Potential hypersensitivity reactions     | Constipation and injection site reactions common |

<sup>6</sup> Silberstein S, Holland S, Freitag F, Dodick D, Argoff C, and E Ashman. Evidence Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults. *Neurology*. 2012 Apr 24; 78(17):1337-1345.

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Emily R. Freilich, MD  
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|                             |       |                                                                            |                                                                                                                            |                                                           |                                                                   |
|-----------------------------|-------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------|
| Fremanezumab                | 2018  | 225 mg SC monthly or 675 mg q3 months                                      | Treatment effect: 1.2-1.5 day reduction in monthly migraine days (EM), 1.8-2.1 day reduction in monthly migraine days (CM) | Potential hypersensitivity reactions                      | Injection site reactions common                                   |
| Galcanezumab                | 2018  | 240 mg SC x 1 followed by 120 mg SC monthly                                | Treatment effect: 1.9-2.0 day reduction in monthly migraine days (EM) , 2.1 day reduction in monthly migraine days (CM)    | Potential hypersensitivity reactions                      | Injection site reactions common                                   |
| Propranolol                 | 1970s | 20-80mg TID-QID                                                            | Treatment effect not in the label                                                                                          | Anaphylaxis, bradycardia                                  | Bronchospasm and hypoglycemia in applicable populations           |
| Timolol                     | 1980s | 10-15mg BID                                                                | Treatment effect not in the label                                                                                          | Anaphylaxis, bradycardia                                  | Bronchospasm and hypoglycemia in applicable populations           |
| Divalproex/sodium valproate | 1996  | 250 -500mg BID                                                             | Treatment effect: 1.5 to 2.2-day reduction in monthly migraine days                                                        | Boxed warning for hepatotoxicity                          | Neural tube defects                                               |
| Topiramate                  | 2004  | 50mg BID                                                                   | Treatment effect: 1.0 to 1.3-day reduction in monthly migraine days                                                        | Paresthesias, weight loss                                 | Cleft lip and palate                                              |
| OnabotulinumtoxinA          | 2010  | Total dose 155 units divided across 7 muscles; administered every 12 weeks | Treatment effect: 1.4 to 2.3-day reduction in monthly headache days from baseline                                          | Transient weakness may occur in muscles that are injected | Approved for CM only; administered intramuscularly by a physician |

*EM = episodic migraine, CM = chronic migraine*

Although there are numerous options for preventive treatment of migraine, the current FDA-approved treatments all have some limitations. The older FDA-approved treatment options all have a very modest effect at reducing the frequency of migraine headaches. Except for onabotulinumtoxinA, all must be taken at least daily, and up to three times daily for propranolol. OnabotulinumtoxinA requires 31 injections in the head and neck, and needs to be administered every three months. None of the currently approved treatments completely ameliorates the condition. Most patients will continue to have migraines even on therapeutic doses of effective medications. Two commonly used agents (topiramate, and sodium valproate) are associated with birth defects notably cleft lip and palate, and neural tube defects. A typical migraine patient is a female of childbearing potential, and the association with birth defects limits the use of these agents in many migraine patients.

The recently-approved CGRP antagonists also have limitations in that they have to be given monthly by self-injection, or may require multiple simultaneous injections to be given at the same time to reach the recommended effective dose. Many currently available treatment options may also take time to achieve optimal efficacy, resulting in lack of compliance, early patient discontinuation and unplanned office and emergency room visits. Further, most migraine treatments reduce the frequency of migraine headaches, but do not prevent them entirely, also leading to more discontinuations because of 'lack of efficacy', or refusal to take a daily medication that 'isn't helping'. In addition, several of the available preventive medications have some intolerable side effects making it even more difficult for patients to justify continuing to take a daily medication that does not completely prevent migraines.

### 3. Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Eptinezumab is a new molecular entity and is not currently marketed in the United States for any indication.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 114647 was opened for ALD403 (eptinezumab) on December 13, 2012 [REDACTED] (b) (4) The end-of-phase-2 meeting was held on October 13, 2016 to discuss overall clinical development, and reach agreement on pivotal study designs and plans for bridging studies. During that meeting the Division recommended that the applicant study at least 100 patients with 2 infusions every 3 months, and at least 60 patients with 4 infusions every 3 months (at highest proposed dose).

A pre-BLA meeting was held on September 5, 2018 to obtain feedback on the acceptability of the proposed BLA for the proposed indication based on the two pivotal studies and other necessary contents of the proposed BLA. At that time, the Division recommended at least 300 patients exposed for 6 months and 100 patients exposed for a year (with 50% at the highest proposed dose). The Division also discussed that the adverse events (AEs) of special interest should include cardiovascular (CV), hepatic, gastrointestinal (GI) and infusion-related AEs. We also requested a table of baseline CV risk factors and an analysis in the change in CV medications to be included in the Integrated Summary of Safety (ISS).

Additionally, an initial pediatric study plan (iPSP) was submitted December 12, 2016 and agreed on December 21, 2018. On July 20, 2018, the Agency conditionally accepted the proposed proprietary name, Vyepti, which is currently under review. (b) (4)



### 3.3. Foreign Regulatory Actions and Marketing History

Eptinezumab is not approved or marketed in any country.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Please refer to the completed OSI review by Cara Alfaro, Pharm.D for full details. Three clinical sites were inspected, as chosen based on enrollment in both studies, in support of the BLA . Both studies appeared to have been conducted adequately, and the data generated by these sites appeared acceptable in support of the respective indication. There were a few observations that prompted further investigation. At one site (PI: Eldeeb), it was noted that approximately 14% of the patients enrolled in one of the studies had been randomized to the incorrect migraine severity stratum. Further information provided by applicant indicate that the strata randomization errors may have been the result of human error, and revised datasets were submitted with corrected severity strata randomization. An additional site revealed a potential unblinding event (PI: Khan), prompting information request from the applicant to provide all potential unblinding events that occurred during both studies. The applicant identified 2 unblinding events involving 6 patients, and 13 potential unblinding events in Study

006, and 4 unblinding events involving 6 patients and 8 potential unblinding events in Study 011. The applicant's description of all events was reviewed by OSI and appeared appropriate. Sensitivity analyses were recommended with the corrected migraine severity stratum and excluding the 12 patients who were unblinded during the study.

#### **4.2. Product Quality**

See completed Quality Reviews by the Office of Biotechnology Products review team.

#### **4.3. Clinical Microbiology**

See completed review by Dr. Candace Gomez-Groughton of the Division of Microbiology Assessment.

#### **4.4. Nonclinical Pharmacology/Toxicology**

See completed Nonclinical review.

#### **4.5. Clinical Pharmacology**

Please refer to the complete Office of Clinical Pharmacology Review (OCP) by Dr. Gopichand Gottipati. OCP recommended approval of the recommended 100 mg and 300 mg doses, once every 3 months, administered intravenously in 100 ml of 0.9% sodium chloride injection, USP, over 30 minutes. No dose adjustments are needed based on age, race, sex, bodyweight, renal or hepatic impairment, food-intake, or drug-drug interactions. Relevant clinical pharmacology properties of eptinezumab include a volume of distribution of 3.6 liters, a mean clearance of 0.006 L/h, and a mean terminal half-life of approximately 27 days.

#### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### **4.7. Consumer Study Reviews**

Not applicable.

### **5. Sources of Clinical Data and Review Strategy**

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#### **5.1. Table of Clinical Studies**

**Table 2 Clinical Trials Relevant to Preventive Treatment of Migraines**

| Trial Identity                                           | NCT no.  | Trial Design                                                            | Regimen/ schedule/ route                  | Study Endpoints                                           | Treatment Duration/ Follow Up            | No. of patients enrolled | Study Population                                                                                                                  | No. of Centers and Countries |
|----------------------------------------------------------|----------|-------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------|------------------------------------------|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| <b>Controlled Studies to Support Efficacy and Safety</b> |          |                                                                         |                                           |                                                           |                                          |                          |                                                                                                                                   |                              |
| ALD403-CLIN-006                                          | 02559895 | Randomized, double-blind, placebo-controlled Phase 3 study              | 30, 100, or 300 mg IV Q3 months x 4 doses | Change in frequency of monthly migraine days (Weeks 1-12) | 36 weeks/ total duration 60 weeks        | 898                      | Adults with episodic migraine; $\leq 14$ headache days, of which at least 4 had to be migraine days over a 28-day period          | 84 sites, 2 countries        |
| ALD403-CLIN-011                                          | 02974153 | Randomized, double-blind, placebo-controlled Phase 3 study              | 100 or 300 mg IV Q3 months x 2 doses      | Change in frequency in monthly migraine days (Weeks 1-12) | 12 weeks/ total duration 36 weeks        | 1121                     | Adults with chronic migraine; $\geq 15$ to $\leq 26$ headache days a month, of which $\geq 8$ days were assessed as migraine days | 128 sites 13 countries       |
| <b>Studies to Support Safety</b>                         |          |                                                                         |                                           |                                                           |                                          |                          |                                                                                                                                   |                              |
| ALD403-CLIN-013                                          | 02985398 | Open-label extension trial                                              | 300 mg IV Q3 months, up to 8 doses        | Safety/tolerability                                       | 84 weeks/Total duration 106 weeks        | 128                      | Adults with chronic migraine                                                                                                      | 20 sites, United States only |
| ALD403-CLIN-005                                          |          | Randomized, double-blind, placebo-controlled Phase 2 dose-ranging study | 10, 30, 100 or 300 mg IV single dose      | 75% migraine responder rate (Weeks 1-12)                  | Single infusion/ total duration 54 weeks | 665                      | Adults with chronic migraine; $\geq 15$ headache days, of which $\geq 8$ days were assessed as migraine days                      | 92 sites, 4 countries        |
| ALD403-CLIN-002                                          |          | Randomized, double-blind, placebo-controlled Phase 1b/2 study           | 1000 mg IV single dose                    | Change in frequency in monthly migraine days (Weeks 5-8)  | Single infusion/ total duration 24 weeks | 163                      | Adults with episodic migraine; $\geq 5$ and $\leq 14$ headache days, of which at least 4 had to be migraine days over a           | 26 sites, United States only |

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Emily R. Freilich, MD  
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|  |  |  |  |  |  |  | 28-day period |  |
|--|--|--|--|--|--|--|---------------|--|

*IV = intravenously, no. = number*

## 5.2. Review Strategy

There are two pivotal Phase 3 efficacy studies (Study 006 and Study 011) that will be reviewed to support the efficacy of eptinezumab in the preventive treatment of migraine, one study in episodic migraine (Study 006) and one study in chronic migraine (Study 011). These studies, in addition to two additional Phase 2 studies (Study 002 and Study 005), and the long-term extension study (Study 013) will be used to support the safety of the product.

The applicant proposes that the drug be available in both 100 mg and 300 mg doses for intravenous administration every 3 months. The available data on the 30 mg dose from one pivotal Phase 3 study (Study 006) and one Phase 2 study (Study 005) which will also be evaluated in this review to determine potential efficacy and relative safety of the 30 mg dose. Most of the safety analyses will be performed on either the pivotal studies population, or the overall eptinezumab population from all of the above studies; however, Study 002 will not be included in some of the analyses given it was a single-dose study of a supratherapeutic dose of 1000 mg and will not contribute much to evaluation of safety of the doses under consideration in this review.

Throughout this review, the term “treatment effect” will refer to the effect that remains after subtracting out the placebo effect. Negative numbers will indicate improvement and positive numbers represent worsening. Also, for this review, one month will refer to 4 weeks, or 28 days.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. Study ALD403-CLIN-006: A Parallel Group Double-Blind Randomized Placebo Controlled Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Frequent Episodic Migraines

#### 6.1.1. Study Design

##### Overview and Objective

The primary objective is to evaluate the efficacy of repeat doses of ALD403 administered intravenously (IV) compared to placebo in patients with Frequent Episodic Migraine (FEM).

##### Trial Design

- **Basic Study Design**

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Study 006 is a parallel group, double-blind, randomized, placebo-controlled trial. Patients were randomized into one of three dose levels of ALD403 (30 mg, 100 mg, and 300 mg) or placebo. Randomization was stratified by migraine days during screening ( $\leq 9$  days or  $> 9$  days). Patients were allocated equally to each treatment group.

The total study duration was 60 weeks with 12 scheduled visits. There was a baseline period to determine eligibility of 4 weeks, followed by treatment on Day 0, 84 (Week 12), 168 (Week 24), and 252 (Week 36), and a follow-up period of 20 weeks following the final dose. All four of the scheduled infusions will be given 12 weeks apart, and patients will keep an eDiary regarding symptoms and migraines in between infusions through Week 48.

***Reviewer's comment: Of note, the patients were blinded for the entire 60 weeks of the study period. However, after the last patient completed week 24, the applicant was unblinded to complete the primary efficacy analyses, so only the first 24 weeks are considered the "primary evaluation treatment period", and the remaining 6 months were considered safety follow-up period.***

- **Trial Location**

Study 006 was conducted at 85 centers in 2 countries, the United States and the Republic of Georgia. Overall, the patient population is primarily composed of patients from the United States (84%), and is therefore expected to be similar to, and generalizable to the overall migraine population in the United States.

- **Choice of Control Group**

The choice of placebo was appropriate for such a study of preventative migraine in the episodic migraine patient population.

- **Diagnostic Criteria**

For purpose of both the inclusion criteria and the efficacy analyses, a migraine day was defined as any day with a migraine or probable migraine as outlined in the IHS classification ICHD-II (2004)) (11 reference).

Migraine was defined as a self-reported headache that:

- 1) Lasted 4 to 72 hours
- 2) Had at least 2 of the following:
  - a. unilateral location,
  - b. pulsating quality,
  - c. moderate or severe pain intensity, and/or
  - d. aggravation by or causing avoidance of routine physical activity.
- 3) Had at least 1 of the following:
  - a. nausea and/or vomiting, and/or
  - b. photophobia and phonophobia

A probable migraine is defined as a headache that meets only 2 of the 3 above criteria.

- **Key inclusion Criteria**

- Male or female between 18 and 75 years of age inclusive (age at time of informed consent);
- Diagnosis of migraine at  $\leq 50$  years of age;
- History of migraine  $\geq 12$  months with
  - $\leq 14$  headache days, of which at least 4 have to be migraine days, in each 28-day period in the 3 months prior to screening
  - During the 28 days following the screening visit, the patient experiences  $\leq 14$  headache days, of which at least 4 have to be migraine days, as recoded in the eDiary;
- Use of acute migraine medications  $\leq 14$  days per 28-day period in the 3 months prior to screening and in the 28-day period prior to randomization
- Use of triptans must be  $\leq 10$  days per 28-day period
- No regular use of prophylactic headache medication within 2 months prior to screening and during the 28-day period prior to randomization; short-term (no more than 7 days per month) menstrual migraine prophylactic medication is allowed
- No use of any botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck 4 months prior to screening and during the 28-day period prior to randomization
- Limited use of barbiturates and prescription opiates by maintaining stable doses for 2 months prior to screening and dosing does not exceed 4 days per month through Week 24. Drugs containing non-prescription codeine (16 mg or less) are permitted
- No use of any approved devices, neuromodulation, neurostimulation, or injectable therapy for headache prophylaxis for 2 months prior to screening and the 28-day period prior to randomization
- Adequate use of contraception throughout study and for up to 6 months after last dose
- Headache eDiary was completed on at least 25 of the 28 days prior to randomization

- **Key Exclusion Criteria**

- Confounding pain syndromes, e.g. fibromyalgia, complex regional pain syndrome, or any pain syndrome that requires regular analgesia
- Known or suspected Temporo-Mandibular Disorders
- History or diagnosis of complicated migraine (ICHD-II, 2004) (11), chronic tension-type headache, hypnic headache, cluster headache, hemicrania

continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine

- o Unable to differentiate migraine from other headaches
- o Have present or previous malignancies, except patients with history of squamous or basal skin cell carcinoma with excision for cure or patients with history of breast or cervical cancer  $\geq 10$  years since diagnosis/treatment with no evidence of recurrence
- o Cardiovascular disease, neurological disease, cerebrovascular disease, diabetes, or Raynaud's disease, life-threatening allergy (e.g., anaphylaxis)
- o Have a clinically significant abnormal ECG at screening or pre-dose on Day 0. An alert for a clinically significant abnormality will be set for the following interval values:
  - RR < 460 msec (or HR > 130 bpm)
  - RR > 1700 msec (or HR < 35 bpm)
  - QRS > 180 msec
  - QtcF > 500 msec (or any other QTc method if QTcF is not utilized)
- o Have any clinically significant concurrent medication condition as shown by, but not limited to:
  - Hepatic  
ALT  $\geq 2\times$  ULN; AST  $\geq 2\times$  ULN
  - Hematology  
Hemoglobin < 10 g/dL  
Absolute neutrophil count < 1000 cells/ $\mu$ L  
Platelet count < 100,000 cells/ $\mu$ L
  - Renal  
Creatinine > 2.0 mg/dL
- o Systolic blood pressure (SBP) 140 mm Hg or greater and/or diastolic blood pressure (DBP) 90 mm Hg or greater at Treatment/ Day 0
- o Beck depression inventory score > 24 at screening
- o At imminent risk of self-harm or harm to others in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS), including if they report suicidal ideation Type 4 or 5 in the past 6 months or suicidal behavior in the past 2 years
- o History of substance abuse within the past 2 years
- o Pregnant, breastfeed, or planning to become pregnant during the trial
- o Receipt of any experimental, unregistered therapy within 30 days or 5 plasma half-lives (whichever is longer) before screening
- o Receipt of any monoclonal antibody treatment within 6 months of screening
- o Previously dosed with ALD403 or any monoclonal antibody targeting CGRP pathway

- **Dose Selection**

The study was designed to explore dose-related efficacy at doses of 30, 100, and 300 mg every 12 weeks. A prior Phase 2 study (ALD403-CLIN-002) in patients with episodic migraine, demonstrated a single infusion of 1000 mg ALD403 produced sustained efficacy in terms of mean change from baseline in migraine days and responder analysis. Another prior study (ALD403-CLIN-001) demonstrated marked suppression of capsaicin-induced skin blood flow at doses ranging from 30 – 1000 mg ALD403 given as a single intravenous infusion.

The estimated systemic exposure of 300 mg ALD403 of Free ALD403 following the fourth dose is  $C_{max}$  110.02  $\mu\text{g/mL}$  and  $AUC_{(0-12\text{ wk})} = 46.648\text{ }\mu\text{g*hr/mL}$ . These ALD403 exposure levels are at least 56- and 19-fold less than the mean  $C_{max}$  and  $AUC_{(0-2\text{ wk})}$  systemic exposures observed in cynomolgus monkeys, following a chronic 6-month evaluation administered at the NOAEL of 150 mg/kg once every 2 weeks.

***Reviewer's comment: The dose range for this study was appropriate, including all three dose levels studied. The 30 mg dose was subsequently dropped from evaluation in the chronic migraine study (See Section 6.2.1), so further information regarding efficacy of this dose in treatment of chronic migraine is not available.***

- **Study treatments**

ALD403 is an anti- (calcitonin gene-related peptide) humanized monoclonal antibody, presented for injection in 2-mL (b) (4) glass vials as single-use preservative-free solution for IV administration, concentrated to 100 mg/mL with a pH of 5.8.

Patients were assigned to one of 4 treatment arms, ALD403 30 mg, 100 mg, 300 mg, or placebo. All doses were administered an IV infusion of ALD403 or placebo in 100 mL of 0.9% saline.

- **Assignment to treatment**

Patients were assigned to one of 4 treatment arms. Randomization occurred 29-35 days after the screening visit after the eligibility assessments were completed. Sites completed the randomization in an Interactive Web or Voice Response System (IWRS/IVRS) and the randomization assignment was obtained by the site's unblinded pharmacist. Patients were randomized in equal ratios to one of the dose groups using stratified permuted block randomization, with stratification by migraine days during the screening period ( $\leq 9$  days vs  $> 9$  days).

- **Blinding**

The placebo drug was supplied as a single-use preservative-free solution in a 2-mL (b) (4) glass vial formulated with the same excipients as ALD403, without the active

ingredient.

All patients and study personnel were blinded to treatment assignment, other than the clinical trial site's unblinded pharmacist or Investigational Product cosignee. Each study site had a written plan in place to ensure blinding is maintained. The blind was only to be broken for reasons in which knowledge of the Investigational Product was critical to the patient safety and/or trial management. Any cases of unblinding were to be reported within 24 hours of the incident to the applicant. The study remained blinded until the last patient completed the Week 24 visit.

- **Dose modification/Dose Discontinuation**

There were no pre-specified dose modifications or reductions in the protocol.

- **Administrative structure**

The clinical trial was conducted in accordance with standards of Good Clinical Practice (GCP). A Data Monitoring Committee (DMC) including appropriately qualified members who are independent of the applicant was formed to consider safety data generated during the clinical trial. The members of the DMC were externally appointed by the applicant and were not connected with management of the clinical trial.

- **Procedures and schedule**

The following table summarizes the schedule of study visits, and includes some of the key assessments that occurred at those visits (Table 3). All patients received an electronic headache eDiary at the time of screening to record information daily regarding headache characteristics, severity, and length.

**Table 3 Schedule of Key Assessments and Procedures Study 006**

| Visit Number                            | Screening   | Primary Efficacy and Safety Period |      |      |       |       |       |       | Long term Safety Period |       |       |              |
|-----------------------------------------|-------------|------------------------------------|------|------|-------|-------|-------|-------|-------------------------|-------|-------|--------------|
|                                         | D-35 to -29 | D0 <sup>1</sup>                    | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 28                   | Wk 36 | Wk 48 | Wk 56 EOS/ET |
| Inclusion/Exclusion evaluation          | X           | X                                  |      |      |       |       |       |       |                         |       |       |              |
| Headache eDiary Review/Compliance Check | X           | X                                  | X    | X    | X     | X     | X     | X     | X                       | X     | X     |              |
| Height/Weight <sup>2</sup>              | X           | X                                  |      |      |       |       |       | X     |                         | X     |       | X            |
| Vital signs                             | X           | X                                  | X    | X    | X     | X     | X     | X     | X                       | X     | X     | X            |
| Physical Exam                           | X           | X                                  |      |      |       |       |       | X     |                         | X     |       |              |
| Urine Pregnancy Test                    | X           | X                                  |      |      | X     |       |       | X     |                         | X     | X     | X            |
| BDI-II                                  | X           |                                    |      |      |       |       |       |       |                         |       |       |              |
| HIV, Hep B/C, Urine drug screen         | X           |                                    |      |      |       |       |       |       |                         |       |       |              |
| C-SSRS                                  | X           | X                                  | X    | X    | X     | X     | X     | X     | X                       | X     | X     | X            |
| Brush Allodynia Test                    |             | X                                  | X    |      | X     | X     | X     | X     |                         |       |       |              |

Clinical Review  
Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

|                                       |   |   |   |   |   |   |   |   |   |   |   |   |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| 12-lead ECG                           | X | X | X | X | X |   |   | X | X | X | X | X |
| Hematology/Chemistry Labs             | X | X | X |   | X |   |   | X | X | X | X | X |
| Plasma PK levels                      |   | X | X | X | X | X | X | X |   | X | X | X |
| Serum Anti-ALD403 Ab <sup>3</sup>     |   | X | X | X | X | X | X | X |   | X | X | X |
| SF-36                                 |   | X | X | X | X | X | X | X |   | X |   | X |
| EQ-5D-5L, ASC-12                      |   | X | X | X | X | X | X | X |   |   |   |   |
| Adverse Event review                  | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Med review                | X | X | X | X | X | X | X | X | X | X | X | X |
| Treatment administration <sup>4</sup> |   | X |   |   | X |   |   | X |   | X |   |   |

**Source: Clinical Reviewer's summary of Study 006 Protocol Schedule of Events and Assessments**

Abbreviations: BDI-II= Beck Depression Inventory; C-SSRS= Columbia-Suicide Severity Rating Scale; SF-36 = Short Form Healthy Survey; EQ-5D-5L = Health-Related Quality of Life; ASC-12 = Allodynia Symptom Checklist; EOS/ET = End-of-Study/Early Termination Visit

<sup>1</sup> Randomization to occur on Day 0 pre-dose

<sup>2</sup> Height at screening, weight only at Day 0, Weeks 24, 36, and 56

<sup>3</sup> Patients who test positive for anti-ALD403 antibodies at the last study visit will be asked to provide up to 2 additional blood samples at approximately 3 month intervals for an additional 6 months

<sup>4</sup> Patients monitored for at least 4 hours after dosing completion

- **Dietary restrictions/instructions**

There were no restricted foods or activity throughout the study.

- **Concurrent Medications**

The use of any concomitant medications must be recorded on the CRF. The use of any regular prescription medications for condition other than migraine must be pre-approved by the medical monitor. The medical monitor should also be notified in advance if any restricted medications were administered.

Those restricted therapies include:

- Any prophylactic headache medication (any preventative medication or supplement with evidence of efficacy from at least 1 placebo-controlled trial)
- Barbiturates and prescription opiates are allowed for  $\leq 4$  days per month through Week 24, provided the patient does not meet the criteria for Medication Overuse Headache and has been on a stable regimen for at least 2 months prior to screening. Drugs containing non-prescription codeine (16 mg or less) are permitted.
- Botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head/face/neck are prohibited from 4 months prior to screening through Week 24.
- Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections, extracranial nerve blocks, facet joint injections) for headache prophylaxis are prohibited from 2 months prior to screening through Week 24.

- **Treatment Compliance**

The headache eDiary was to be completed daily whether or not the patient had a headache, and also recorded if the patient took acute migraine medication on that day. The compliance data was available to the trial site for review at each visit, and patients were to be counseled on completing the diary if it was not completed daily.

***Reviewer's comment: The eDiary was monitored throughout the study for compliance at every visit. There was no concern for compliance with treatment administration, as the treatment was administered intravenously at the clinical trial site.***

- **Patient completion, discontinuation, or withdrawal**

Patients could discontinue treatment or withdraw from the study at any time. The main criteria for treatment discontinuation or study withdrawal included adverse event, patient or investigator decision, lost to follow-up, termination of the study, or withdrawal of consent.

All reasons for withdrawal and treatment discontinuation, as well as time of withdrawal was recorded on the CRF. Patients that discontinued treatment for any reason were encouraged to continue with study assessments until end of study. Patients that chose to withdraw consent, were scheduled for an early termination visit with associated assessments.

Patients who were withdrawn from the study after randomization were not replaced.

## **Study Endpoints**

- **Primary Efficacy Endpoint**

The primary efficacy endpoint was the change in frequency of migraine days (Weeks 1-12).

- A migraine day is defined as any day with a headache that meets the migraine or probable migraine characteristics as outlined above in *Diagnostic Criteria*.
- Headache episodes were self-reported by the patients and an "episode" is a single headache event that the patient reports as having a start and an end and lasts at least 30 minutes.
- The frequency of migraine days is the number of migraine days within four week intervals and the average four-week frequency in 12- and 24- week intervals.
- Change from baseline is the difference in frequency of migraine days

between baseline and the counts within these four-week intervals.

- o The 12- and 24- week change is the difference in the frequency between baseline and the average of the 4 week intervals. Percent change is 100 times the ratio of the change and the baseline frequency.

***Reviewer's comments: The primary endpoint was changed in 2016 with Protocol Amendment # 3 (see Table 4 below) after discussion with the FDA, rather than using the 75% responder rate which was initially planned as the primary endpoint. The final choice of primary endpoint is consistent with the primary endpoint used in the pivotal studies for the recently approved CGRP antagonists for preventive treatment of episodic migraine. All of these recently approved products used change in frequency of migraine days, although with slight variation of definition of migraine days and/or the intervals over which the migraine days were measured. Overall, the use of Weeks 1-12 is consistent with what has been accepted in other preventive treatment of migraine studies and is considered to be clinically meaningful for measuring efficacy in terms of preventive treatment.***

- **Key Secondary Endpoints**

- o 75% migraine responder rate (Weeks 1-4)
- o 75% migraine responder rate (Weeks 1-12)
- o 50% migraine responder rate (Weeks 1-12)
- o Percentage of subjects with a migraine on the day after dosing

A responder is a patient who achieves the specified percent reduction in migraine headache days within these intervals based upon the average change from baseline measures. Reductions will be evaluated by comparing baseline frequency of migraine days to the migraine frequency in four-week intervals. Results from the 4 week intervals will be combined to produce 12- and 24- week responder endpoints.

The percent of patients with a migraine on the day after the first dose will be summarized.

***Reviewer's comment: The above key secondary endpoints are included in the statistical hierarchical testing as outlined below.***

(b) (4)

- **Other Secondary Endpoints**

- o Change in acute migraine medication days (Weeks 1-12)
- o Headache/migraines with acute medication usage
- o 100% migraine responder rates (Weeks 1-12)

- o Short-Form Health Survey (SF-36)
- o Health-Related Quality of Life (EQ-5D-5L)
- o Allodynia Symptom Checklist-12 (ASC-12)
- o Brush (dynamic mechanical) Allodynia
- o Migraine responder rates for time periods other than Weeks 1-12
- o Change in frequency of migraine days between baseline and time periods other than Weeks 1-12
- o Headache responder rates
- o Change in the frequency of headache days
- o Percent change in headache/migraine days
- o Time to first migraine after dosing
- o Headache/migraine hours
- o Headache/migraines with severe intensity

Headache severity will be collected on a 3 point scale: mild, moderate, or severe pain. Patients with no migraines/headaches will be included with a scale of zero.

The percent of migraines and headaches with acute medication usage will be summarized, and patients with no migraines/headaches will be included with a rate of zero. The number of days within 4 week intervals that patients used acute migraine medication will be summarized in 4, 12, and 24 week intervals.

- **Tertiary Endpoints:**

- o Headache episodes/migraine attacks

A migraine attack is defined as one continuously recorded migraine. One attack may result in multiple migraine days. Headache episodes are defined similarly.

- **Safety Endpoints:**

- o Adverse events and serious adverse events (SAEs)
- o Changes in clinical laboratory assessments
- o Vital Signs
- o ECGs
- o Suicidal ideation and behavior as measured by the C-SSRS

- **Pharmacokinetic Endpoints:**

- o Free ALD403 plasma concentrations

- **Immunogenicity Endpoints**

- o Development of specific anti-ALD403 antibodies
- o Characterization of specific anti-ALD403 antibodies for neutralizing activity

## Statistical Analysis Plan

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review  
Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

The final statistical analysis plan, Version 1.4 was updated per FDA feedback on May 18, 2017 prior to database lock. For further details of the statistical analysis plan, please refer to the complete statistical review by Dr. Steven Bai.

**Analysis populations**

Full analysis population (to be used for efficacy analyses): all randomized patients who received investigational product/placebo. Patients will be summarized within the treatment group to which they were randomized.

Safety population (to be used for safety analyses): all patients who received investigational product/placebo, summarized within the treatment group for which they actually received treatment.

Demographic, baseline characteristics, migraine history and concomitant medications will be summarized by treatment group.

#### Primary Endpoint Analyses

- o The null hypothesis is the change in migraine days for patients in the ALD403 treatment arm will be equal to the change in migraine days for patients in the placebo arm.
- o The alternate hypothesis is that the change in migraine days for patients in the ALD403 arm is not equal to the change in migraine days for patients in the placebo arm. The change from baseline is expected to be negative as migraines are being reduced.
- o While the test outlined above is two-sided, as is the alpha level used for the study (5%), clinically relevant results require a larger reduction of migraines on the ALD403 treatment arms.
- o ANCOVA model will be used to test for a difference between treatment arms.
- o Treatment and the stratification variable of baseline migraine days will be the independent variables.

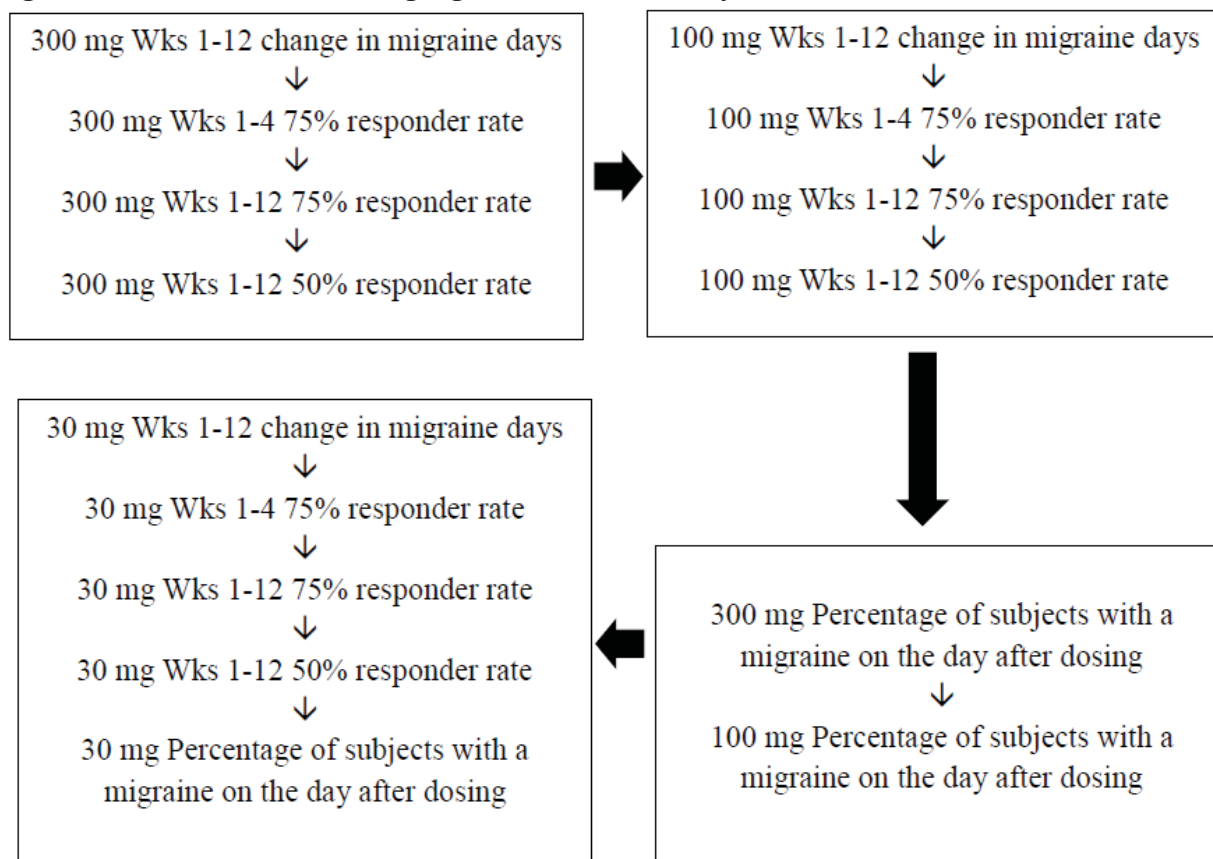
#### Secondary Efficacy Analyses

- o Testing will be performed for the key secondary endpoints and the change in acute migraine medication days endpoint
- o Key secondary endpoints will be tested using a CMH/extended CMH test
- o Will be stratified by the randomization stratification factor
- o Change in acute migraine medication days will be tested using an ANCOVA model similar to primary endpoint: change from baseline measure
- o Time to first migraine will be summarized using Kaplan-Meier methods

#### Multiplicity Adjustment

A serial procedure will be used to account for multiplicity of dose level for the primary and key secondary endpoints, as outlined in Figure 1 below. The procedure will start with 300 mg vs placebo comparison for primary endpoint. If significant, testing will continue to a subset of the key secondary endpoints for 300 mg, then follow the same steps for the 100 mg group. The procedure will then move on to the remaining key secondary endpoint (% of patients with a migraine on the day after dosing) for both the 300 mg and 100 mg. If all of the above secondary endpoints reach statistical significance, then the 30 mg group will be tested.

**Figure 1 Serial statistical testing algorithm at the 5% alpha level**



Source: Study 006 Statistical Analysis Plan Section 2.7.5 Figure

### Handling of Missing Data

Summary statistics will be reported based upon observed data except for the diary data which will utilize the imputation outlined below. If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (month and year) clearly indicates that the event started prior to treatment.

Patients who do not complete the eDiary will have missing data. It is expected that the missing data will be sporadic. If the diary has been completed at least 21 days in a 28-day interval, then normalization will be used. The results will be normalized to 28 days by multiplying the observed results by the inverse of the completion rate. If the diary has been completed less than 21 days in the 28-day interval, then the results for the 28-day interval will be a weighted function of the observed data for the current four-week interval and the results from the previous interval. The weights will be proportional to how many days the diary was completed. The results will be derived as

$$28 (W X_c + (1-W)X_p),$$

where  $W$  is the days the diary was completed / 20,  $X_c$  is the available average daily results for the current interval, and  $X_p$  are the daily results for the previous interval.

### Sample Size Determination

The planned sample size was 800 randomized and treated patients, allocated into 4 treatment groups in a 1:1:1:1 ratio. Pair-wise testing of each ALD403 group vs placebo was to be performed. Two hundred patients per group provides at least 95% power for each change in frequency of migraine days test, individually assuming a treatment effect of at least 1 day and a common standard deviation of 2.7 days or less. Ninety percent power is retained for a standard deviation up to 3 days. For the key secondary endpoint of 75% responder rate, 95% power is achieved assuming rates of 24% for placebo and 42% for ALD403, and for the 50% responder rate, 95% power is achieved assuming rates of 50% for placebo and 68% for ALD403. For the percentage of patients with a migraine on the day after dosing endpoint, 95% power is achieved for pair-wise comparisons assuming rates of 15% for placebo and 4% for ALD403.

### Protocol Amendments

The original protocol was dated June 30, 2015. Four amendments were made to the original protocol, which are summarized below in Table 4.

**Table 4 Summary of Major Protocol Amendments, Study 006**

| Amendment Number | Date             | Major Changes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                | 05 February 2016 | <ul style="list-style-type: none"> <li>Changes were made to allow for more robust long-term safety data including increased study duration from 28 to 60 weeks</li> <li>Increased number of infusions from 2 to 4, and number of visits from 8 to 12</li> <li>Decreased number of study sites from 100 to 75</li> <li>Updated inclusion criteria to prevent enrollment of chronic migraine patients</li> <li>Updated exclusion criteria to exclude patients who tampered with eDiary</li> <li>Clarified study would be unblinded to aggregate efficacy and safety data after last subject has completed Week 24 visit</li> <li>Decision rule for multiplicity analysis was put in place for key secondary endpoints</li> </ul> |
| 2                | 14 June 2016     | <ul style="list-style-type: none"> <li>Added language of desired indication to study title</li> <li>Increased number of study sites to 85 and included sites in Republic of Georgia</li> <li>Increased sample size from 600 to 800 patients</li> <li>Clarified only selected samples in the placebo arm would be analyzed for PK/immunogenicity</li> </ul>                                                                                                                                                                                                                                                                                                                                                                     |

|   |                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                  | <ul style="list-style-type: none"> <li>• <i>Changed PK endpoint to free ALD403 plasma concentrations only</i></li> <li>• <i>Endpoint changed for time to first migraine after dosing to be analyzed using eDiary data only, and no self-report time</i></li> <li>• <i>Additional testing added to characterize potential for neutralizing (Nab) ALD403 activity when antibody positive</i></li> </ul>                                                                                                                                                                                                                                                                                                                                               |
| 3 | 22 November 2016 | <ul style="list-style-type: none"> <li>• <i>Changed primary efficacy endpoint from 75% migraine responder rate (Weeks 1-12) to change in frequency of migraine days (Weeks 1-12)</i></li> <li>• <i>Updated key secondary endpoints and tertiary endpoints</i></li> <li>• <i>Step-down procedure changed to a serial procedure for primary and key secondary endpoints</i></li> <li>• <i>Updated statistical analysis plan given changes to primary endpoint</i></li> <li>• <i>Clarified that results from 4-week intervals would be combined to produce 12- and 24-week responder endpoints</i></li> <li>• <i>Additional immunogenicity testing added for patients that test positive for anti-ALD403 antibodies at last study visit</i></li> </ul> |
| 4 | 24 April 2017    | <ul style="list-style-type: none"> <li>• <i>Added summary information from completed and ongoing trials and relevant clinical findings</i></li> <li>• <i>Included additional key secondary efficacy endpoint of 50% migraine responder rate (Weeks 1-12) and Percentage of subjects with migraine on day after dosing</i></li> <li>• <i>Added change in acute migraine medication days as other secondary endpoint per FDA request</i></li> <li>• <i>Statistical analysis methods changed because of updated key secondary endpoints</i></li> <li>• <i>Updated multiplicity rules to reflect new secondary endpoints</i></li> </ul>                                                                                                                 |

Source: Adapted from Study 006 Clinical Study Report Table 6

### 6.1.2. Study Results

#### Compliance with Good Clinical Practices

The applicant provided attestation that Study 006 was conducted in accordance with standards of Good Clinical Practice (GCP) as defined by the International Council for Harmonisation (ICH) and all application federal and local regulations.

#### Financial Disclosure

See Appendix 13.2.

#### Patient Disposition

There were 2413 patients screened for Study 006, with 898 randomized patients and a total of 888 patients who were treated. They were equally distributed throughout the treatment arms (Table 5).

**Table 5 Patient Disposition for Study 006**

|                                |      |             |
|--------------------------------|------|-------------|
| Screened Population            |      | <b>2413</b> |
| Screen Failures                | 1515 |             |
| Randomized Population          |      | <b>898</b>  |
| ALD403 300 mg                  |      | 224         |
| ALD403 100 mg                  |      | 225         |
| ALD403 30 mg                   |      | 224         |
| Placebo                        |      | 225         |
| Treated Population             |      | <b>888</b>  |
| ALD403 300 mg                  |      | 222         |
| ALD403 100 mg                  |      | 221         |
| ALD403 30 mg                   |      | 223         |
| Placebo                        |      | 222         |
| Completed Study                |      | <b>676</b>  |
| Discontinued Study Prematurely |      | <b>212</b>  |
| Withdrawal by subject          | 133  |             |
| Lost to follow-up              | 67   |             |
| Physician decision             | 5    |             |
| Other                          | 7    |             |

Source: Reviewer adapted from Study 006 CSR Figure 2 and Table 7 (14.1.1.1)

**Table 6 Reasons for Randomized but Not Treated by Treatment Arm**

|                                               | ALD403 300 mg<br>n (%) | ALD403 100 mg<br>n (%) | ALD403 30 mg<br>n (%) | Placebo<br>n (%) | Total<br>n (%) |
|-----------------------------------------------|------------------------|------------------------|-----------------------|------------------|----------------|
| <b>Total Randomized</b>                       | 224                    | 225                    | 224                   | 225              | 898            |
| Randomized not Treated                        | 2 (< 1)                | 4 (1.8)                | 1 (< 1)               | 3 (1.3)          | 10 (1.1)       |
| <b>Total Treated</b>                          | 222                    | 221                    | 223                   | 222              | 888            |
| <b>Reason for Discontinuation<sup>a</sup></b> |                        |                        |                       |                  |                |
| Withdrawal by Subject                         | 1 (< 1)                | 2 (< 1)                | 1 (< 1)               | 1 (< 1)          | 5 (< 1)        |
| Adverse Event                                 | 0                      | 0                      | 0                     | 0                | 0              |
| Study Burden                                  | 0                      | 1 (< 1)                | 0                     | 1 (< 1)          | 2 (< 1)        |
| Lack of Efficacy                              | 0                      | 0                      | 0                     | 0                | 0              |
| Other                                         | 1 (< 1)                | 1 (< 1)                | 1 (< 1)               | 0                | 3 (< 1)        |
| Physician Decision                            | 0                      | 0                      | 0                     | 0                | 0              |
| Lost to Follow-up                             | 0                      | 0                      | 0                     | 0                | 0              |
| Death                                         | 0                      | 0                      | 0                     | 0                | 0              |
| Study terminated by sponsor                   | 0                      | 0                      | 0                     | 0                | 0              |
| Other                                         | 1 (< 1)                | 2 (< 1)                | 0                     | 2 (< 1)          | 5 (< 1)        |

<sup>a</sup> Percentages based upon all patients randomized. These patients were not included in full analysis population

Source: Reviewer Adapted from Study 006 CSR Table 14.1.1.1

**Table 7 Reasons for Early Study Discontinuation (Amongst Treated Patients)**

|                       | ALD403 300 mg<br>N = 222<br>n (%) | ALD403 100 mg<br>N = 221<br>n (%) | ALD403 30 mg<br>N = 223<br>n (%) | Placebo<br>N = 222<br>n (%) | Total<br>N = 888<br>n (%) |
|-----------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|---------------------------|
| Withdrawal by Subject | 30 (13.5)                         | 29(13.1)                          | 35 (15.7)                        | 39 (17.6)                   | 133 (15.0)                |
| Adverse Event         | 3 (1.4)                           | 3 (1.4)                           | 2 (< 1)                          | 1 (< 1)                     | 9 (1.0)                   |
| Study Burden          | 10 (4.5)                          | 15 (6.8)                          | 12(5.4)                          | 21 (9.5)                    | 58 (6.5)                  |
| Lack of Efficacy      | 2 (<1)                            | 3 (1.4)                           | 2 (< 1)                          | 8 (3.6)                     | 15 (1.7)                  |
| Other                 | 15 (6.8)                          | 8(3.6)                            | 19 (8.5)                         | 9 (4.1)                     | 51 (5.7)                  |
| Physician Decision    | 1 (< 1)                           | 1(< 1)                            | 3 (1.3)                          | 0                           | 5 (< 1)                   |
| Lost to Follow-up     | 22 (9.9)                          | 16 (7.2)                          | 12 (5.4)                         | 17 (7.7)                    | 67 (7.5)                  |
| Death                 | 0                                 | 0                                 | 0                                | 0                           | 0                         |
| Other                 | 0                                 | 3 (1.4)                           | 3 (1.3)                          | 1 (< 1)                     | 7 (< 1)                   |

Source: Adapted from Study 006 CSR Table 14.1.1.1, Reviewer verified

**Reviewer's comment:** Overall the treatment arms were generally similar in numbers for patients who were randomized and treated and who completed the study and discontinued early. There was no significant increase in patients who withdrew for adverse events among treated patients compared to placebo-treated patients. There were a greater number of patients who withdrew for study burden and lack of efficacy among the placebo patients compared to all dose levels of treatment, which may be another indicator supportive of efficacy.

### Protocol Violations/Deviations

There were important protocol deviations in 213 patients (23.7%). No patients were reported to be unblinded during the study. The deviations reported were evaluated and were determined to have no overall effect on the conclusions of the study. The protocol deviations were evenly distributed among the treatment arms.

There were a total of 7 patients who had major protocol deviations which resulted in dosing error. Two of these patients were each randomized twice at two different sites and received 2 different doses. Thus, for the analysis, the first randomized treatments were determined as the planned dose, and they were considered dosing errors.

**Table 8 Summary of Important Protocol Deviations among Randomized Patients**

|                               | ALD403 300 mg<br>N = 224<br>n (%) | ALD403 100 mg<br>N = 225<br>n (%) | ALD403 30 mg<br>N = 224<br>n (%) | Placebo<br>N = 225<br>n (%) | Overall<br>N = 898<br>n (%) |
|-------------------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|-----------------------------|
| At least 1 Protocol Deviation | 51 (22.8)                         | 50 (22.2)                         | 60 (26.8)                        | 52 (23.1)                   | 213 (23.7)                  |
| Concomitant Medication        | 3 (1.3)                           | 4 (1.8)                           | 8 (3.6)                          | 5 (2.2)                     | 20 (2.2)                    |
| Exclusion Criteria            | 1 (< 1)                           | 7 (3.1)                           | 9 (4.0)                          | 9 (4.0)                     | 26 (2.9)                    |
| Inclusion Criteria            | 5 (2.2)                           | 2 (< 1)                           | 4 (1.8)                          | 4 (1.8)                     | 15 (1.7)                    |
| Study procedures/assessments  | 17 (7.6)                          | 16 (7.1)                          | 24 (10.7)                        | 14 (6.2)                    | 71 (7.9)                    |
| Study treatment admin         | 10 (4.5)                          | 6 (2.7)                           | 11 (4.9)                         | 7 (3.1)                     | 34 (3.8)                    |
| Visit scheduling              | 5 (2.2)                           | 5 (2.2)                           | 6 (2.7)                          | 9 (4.0)                     | 25 (2.8)                    |
| ICH/GCP Deviations            |                                   |                                   |                                  |                             |                             |
| ICF process/timing            | 15 (6.7)                          | 16 (7.1)                          | 13 (5.8)                         | 10 (4.4)                    | 54 (6.0)                    |
| Inv adequate resources        | 0                                 | 0                                 | 1 (< 1)                          | 0                           | 1 (< 1)                     |
| Other CGP deviation           | 1 (< 1)                           | 0                                 | 0                                | 2 (< 1)                     | 3 (< 1)                     |

ICH/GCP = International Council for Harmonization/Good Clinical Practice; ICF = informed consent form

Source: Reviewer adapted from Study 006 CSR Table 14.1.1.3

**Reviewer's comment:** After completion of one of the clinical site visits, it was determined that there may have been possible unblinding events that were not reported in the CSR. Upon further information provided by the applicant in response to an information request, there were actually 6 patients who were unblinded during the study. As noted below, a sensitivity analysis which removed these patients from the primary efficacy analysis did not alter the primary endpoint results.

#### Table of Demographic Characteristics

A total of 898 patients were randomized, and of those, 888 patients received treatment and were included in the FAS and safety population. The baseline demographics are summarized below in Table 9.

**Table 9 Demographic Characteristics of Primary Efficacy Analysis Population**

| Demographic Parameters                           | Treatment Group                   |                                   |                                  | Placebo<br>N = 222<br>n (%) | Overall<br>N = 888<br>n (%) |
|--------------------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|-----------------------------|
|                                                  | ALD403 300 mg<br>N = 222<br>n (%) | ALD403 100 mg<br>N = 221<br>n (%) | ALD403 30 mg<br>N = 223<br>n (%) |                             |                             |
| <b>Sex</b>                                       |                                   |                                   |                                  |                             |                             |
| Male                                             | 25 (11.3)                         | 44 (19.9)                         | 34 (15.2)                        | 36 (16.2)                   | 139 (15.6)                  |
| Female                                           | 197 (88.7)                        | 177 (80.1)                        | 189 (84.8)                       | 186 (83.8)                  | 749 (84.3)                  |
| <b>Age</b>                                       |                                   |                                   |                                  |                             |                             |
| Mean years (SD)                                  | 40.1 (11.8)                       | 39.8 (10.6)                       | 39.3 (11.6)                      | 39.9 (11.7)                 | 39.8 (11.4)                 |
| Median (years)                                   | 40                                | 40                                | 38                               | 39.5                        | 39                          |
| Min, max (years)                                 | 18, 71                            | 18, 68                            | 18, 69                           | 20, 68                      | 18, 71                      |
| <b>Age Group</b>                                 |                                   |                                   |                                  |                             |                             |
| ≤ 35 years                                       | 89 (40.1)                         | 73 (33.0)                         | 93 (41.7)                        | 88 (39.6)                   | 343 (38.6)                  |
| > 35 years                                       | 133 (59.9)                        | 148 (67.0)                        | 130 (58.3)                       | 134 (60.4)                  | 545 (61.4)                  |
| <b>Race</b>                                      |                                   |                                   |                                  |                             |                             |
| White                                            | 187 (84.2)                        | 193 (87.3)                        | 183 (82.1)                       | 181 (81.5)                  | 744 (83.8)                  |
| Black or African American                        | 25 (11.3)                         | 18 (8.1)                          | 32 (14.4)                        | 30 (13.5)                   | 105 (11.8)                  |
| Other                                            | 10 (4.5)                          | 10 (4.5)                          | 8 (3.6)                          | 11 (4.9)                    | 39 (4.4)                    |
| <b>Ethnicity</b>                                 |                                   |                                   |                                  |                             |                             |
| Hispanic or Latino                               | 39 (17.6)                         | 40 (18.1)                         | 48 (21.5)                        | 25 (15.3)                   | 161 (18.1)                  |
| Not Hispanic or Latino                           | 183 (82.4)                        | 181 (81.9)                        | 175 (78.5)                       | 188 (84.7)                  | 727 (81.9)                  |
| <b>Region/Country</b>                            |                                   |                                   |                                  |                             |                             |
| United States                                    | 184 (82.9)                        | 182 (82.4)                        | 198 (88.8)                       | 185 (83.3)                  | 749 (84.4)                  |
| Republic of Georgia                              | 38 (17.1)                         | 39 (17.6)                         | 25 (11.2)                        | 37 (16.7)                   | 139 (15.6)                  |
| <b>BMI (kg/m<sup>2</sup>)</b>                    |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                        | 28.9 (7.2)                        | 29.4 (7.6)                        | 30.0 (8.3)                       | 29.6 (7.3)                  | 29.4 (7.6)                  |
| Median                                           | 27.2                              | 27.8                              | 28.2                             | 28.0                        | 27.8                        |
| Min, max                                         | 16.2, 49.8                        | 15.6, 59.3                        | 17.8, 67.5                       | 17.7, 52.6                  | 15.6, 67.5                  |
| <b>Baseline Migraine Days, n (%)<sup>1</sup></b> |                                   |                                   |                                  |                             |                             |
| ≤ 9 days                                         | 142 (64.0)                        | 142 (62.3)                        | 144 (64.6)                       | 144 (64.9)                  | 572 (64.4)                  |
| > 9 days                                         | 80 (36.0)                         | 79 (35.7)                         | 79 (35.4)                        | 78 (35.1)                   | 316 (35.6)                  |

<sup>1</sup> As entered at randomization by the site

Source: Clinical reviewer's analysis of Study 006 ADSL dataset

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Migraine history characteristics are summarized below, based on age of migraine diagnosis, and average number of headache days and migraine days per 28-day period, both in the 3 months prior to screening, and as recorded in the eDiary during the baseline screening period. Overall the migraine and headache characteristics were similar across the treatment groups. The mean baseline number of migraine days and migraine attacks were also similar across treatment groups.

**Table 10 Migraine History Characteristics of Full Analysis Population**

| Demographic Parameters                                            | Treatment Group                   |                                   |                                  | Placebo<br>N = 222<br>n (%) | Overall<br>N = 888<br>n (%) |
|-------------------------------------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|-----------------------------|
|                                                                   | ALD403 300 mg<br>N = 222<br>n (%) | ALD403 100 mg<br>N = 221<br>n (%) | ALD403 30 mg<br>N = 223<br>n (%) |                             |                             |
| <b>Duration since diagnosis (years)</b>                           |                                   |                                   |                                  |                             |                             |
| Mean years (SD)                                                   | 18.2 (11.8)                       | 17.4 (11.2)                       | 17.0 (10.9)                      | 16.9 (11.2)                 | 17.4 (11.3)                 |
| Median (years)                                                    | 18                                | 16                                | 15                               | 14.5                        | 16                          |
| Min, max                                                          | 0, 50                             | 0, 45                             | 0, 45                            | 0, 56                       | 0, 56                       |
| <b>Prior Avg No. of Migraine Days<sup>1</sup></b>                 |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 7.8 (2.6)                         | 7.5 (2.6)                         | 7.8 (2.7)                        | 7.5 (2.4)                   | 7.7 (2.6)                   |
| <b>Prior Avg No. of Headache Days<sup>1</sup></b>                 |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 10.1 (3.2)                        | 10.0 (3.5)                        | 10.3 (3.3)                       | 10.0 (2.9)                  | 10.1 (3.2)                  |
| <b>Baseline Migraine days (eDiary)</b>                            |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 8.6 (2.9)                         | 8.7 (2.9)                         | 8.7 (3.1)                        | 8.4 (2.7)                   | 8.6 (2.9)                   |
| <b>Baseline Headache Days (eDiary)</b>                            |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 10.1 (3.1)                        | 10.0 (3.0)                        | 10.2 (3.4)                       | 9.9 (2.8)                   | 10.1 (3.1)                  |
| <b>Any Acute Medications at Baseline (%days used)<sup>2</sup></b> | N = 223                           | N = 221                           | N = 219                          | N = 221                     | N = 884                     |
| Mean (SD)                                                         | 26.14 (19.4)                      | 24.7 (17.4)                       | 24.9 (18.6)                      | 24.7 (19.1)                 | 25.1 (18.7)                 |
| <b>Ergotamine Usage</b>                                           |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 0.1 (0.8)                         | 0.2 (2.4)                         | 0.2 (1.9)                        | 0.0 (0)                     | 0.1 (1.6)                   |
| <b>Triptan Usage</b>                                              |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 5.8 (10.0)                        | 5.3 (9.5)                         | 5.2 (9.0)                        | 5.5 (9.1)                   | 5.4 (9.4)                   |
| <b>Opioid Usage</b>                                               |                                   |                                   |                                  |                             |                             |
| Mean (SD)                                                         | 0.5 (2.9)                         | 0.2 (0.9)                         | 0.5 (2.8)                        | 0.6 (3.0)                   | 0.4 (2.6)                   |

<sup>1</sup>Average number per 28-day period in the 3 months prior to screening (reported)

<sup>2</sup> Denominator is the number of days with a non-missing evening report for the selected interval. Only patients who completed the evening report at least half the time for the selected interval are included

Source: Clinical reviewer's analysis of Study 006 ADSL dataset, and adapted from Study 006 CSR 14.1.3.2, 14.1.4.3

**Reviewer's comments:** The baseline headache/migraine days as recorded in the eDiary for the screening 28-day period were very similar to the average number of headache/migraine days reported in the 3-months prior to screening, although there was an average of one additional migraine day per month in each treatment arm. Overall the treatment arms were all quite similar in terms of baseline migraine history.

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not measured in this study as the treatments were administered intravenously at the site visits. However, compliance with daily recording in the eDiary was monitored and patients were counseled. The missing eDiary rate was evenly distributed across the treatment arms throughout the study period.

Concomitant medications were also evaluated in terms of baseline use of acute and prophylactic migraine medications. The regular use (> 7 days per month) of prophylactic medications for migraine was restricted in this study, so the overall use of migraine preventive treatment in the study was low. There was an average of 4.6% of patients who used a prophylactic medication, and this was evenly distributed throughout the treatment arms with slightly higher use in those in the ALD403 30 mg arm. The most frequently reported prophylactic headache medication in > 1 % of patients was magnesium (1.4%).

Approximately 96.4% of patients reported as least one acute concomitant medication for migraines. The most frequently reported acute concomitant headache medications were similar across treatment arms and were ibuprofen (41.6%), thomapyrin N (acetaminophen-aspirin-caffeine; 37.7%), sumatriptan (28.2%), and paracetamol (17.7%). A formal analysis of reduction in the use of acute migraine medications is outlined below in efficacy results – Secondary Endpoints.

At the Division's request, the applicant also analyzed the use of concomitant cardiovascular medications, which were used in approximately 6.5% of patients in the study. The percent of patients on concomitant cardiovascular medication was similar across treatment arms, with 6.2% of all ALD403-treated patients and 7.7% of placebo patients (See Table 11). Further analyses regarding need for new cardiovascular medications is included as a safety analysis in Section 8.5.1. It should be noted that patients with cardiovascular risk factors were excluded from the study, so the percent of patients taking concomitant CV medications is likely not generalizable to the population of patients who may ultimately take the medication in the postmarket setting.

**Table 11 Use of Concomitant Cardiovascular Medications**

| Demographic Parameters    | Treatment Group                   |                                   |                                  | Placebo<br>N = 222<br>n (%) | Overall<br>N = 888<br>n (%) |
|---------------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|-----------------------------|
|                           | ALD403 300 mg<br>N = 222<br>n (%) | ALD403 100 mg<br>N = 221<br>n (%) | ALD403 30 mg<br>N = 223<br>n (%) |                             |                             |
| Cardiovascular Medication | 10 (4.5)                          | 13 (5.8)                          | 18 (8.2)                         | 17 (7.7)                    | 58 (6.5)                    |

Source: Adapted from Study 006 CSR, Table 14.1.4.1

## Efficacy Results – Primary Endpoint

The primary efficacy endpoint for this study is the change from baseline in frequency of monthly migraine days over Weeks 1-12. The primary endpoint was calculated as the number of migraine days within 4-week intervals that were averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in the frequency of monthly migraine days over Weeks 1-12. Migraine was defined as per Section 6.1.1 above.

The primary endpoint was statistically significant for the ALD403 300 mg and 100 mg treatment groups. The primary endpoint for the ALD403 30 mg arm was nominally significant, with an effect size that was numerically greater than the 100 mg arm, and less than the 300 mg arm. However, using the decision rule outlined above in Figure 1, the 30 mg treatment arm was not statistically significant.

**Table 12 Analysis of Migraine Days by 12-Week Interval and Treatment Effect**

| Interval                     | Treatment Group          |                          |                         | Placebo<br>N = 222 |
|------------------------------|--------------------------|--------------------------|-------------------------|--------------------|
|                              | ALD403 300 mg<br>N = 222 | ALD403 100 mg<br>N = 221 | ALD403 30 mg<br>N = 223 |                    |
| Baseline                     |                          |                          |                         |                    |
| Mean (SD)                    | 8.6 (2.9)                | 8.7 (2.9)                | 8.7 (3.1)               | 8.4 (2.7)          |
| Weeks 1-12                   |                          |                          |                         |                    |
| Estimated Mean               | 4.3                      | 4.7                      | 4.6                     | 5.4                |
| Mean difference from placebo | -1.11                    | -0.69                    | -0.82                   |                    |
| 95% CI                       | (-1.68, -0.54)           | (-1.25, -0.12)           | (-1.39, -0.25)          |                    |
| <b>Change from baseline</b>  |                          |                          |                         |                    |
| Estimated Mean               | -4.29                    | -3.88                    | -4.01                   | -3.19              |
| Mean difference from placebo | -1.11                    | -0.69                    | -0.82                   |                    |
| 95% CI                       | (-1.68, -0.54)           | (-1.25, -0.12)           | (-1.39, -0.25)          |                    |
| p-value                      | 0.0001                   | 0.0181                   | 0.0046*                 |                    |

CI = Confidence interval

Migraine days over 12-week periods were all monthly migraine days

Change from baseline was the difference in migraine days between baseline and the selected Week 1-12 interval

\*nominally significant, but not statistically significant based on the decision rule (Section 6.1.1, Figure 2)

Source: Adapted from Study 006 CSR Table 16, Reviewer and statistician verified

The applicant also calculated the mean change from baseline in monthly migraine days over Weeks 1-24. Sensitivity analyses with change from baseline in monthly migraine days over Weeks 1-24, as well as sensitivity analyses based on a modified missing data imputation rule and with modified definition of baseline were also completed and both support the primary efficacy endpoint analysis.

**Reviewer's note:**

***This reviewer removed the patients who received the wrong dose (4 from 30 mg group, and 1 from 100 mg group) from the full analysis population, and re-ran an analysis of the primary***

***endpoint, and the results were consistent with the original primary analysis. Also re-ran the primary efficacy analysis on the full analysis population according to the treatment they received vs. the treatment to which they were assigned (safety population), and these results were also consistent with the primary efficacy endpoint with no impact on the size of the treatment effect.***

### **Data Quality and Integrity**

There were no identified major concerns with regard to data quality or integrity. The OSI site inspections did uncover a few examples of unblinding and many cases of possible unblinding. There were 6 patients at two sites in Study 006 [REDACTED] (b) (6) [REDACTED] that had unblinding events. A sensitivity analyses was conducted with removal of these patients with no impact on the primary outcome. The treatment effect was maintained at -1.11 for the 300 mg arm, -0.72 for the 100 mg arm, and -0.81 for the 30 mg arm.

See OSI review for complete details.

### **Efficacy Results – Secondary and other relevant endpoints**

The key secondary endpoints were analyzed by dose per the algorithm outlined above in Section 6.1.1 (Figure 1). The key secondary endpoints are summarized below in the following tables.

**Table 13 Summary of Key Secondary Endpoint Outcomes for Study 006**

|                                      | ALD403 300 mg<br>N = 222 | ALD403 100 mg<br>N = 221 | ALD403 30 mg<br>N = 223 | Placebo<br>N = 222 |
|--------------------------------------|--------------------------|--------------------------|-------------------------|--------------------|
| <b>75% responder rate Weeks 1-4</b>  |                          |                          |                         |                    |
| n (%)                                | 70 (31.5)                | 68 (30.8)                | 67 (30.0)               | 45 (20.3)          |
| Diff from placebo (%)                | 11.3                     | 10.5                     | 9.8                     |                    |
| 95% CI                               | (3.2, 19.3)              | (2.4, 18.6)              | (1.8, 17.8)             |                    |
| p-value (OR)                         | 0.006 (1.82)             | 0.011 (1.75)             | 0.017 (1.69)            |                    |
| <b>75% responder rate Weeks 1-12</b> |                          |                          |                         |                    |
| n (%)                                | 66 (29.7)                | 49 (22.2)                | 55 (24.7)               | 36 (16.2)          |
| Diff from placebo (%)                | 13.5                     | 6.0                      | 8.4                     |                    |
| 95% CI                               | (5.8, 21.2)              | (-1.4, 13.3)             | (1.0, 15.9)             |                    |
| p-value (OR)                         | 0.0007 (2.18)            | 0.113 (1.47)*            | 0.027 (1.69)**          |                    |
| <b>50% responder rate Weeks 1-12</b> |                          |                          |                         |                    |
| n (%)                                | 125 (56.3)               | 110 (49.8)               | 112 (50.2)              | 83 (37.4)          |
| Diff from placebo (%)                | 18.9                     | 12.4                     | 12.8                    |                    |
| 95% CI                               | (9.8, 28.0)              | (3.2, 21.5)              | (3.7, 22.0)             |                    |
| p-value (OR)                         | 0.0001 (2.16)            | 0.0085 (1.66)**          | 0.0064 (1.69)**         |                    |

OR – Odds Ratio vs. Placebo

\*not statistically significant, therefore decision rule stops testing for all remaining endpoints

\*\* nominally significant

Source: Adapted from Study 006 CSR Table 17, 18, 19; reviewer- verified

**Reviewer's comment: The key secondary endpoints demonstrated statistically significant improvement over placebo at 300 mg for a 75% responder rate over Weeks 1-4, Weeks 1-12, and a 50% responder rate over Weeks 1-12. The 100 mg dose demonstrated statistically significant improvement over placebo for the 75% responder rate over Weeks 1-4, but not the 75% responder rate over Weeks 1-12. This stopped the decision rule for further testing of remaining endpoints. However, the 100 mg dose did demonstrate nominally significance in a 50% responder rate over Weeks 1-12 compared to placebo, and the 30 mg dose was nominally significant for all 3 key secondary endpoints compared to placebo.**

#### Percentage of Patients with Migraine on Day after Dosing (Day 1 Effect)

The applicant summarized the percentage of patients who had a migraine on the day after dosing, where Day 0 is the day treatment is administered, and Day 1 is the day after dosing. To calculate the baseline migraine prevalence rate, the applicant used the daily migraine prevalence, where on average, 30% of patients had a migraine on any given day during the 28-day screening period, based on eDiary entries. When comparing migraine prevalence on the day of dosing and on the day after dosing (Day 1) in the treatment arms compared to placebo, the percentage of patients with a migraine on Day 1 in the treatment arms were both numerically lower than the placebo arm.

At the Division's request, the applicant also provided subgroup analyses to look specifically at the incidence of migraine on Day 1, separated by patients who had a migraine on day 0, and those that did not have a migraine on Day 0. The two subgroup analyses presented in the table below vary by how a migraine on day of dosing was defined. For the initial subgroup analysis, migraine on day of dosing includes any migraine present at any time on Day 0, and migraine on Day 1 is defined as migraine present at any time on Day 1. For the alternate subgroup analysis, migraine on day of dosing includes only those patients who had a migraine ongoing at the start of the treatment, and migraine on Day 1, includes only those patients who had a new migraine starting between the end of infusion on Day 0 and the end of Day 1.

**Table 14 Daily Migraine Prevalence at Baseline and on Day 1 (per Applicant)**

|                                                | <b>ALD403<br/>300 mg</b> | <b>ALD403<br/>100 mg</b> | <b>ALD403<br/>30 mg</b> | <b>Placebo</b> |
|------------------------------------------------|--------------------------|--------------------------|-------------------------|----------------|
| <b>Percentage of Patients with a Migraine</b>  | <b>N = 222</b>           | <b>N = 221</b>           | <b>N = 223</b>          | <b>N = 222</b> |
| Day 0                                          | 18.5                     | 19.4                     | 19.9                    | 20.5           |
| Day 1                                          | <b>13.9</b>              | <b>14.8</b>              | <b>17.3</b>             | <b>22.5</b>    |
| p-value <sup>1</sup>                           | 0.0159                   | 0.0312                   | 0.1539                  |                |
| <b>Subgroup analysis<sup>2</sup></b>           |                          |                          |                         |                |
| Yes Migraine on Day of Dosing (Day 0)          | N = 38                   | N = 41                   | N = 42                  | N = 42         |
| Day 1 Migraine                                 | <b>35.3</b>              | <b>35.5</b>              | <b>36.0</b>             | <b>50.0</b>    |
| p-value*                                       | 0.1814                   | 0.2118                   | 0.1946                  |                |
| No Migraine on Day of Dosing (Day 0)           | N = 173                  | N = 172                  | N = 171                 | N = 165        |
| Day 1 Migraine                                 | <b>8.9</b>               | <b>9.9</b>               | <b>12.0</b>             | <b>14.4</b>    |
| p-value*                                       | 0.1001                   | 0.1829                   | 0.4925                  |                |
| <b>Alternate Subgroup Analysis<sup>3</sup></b> |                          |                          |                         |                |
| Yes Migraine on Day of Dosing (Day 0)          | N = 20                   | N = 21                   | N = 22                  | N = 13         |
| Day-1 Migraine                                 | <b>5.0</b>               | <b>9.5</b>               | <b>11.7</b>             | <b>38.5</b>    |
| p-value*                                       | 0.0193                   | 0.0385                   | 0.0695                  |                |
| No Migraine on Day of Dosing (Day 0)           | N = 191                  | N = 192                  | N = 190                 | N = 191        |
| Day 1 Migraine                                 | <b>14.0</b>              | <b>13.5</b>              | <b>16.6</b>             | <b>23.5</b>    |
| p-value*                                       | 0.01254                  | 0.0100                   | 0.0854                  |                |

<sup>1</sup> p-values were obtained from an extended Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days. They were not statistically significant based on the multiplicity adjustment decision rule outlined in the SAP but were nominally significant

<sup>2</sup> Migraine on day of dosing includes any migraine present at any time during Day 0, and Migraine on Day 1 defined as migraine present at any time on Day 1

<sup>3</sup> Migraine on day of dosing includes only those patients who had a migraine that was ongoing at the start of treatment and Migraine on Day 1 includes only those that were new migraines starting between the infusion on Day 0 and the end of Day 1

\*p-values not reliable for these subgroup analyses given the small number of patients in each group

Source: Reviewer verified and adapted from Study 011 CSR Table 20 (14.2.2.4.2) and tables 14.2.2.4.1a and 14.2.2.4.1c

**Reviewer's comment: The above analyses demonstrate that the overall prevalence of migraine on Day 1 was lower in the treatment arms than in the placebo arm, and this**

*difference was nominally significant in the 100 mg and 300 mg treatment arms, but not statistically significant based on the multiplicity adjustment decision rule outlined in the SAP (Figure 1 above).*

*The two subgroup analyses demonstrate that amongst only those patients who had a migraine on Day 0, they were more likely to also have a migraine on Day 1 in the placebo arm than in the treatment arm. For those patients who had a migraine ongoing during the infusion (alternate subgroup analysis), they were also more likely to have a migraine on Day 1 with placebo rather than treatment. The small numbers prevent any true statistical analysis of these subgroups. However, it appears to be a trend that those patients who receive placebo are more likely to have a migraine on Day 1, indicating that “preventive treatment” has not yet started.*

*Of those patients who did not have a migraine during infusion, the percent of patients who had a migraine on Day 1 after receiving placebo was only slightly higher than those receiving treatment. This is a post-hoc analysis on small numbers of patients, and conclusions are difficult to make. The study population for this episodic migraine study includes patients who have migraines less than 14 days per month, so most patients do not have daily migraines. Therefore, those who do not have a migraine on day 0 are not significantly more likely to have a migraine on day 1. Therefore, it would not necessarily be expected that there would a large difference in the prevalence of migraines on day 1 between placebo and treatment for this subgroup analysis. The expectations for migraine on Day 1 may be different in the chronic migraine study.*

**Table 15 Analysis of Reduction in Migraine Prevalence by Weeks 1-4**

|                                         | ALD403 300 mg<br>N = 222 | ALD403 100 mg<br>N = 221 | ALD403 30 mg<br>N = 223 | Placebo<br>N = 222 |
|-----------------------------------------|--------------------------|--------------------------|-------------------------|--------------------|
| <b>Migraine Prevalence</b>              |                          |                          |                         |                    |
| Baseline <sup>1</sup>                   | 30.8                     | 31.0                     | 31.0                    | 29.8               |
| Overall Weeks 1-4                       |                          |                          |                         |                    |
| Estimated Mean                          | 16.1                     | 16.6                     | 16.2                    | 21.0               |
| Mean difference from placebo            | -4.9                     | -4.35                    | -4.79                   |                    |
| 95% CI                                  | (-7.28, -2.52)           | (-6.73, -1.97)           | (-7.16, -2.14)          |                    |
| <b>Change from baseline<sup>2</sup></b> |                          |                          |                         |                    |
| Estimated Mean                          | -14.6                    | -14.0                    | -14.5                   | -9.7               |
| Mean difference from placebo            | -4.9                     | -4.35                    | -4.79                   |                    |
| 95% CI                                  | (-7.28, -2.52)           | (-6.73, -1.97)           | (-7.16, -2.14)          |                    |
| p-value <sup>3</sup>                    | < 0.0001                 | 0.0004                   | < 0.0001                |                    |

<sup>1</sup> Baseline Migraine Prevalence was the average over the 28-day screening period prior to treatment as recorded in eDiary

<sup>2</sup> Change from baseline is the model-estimated difference in migraine prevalence between baseline and the selected week interval

<sup>3</sup> Nominal p-values are obtained from a repeated measure model including group, visit (Weeks 1, 2, 3 and 4), baseline migraine prevalence and treatment group-by-visit interaction

Source: Table 14.2.2.4.3a, reviewer verified

**Reviewer's comment: The above table demonstrates that there is a statistically significant change in migraine prevalence based on percentage of patients with a migraine on any given day in the treatment groups compared to placebo over weeks 1-4 compared to the 28-day baseline period. The reduction in migraine prevalence was added as a key secondary endpoint for Study 011, although it was not a key secondary endpoint for this study.**

#### Changes in acute medication usage

The change from baseline in the use of acute migraine medication over Weeks 1-12 was added as a secondary endpoint at the request of the Division. The nominal p-values and 95% confidence interval for the endpoint were obtained from an analysis of covariance model with treatment as a factor and baseline migraine days as a covariate.

**Table 16 Analysis of Change in Acute Migraine Medication Days for Weeks 1-12 (Full Analysis Population)**

|                                       | ALD403 300 mg<br>N = 222 | ALD403 100 mg<br>N = 221 | ALD403 30 mg<br>N = 223 | Placebo<br>N = 222 |
|---------------------------------------|--------------------------|--------------------------|-------------------------|--------------------|
| <b>Acute Migraine Medication Days</b> |                          |                          |                         |                    |
| Baseline Mean (SD)                    | 1.6 (2.65)               | 1.5 (2.58)               | 1.4 (2.5)               | 1.5 (2.46)         |
| Weeks 1-12                            |                          |                          |                         |                    |
| Mean (SD)                             | 0.7 (1.68)               | 0.6 (1.17)               | 0.8 (1.73)              | 1.1 (2.01)         |
| Change from baseline                  |                          |                          |                         |                    |
| Mean (SD)                             | -0.8                     | -0.9                     | -0.6                    | -0.4               |
| Mean difference from placebo          | -0.36                    | -0.47                    | -0.18                   |                    |
| 95% CI                                | (-0.56, -0.15)           | (-0.68, -0.27)           | (-0.38, 0.02)           |                    |
| p-value                               | 0.0006                   | <0.0001                  | 0.0832                  |                    |

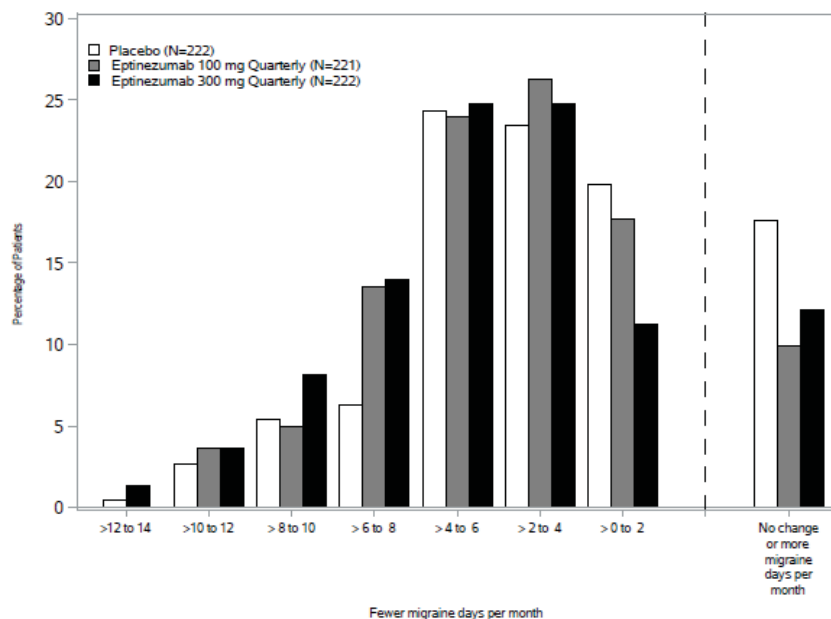
Source: Study 006 CSR Table 23, Table 14.2.2.3.2 and Table 14.2.2.3.2a

**Reviewer's comment: The use of acute migraine medications (triptans and ergotamines) was low at baseline in this episodic migraine population. This lower-than-expected rate of observed acute rescue medication may partially be due to the use of over-the-counter products such as NSAIDs and acetaminophen which were not included in this calculation. The observed reduction in migraine days was also consistent with a reduction in acute migraine medication use as demonstrated in the above Table 16. However, because of the serial procedure used to account for multiplicity, the use of acute migraine medications was not statistically significant; it was nominally significant.**

#### **Dose/Dose Response**

Overall, the doses demonstrated similar efficacy over placebo at all doses tested. The Figure 2 demonstrates the distribution of change from baseline in mean monthly migraine days over Months 1-3 by treatment arm.

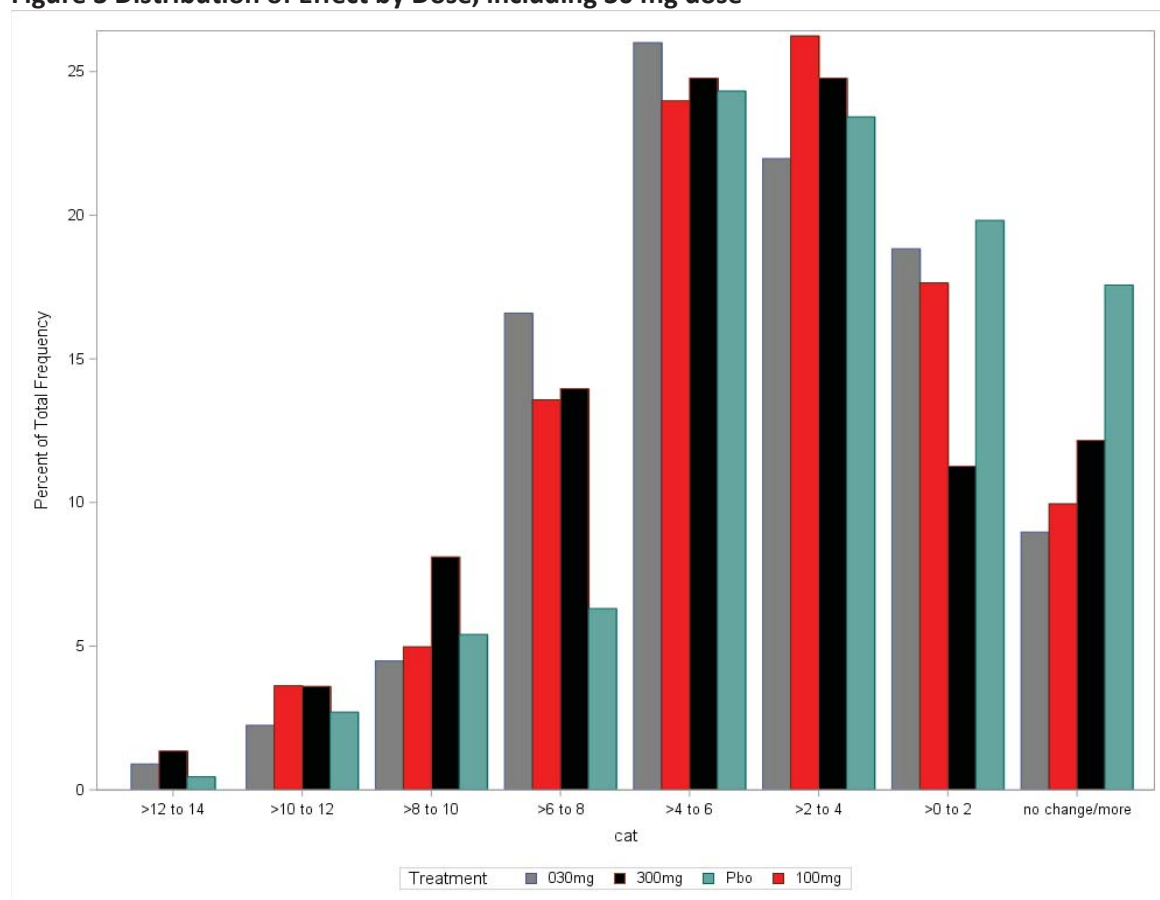
**Figure 2 Study 006: Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1-3**



Source: Applicant-provided Figure 14.2.2.8.1 (Integrated Summary of Efficacy)

The 30 mg dose was not statistically significant because of the complex decision rule which required testing of all primary and key secondary endpoints on the 300 mg and 100 mg doses before evaluating significance of the 30 mg dose (see Figure 1). However, it appears there was still a treatment effect noted at 30 mg that demonstrated a nominally significant improvement over placebo. There may be a slight dose-response when studying the 100% responder rates (See 7.1.4). However, the 30 mg and 100 mg dose appear nearly identical in their treatment effect size. The following histogram provided by the Dr. Steven Bai includes the 30 mg dose alongside the 100 mg and 300 mg dose effects, and demonstrates similar treatment effect of the 30 mg dose and the 100 mg dose (Figure 3).

**Figure 3 Distribution of Effect by Dose, including 30 mg dose**



Source: Dr. Steven Bai's statistical analysis

**Reviewer's comment:** Based on the above histogram, as well as the treatment effect tables above, it appears that the 30 mg dose is numerically similar or even better than the 100 mg dose. However, based on the decision rule to control for multiplicity, the 30 mg dose was only nominally significant and did not meet statistical significance. See further discussion in 7.1.4.

### Migraine Freedom

There were small numbers of patients who had 100% reduction in migraine days for any given 4-week interval, and an even smaller number of patients who became migraine-free for the entire primary treatment period. The 100% responder rate was greater in the 300 mg treatment arm compared to placebo for every 4 week interval. The 30 mg and 100 mg treatment arms were less consistently better than placebo.

**Table 17 100% Responder Rate by 4-week Interval and Treatment During Primary Efficacy Treatment Period**

|  | ALD403 300 mg | ALD403 100 mg | ALD403 30 mg | Placebo |
|--|---------------|---------------|--------------|---------|
|--|---------------|---------------|--------------|---------|

| 100% responder rates<br>Interval | N = 222<br>(%) | N = 221<br>(%) | N = 219<br>(%) | N = 222<br>(%) |
|----------------------------------|----------------|----------------|----------------|----------------|
| Weeks 1-4                        | 14.9           | 8.6            | 10.3           | 5.9            |
| Weeks 5-8                        | 19.4           | 12.7           | 8.5            | 12.2           |
| Weeks 9-12                       | 16.2           | 13.1           | 13.5           | 9.5            |
| Weeks 1-12                       | 4.1            | 0.5            | 1.8            | 1.8            |

100% migraine responder was a patient who achieved a 100% reduction in migraine days (i.e. migraine free) for that interval of time

Source: Study ALD403 CSR, Table 22 (14.2.2.2.1 and 14.2.2.2.2)

### Persistence of Effect/Durability of Response

This reviewer also evaluated the mean change from baseline in monthly migraine days over Weeks 1-24 to look for a sustained treatment effect, summarized below in Table 18. Migraine responder rates over weeks 13-24 and over weeks 1-24 were similar to those seen over Weeks 1-12, demonstrating a durability of response.

**Table 18 Study 006 Sensitivity Analysis of Mean Monthly Migraine Days Through Week 24, Full Analysis Population**

| Interval                             | Treatment Group             |                             |                            | Placebo<br>N =222 |
|--------------------------------------|-----------------------------|-----------------------------|----------------------------|-------------------|
|                                      | ALD403<br>300 mg<br>N = 222 | ALD403<br>100 mg<br>N = 221 | ALD403<br>30 mg<br>N = 223 |                   |
| <b>Baseline</b>                      |                             |                             |                            |                   |
| Mean Monthly Migraine Days           | 8.6                         | 8.7                         | 8.7                        | 8.4               |
| <b>Weeks 13-24</b>                   |                             |                             |                            |                   |
| Estimated Mean Monthly Migraine Days | 3.7                         | 4.1                         | 4.1                        | 4.8               |
| Mean difference from placebo         | -1.0                        | -0.7                        | -0.7                       |                   |
| Change from baseline (mean)          | -4.6                        | -4.3                        | -4.3                       | -3.6              |
| Mean difference from placebo         | -1.1                        | -0.7                        | -0.7                       |                   |
| <b>Weeks 1-24</b>                    |                             |                             |                            |                   |
| Estimated Mean Monthly Migraine Days | 4.0                         | 4.4                         | 4.3                        | 5.1               |
| Mean difference from placebo         | -1.1                        | -0.7                        | -0.8                       |                   |
| Change from baseline (mean)          | -4.4                        | -4.0                        | -4.0                       | -3.3              |
| Mean difference from placebo         | -1.1                        | -0.7                        | -0.8                       |                   |

Source: Reviewer analysis of ADEFFCE dataset, adapted from Clinical study Report 14.2.1.2.1d)

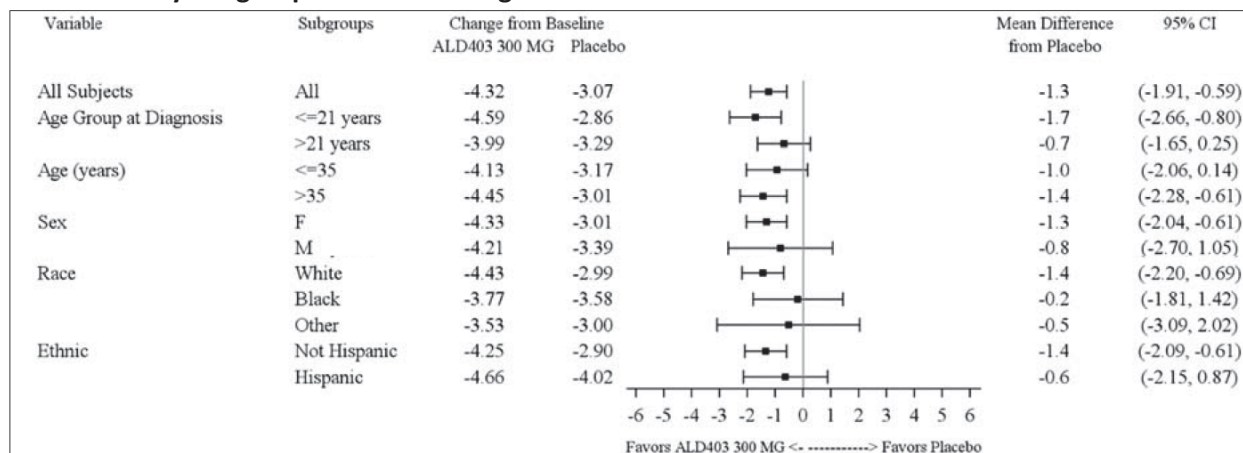
### Additional Analyses Conducted on the Individual Trial

#### Subgroup analyses

The following figures present a forest plot of differences from placebo in migraine days change from baseline over Weeks 1-12 (primary endpoint) by subgroup for the 300 mg and 100 mg treatment arms. The 300 mg group showed consistent reductions from baseline in monthly migraine days when compared with placebo across all clinically important subgroups, including

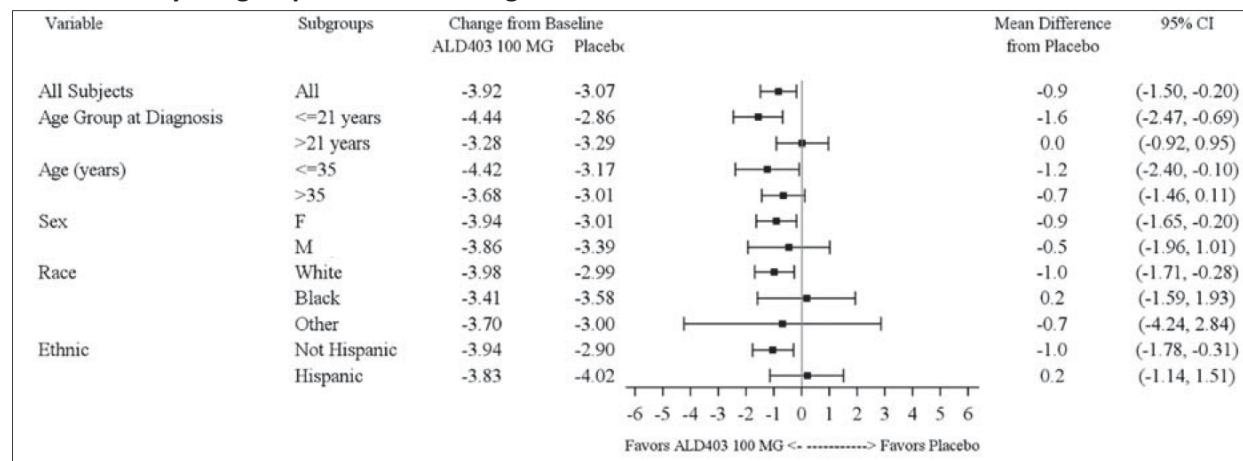
age, gender, race, and ethnicity. The reductions from baseline in the 300 mg group were more robust and consistent across the analyzed subgroups compared to the 100 mg group.

**Figure 4 Forest Plot of Difference from Placebo in Monthly Migraine Days Change from Baseline over Weeks 1-12 by Subgroup- ALD403 300 mg**



Source: Dr. Bai's statistical review, Figure 4-1

**Figure 5 Forest Plot of Difference from Placebo in Monthly Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup - ALD403 100 mg**



Source: Dr. Bai's Statistical Review, Table 4-2

The applicant also looked at subgroup analyses by patients' baseline migraine days (<= or > 9 days) and migraine history (<= 15 years, or > 15 years). These subgroups numerically favor the ALD403 300 mg and 100 mg treatment arms over placebo, as demonstrated below (Figure 6).

**Figure 6 Forest Plot of Subgroup Analyses by Migraine History**  
ALD403 300 mg vs. placebo

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Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

| Variable                      | Subgroups  | Change from Baseline |         |                                                                                   | Mean Difference from Placebo | 95% CI         |
|-------------------------------|------------|----------------------|---------|-----------------------------------------------------------------------------------|------------------------------|----------------|
|                               |            | ALD403 300 MG        | Placebo |                                                                                   |                              |                |
| All Subjects                  | All        | -4.32                | -3.07   |  | -1.3                         | (-1.91, -0.59) |
| Baseline Migraine Days        | <=9        | -3.61                | -2.13   |  | -1.5                         | (-2.22, -0.73) |
|                               | >9         | -5.58                | -4.80   |  | -0.8                         | (-1.94, 0.37)  |
| Duration of Migraines (years) | <=15 years | -4.20                | -3.20   |  | -1.0                         | (-2.03, 0.03)  |
|                               | >15 years  | -4.41                | -2.93   |  | -1.5                         | (-2.36, -0.62) |

#### ALD403 100 mg vs. placebo

| Variable                      | Subgroups  | Change from Baseline |         |                                                                                   | Mean Difference from Placebo | 95% CI         |
|-------------------------------|------------|----------------------|---------|-----------------------------------------------------------------------------------|------------------------------|----------------|
|                               |            | ALD403 100 MG        | Placebo |                                                                                   |                              |                |
| All Subjects                  | All        | -3.92                | -3.07   |  | -0.9                         | (-1.50, -0.20) |
| Baseline Migraine Days        | <=9        | -3.25                | -2.13   |  | -1.1                         | (-1.85, -0.38) |
|                               | >9         | -5.14                | -4.80   |  | -0.3                         | (-1.45, 0.78)  |
| Duration of Migraines (years) | <=15 years | -3.60                | -3.20   |  | -0.4                         | (-1.40, 0.61)  |
|                               | >15 years  | -4.22                | -2.93   |  | -1.3                         | (-2.12, -0.47) |

Source: Adapted from Study 006 CSR Figure 9,10 and Dr. Bai's Statistical Review

#### Sensitivity Analyses

As noted above, there were sensitivity analyses performed based upon the modified missing data imputation rule which supported the primary endpoint analysis. There was also a sensitivity analysis performed to remove the 6 patients that were unblinded during the study. The treatment effect remained nearly the same with the change from baseline in frequency of migraine days (Table 19).

**Table 19 Sensitivity Analysis of Primary Endpoint with Removal of Unblinded Patients**

|                                          | 300 mg | 100 mg | 30 mg |
|------------------------------------------|--------|--------|-------|
| Primary Endpoint Difference from Placebo | -1.11  | -0.69  | -0.82 |
| After removal of patients                | -1.11  | -0.72  | -0.81 |

Source: Reviewer-created table of Statistician's analysis of Primary Efficacy Endpoint with 6 unblinded patients removed from the analysis

**Reviewer's comment: The events of unblinding during the study did not impact the primary efficacy results.**

## 6.2. Study ALD403-CLIN-011 A Parallel Group, Double-Blind, Randomized, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine

### 6.2.1. Study Design

#### Overview and Objective

The primary objective of Study ALD-CLIN-011(Study 011) is to evaluate the efficacy of repeat doses of ALD403 administered intravenously (IV) compared to placebo in patients with chronic migraine. Study 011 has many similarities to Study 006. The differences between the two studies will be highlighted below in the trial design section. Study 011 enrolled patients with chronic migraine as opposed to episodic migraine, which was the key difference between Study 006.

## **Trial Design**

- **Basic Study Design**

Study 011 is a parallel-group, double-blind, randomized, placebo-controlled trial, and patients were randomized into one of two dose levels of ALD403 (100 mg or 300 mg) or placebo, whereas Study 006 studied three dose levels of ADL403 including 30 mg. Patients were randomized 1:1:1, and randomization was stratified by baseline migraine days during screening ( $< 17$  or  $\geq 17$  days), as well as prophylactic medication use during the 3 months prior to screening. Patients were allocated equally to each treatment group.

The total study duration was 36 weeks with 10 scheduled visits. There was a baseline period of 4 weeks to determine eligibility, followed by treatments on Day 0 and Day 84 (Week 12), and a follow-up visit 20 weeks after the final dose (Week 32). The scheduled infusions were given 12 weeks apart, and patients were required to complete the headache eDiary during the screening period and throughout the study.

- **Trial Location**

Study 011 was planned at approximately 150 centers in the United States and worldwide. Ultimately, the study was conducted in 13 countries with the majority of sites (53%) in the US. Overall the patient population is expected to be similar to, and thus generalizable to, the overall migraine population in the United States.

- **Choice of Control Group**

The choice of placebo was appropriate for such a study of preventative migraine in this chronic migraine patient population.

- **Diagnostic Criteria**

For the purpose of both the inclusion criteria and the efficacy analyses, a migraine day was defined as any day with a headache that meets the chronic migraine definition as outlined in the IHS International Classification of Headache Disorders - III (2013) Section 1.3 with diagnostic Criteria C limited to items 1 and 3 (the

characteristics that must be present for a headache to be considered a migraine)<sup>7</sup>.  
The presence or absence of aura did not impact the classification of a headache as a migraine.

Migraine was thus defined as a self-reported headache that:

- 1) Lasted
  - a) 4 hours or more OR
  - b) 30 minutes to 4 hours and believed by the patient to be a migraine that was relieved by medication
- 2) Had at least 2 of the following:
  - a) unilateral location,
  - b) pulsating quality,
  - c) moderate or severe pain intensity, and/or
  - d) aggravation by or causing avoidance of routine physical activity.
- 3) Had at least 1 of the following:
  - a) nausea and/or vomiting, and/or
  - b) photophobia and phonophobia

- **Key inclusion Criteria**

- o Male or female, between the ages of 18 and 65 years of age inclusive, at time of informed consent;
- o Diagnosis of migraine at ≤ 50 years of age with history of chronic migraine ≥ 1 year prior to screening
- o Prescription or over the counter medication for acute and/or prophylactic treatment of migraine has been prescribed or recommended by a healthcare professional
- o During the 28 day screening period, must have ≥ 15 to < 26 headache days, of which ≥ 8 days were assessed as migraine days as documented in the eDiary
- o Headache eDiary was completed on at least 24 of the 28 days prior to randomization
- o Any prophylactic use of medications for headaches must be stable for at least 3 months prior to screening
- o Limited use of barbiturates, or prescription opiates by maintaining a stable dose for 2 months prior to screening and dosing is not expected to exceed 4 days per month through Week 24.

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<sup>7</sup> Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3<sup>rd</sup> edition (beta version). Cephalalgia 2013;33(9): 629-808.

- **Key Exclusion Criteria**

- History of diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine, ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura
- Any use of monoamine oxidase inhibitors (MAOIs) ketamine, methylsergide, methylergonovine, or nimesulide within 3 months prior to screening or during screening period
- BMI  $\geq$  39 kg/m<sup>2</sup> at screening
- Primary hypertension that is uncontrolled or newly diagnosed (SBP > 139 mm Hg or DBP > 89 mm Hg)

***Reviewer's comment: The other exclusion criteria are identical to those found in Study 006 and are outlined above in Section 6.1.1 Study Design. The key difference in the inclusion criteria are the description of the migraine history as these were patients with chronic migraines, and also that patients in this study were limited to patients  $\leq$  65 years of age in this study.***

- **Dose Selection**

ALD403 doses of 100 mg and 300 mg met the primary efficacy endpoint and had an acceptable safety profile in a prior Phase 2 study ALD403-CLIN-005. Therefore, these two doses were selected for this study to be administered every 12 weeks.

- **Study treatments**

ALD403 is an anti-(calcitonin-gene-related-peptide) humanized monoclonal antibody. Patients were assigned to one of 3 treatment arms, ALD403 100 mg, 300 mg, or placebo. All doses were administered as an IV infusion of ALD403 or placebo in 100 mL of 0.9% saline.

- **Assignment to treatment**

Patients were assigned to one of 3 treatment arms, and randomization occurred 28-30 days after the screening visit, after eligibility assessments were completed. Sites completed the randomization in IWRS, and the randomization assignment will be obtained by the clinical trial sites' unblinded pharmacist. Patients were randomized in equal ratios to one of the treatment groups, using stratified permuted block randomization, with stratification by migraine days during the screening period (< 17 days or  $\geq$  17 days) and prophylactic medication use during the 3 months prior to screening.

The patient's use of preventive medication for migraine was determined at

screening based upon medical history, and was defined as any migraine preventive therapy taken as a stable regimen for 3 months prior to screening.

- **Blinding**

All patients and site personnel are blinded to treatment assignment, except for the clinical trial sites' unblinded pharmacist or designee. Each site must have a written plan in place to ensure blinding is adequately maintained for the study. If the blind is broken, the date, time and reason must be recorded, and blind should only be broken for reasons in which knowledge of the treatment assignment is critical to the management of patient safety. Any cases of unblinding were to be reported within 24 hours of the incident to the applicant.

- **Dose modification/Dose Discontinuation**

There were no pre-specified dose modifications or dose reductions in the protocol.

- **Administrative structure**

The clinical trial was conducted in accordance with standards of Good Clinical Practice (GCP). A Data Monitoring Committee (DMC) including appropriately qualified members who are independent of the applicant was formed to consider safety data generated during the clinical trial.

- **Procedures and schedule**

The following table summarizes the schedule of study visits, and includes some of the key assessments that occurred at those visits.

**Table 20 Schedule of Key Assessments and Procedures Study 011**

| Visit Number                            | Screen | Rand <sup>1</sup> | Day 0 | Wk 2 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Wk 32 EOS/ET |
|-----------------------------------------|--------|-------------------|-------|------|------|------|-------|-------|-------|-------|--------------|
| Inclusion/Exclusion evaluation          | X      | X                 | X     |      |      |      |       |       |       |       |              |
| Headache eDiary Review/Compliance Check | X      | X                 | X     | X    | X    | X    | X     | X     | X     | X     |              |
| Height/Weight <sup>2</sup>              | X      |                   | X     |      |      |      | X     |       |       | X     | X            |
| Vital signs                             | X      |                   | X     |      | X    | X    | X     | X     | X     | X     | X            |
| Physical Exam                           | X      |                   | X     |      |      |      | X     |       |       | X     | X            |
| Urine Pregnancy Test                    | X      |                   | X     |      |      |      | X     |       |       |       | X            |
| Patient Global Impression of Change     |        |                   |       |      | X    | X    | X     | X     | X     | X     | X            |
| HIV, Hep B/C, Urine drug screen         | X      |                   |       |      |      |      |       |       |       |       |              |
| C-SSRS                                  | X      |                   | X     | X    | X    | X    | X     | X     | X     | X     | X            |
| Most Bothersome Symptom                 | X      |                   | X     |      | X    | X    | X     | X     | X     | X     | X            |
| 12-lead ECG                             | X      |                   | X     |      |      |      | X     |       |       |       | X            |
| Hematology/Chemistry Labs               | X      |                   | X     |      |      |      | X     |       |       |       | X            |
| Plasma PK levels                        |        |                   | X     | X    | X    | X    | X     |       |       | X     | X            |
| Serum Anti-ALD403 Ab <sup>3</sup>       |        |                   | X     | X    | X    | X    | X     |       |       | X     | X            |

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Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

|                                       |   |   |   |   |   |   |   |   |   |   |   |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|
| SF-36, EQ-5D-5L, and HIT-6            | X |   | X |   | X |   | X | X |   | X | X |
| Adverse Event review                  | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Med review                | X | X | X | X | X | X | X | X | X | X | X |
| Treatment administration <sup>4</sup> |   |   | X |   |   |   | X |   |   |   |   |

**Source: Clinical Reviewer's summary of Study 011 Protocol Schedule of Events and Assessments**

Abbreviations: C-SSRS= Columbia-Suicide Severity Rating Scale; SF-36 = Short Form Healthy Survey; EQ-5D-5L = Health-Related Quality of Life; HIT-6 = Headache Impact Test; EOS/ET = End-of-Study/Early Termination Visit

<sup>1</sup> Randomization to occur 28-30 days after screening visit; a phone visit is acceptable in cases where patients' schedule will not permit an on-site visit; Dosing must occur within 8 days of randomization

<sup>2</sup> Height and weight at screening; weight only at Day 0, Weeks 12, 24, and 32/ET 32

<sup>3</sup> Patients who test positive for anti-ALD403 antibodies at the last study visit will be asked to provide up to 2 additional blood samples at approximately 3 month intervals for an additional 6 months

<sup>4</sup> Patients monitored for at least 2 hours after dosing completion

- **Dietary restrictions/instructions**

There were no restrictions in food or activity throughout the study.

- **Concurrent Medications**

The use of any concomitant medications was recorded on the CRF. The medical monitor would be notified in advance if any restricted medications were administered. Unlike Study 006, prophylactic headache medications were permitted, granted the dose had been stable for at least 3 months with no changes allowed through Week 24, unless special approval was granted by medical monitor at the discretion of the Investigator. This study also additionally restricted the use of MAOIs, ketamine, methylsergide, methylergonovine, and nimesulide within 3 months prior to screening and through week 24. The other restricted therapies are the same as described in Section 6.1 above for Study 006. Any hormonal therapy use must have been stable for 3 months prior to screening and remain stable through Week 32.

- **Treatment Compliance**

The headache eDiary was to be completed daily whether or not the patient had a headache, and also recorded if they took acute migraine medication on that day. The compliance data was available to the trial site for review at each visit, and patients were counseled on completing the diary if it was not being completed daily.

**Reviewer's comment: The eDiary was monitored throughout the study for compliance at every visit. There was no concern for compliance with treatment administration, as the treatment was administered intravenously at the clinical trial site.**

- **Patient completion, discontinuation, or withdrawal**

Patients were discontinued for pregnancy or suicidal ideation with intent, with or without a plan.

Treatment was also to be discontinued from the study for adverse events, patient or investigator decision, study termination, or withdrawal of consent or lost to follow-up. All reasons for withdrawal and treatment discontinuation, as well as time of withdrawal, will be recorded on the CRF. Patients that discontinued treatment for any reason were encouraged to continue with study assessments until end of study. If patients chose to withdraw consent, they were scheduled for an early termination visit with associated assessments.

Patients who were withdrawn from the study after randomization would not be replaced.

## Study Endpoints

- **Primary Efficacy Endpoint**

The primary efficacy endpoint was the change in frequency of migraine days (Weeks 1-12).

- A migraine day is defined as any day with a headache that meets the chronic migraine definition as outlined above in *Diagnostic Criteria*.
- Headaches were self-reported by the patient, and an episode is a single headache event that the patient reports as having a start and an end and lasts at least 30 minutes.
- The migraine and headache endpoints were summarized in 4-week intervals.
- The frequency of migraine days is the number of migraine days within four-week intervals and the average four-week frequency in 12- and 24- week intervals.
- Change from baseline is the difference in frequency of migraine days between baseline and the counts within these four week intervals.
- The 12- and 24- week change is the difference in the frequency between baseline and the average of the 4-week intervals.

***Reviewer's comment: The primary efficacy endpoint is the same as that used in Study 006, although the definition for migraine is slightly different given the population of patients with chronic, rather than episodic migraine, and updated ICHD classification that was published in 2013. The choice of primary endpoint is consistent with the primary endpoint used in most of the studies of other recently approved CGRP antagonists.***

- **Key Secondary Endpoints**

- 75% migraine responder rate (Weeks 1-4)
- 75% migraine responder rate (Weeks 1-12)

- o 50% migraine responder rate (Weeks 1-12)
- o Percentage of subjects with a migraine on the day after dosing
- o Reduction in migraine prevalence from baseline to Week 4

The reduction in migraine prevalence would be calculated as the average percent of subjects with a migraine on any given day during baseline and the equivalent average migraine rate over Weeks 1, 2, 3 and 4, which would be evaluated for each treatment arm.

***Reviewer's comment: These key secondary endpoints are similar to the key secondary endpoints in Study 006 with the same definition of responder. This study also added the reduction in migraine prevalence from baseline to Week 4 for this study (which was analyzed above for comparison although it wasn't a key secondary). The above key secondary endpoints are included in the statistical hierarchical testing as outlined below.***

(b) (4)

- **Other Secondary Endpoints**

- o Headaches/migraines with acute medication usage
- o Acute migraine medication usage
- o Change in frequency of migraine days (Weeks 1-24)
- o 100% migraine responder rate (Weeks 1-12)
- o Migraine responder rates for time periods other than Weeks 1-12
- o Change in frequency of migraine days between baseline and time periods other than Weeks 1-12
- o Headache responder rates
- o Change in the frequency of headache days
- o Percent change in headache/migraine days
- o Time to first migraine after dosing
- o Headache/migraine hours
- o Headache/migraines with severe intensity
- o Patient Global Impression of Change
- o Short-Form Health Survey
- o Health-Related Quality of Life
- o Headache Impact Test

Overall, the secondary endpoints are similar to those in Study 006, with the addition of the Patient Global Impression of Change, a single question concerning the patient's impression of the change since the start of the study with seven possible responses, and

the Headache Impact Test (HIT), a 6-question, Likert-type, self-reporting questionnaire used to measure the impact and effect of the headaches on the ability to function normal in daily life.

- **Tertiary Endpoints:**

- Headache episodes/migraine attacks
- Migraine symptom-free days
- Most Bothersome Symptom (MBS)

The study added the tertiary endpoints of migraine symptom-free days, the number of days the patient is free of migraine symptoms, summarized over each 4-week period, and MBS, which will be identified by the patients at screening. Patients will be asked to rate the improvement in this symptom from screening on a seven-point scale.

The study had the same safety, pharmacokinetic and immunogenicity endpoints as Study 006, noted above.

## **Statistical Analysis Plan**

The final statistical analysis plan, Version 1.0 was finalized on November 8, 2017, prior to unblinding for the 12-week analyses which occurred on January 5, 2018. The primary analysis was done on June 8, 2018. For further details of the statistical analysis plan, please refer to the complete statistical review by Dr. Steven Bai.

### **Analysis Populations**

As in Study 006, the full analysis population will be used for efficacy analyses and include all randomized patients who received treatment according to the treatment group to which they were randomized. The safety population will be used for the safety analyses and includes all patients who received at least one dose of treatment according to the treatment that they actually received. Demographics, baseline characteristics, migraine history and concomitant medications will be summarized by treatment group.

- **Primary Endpoint Analyses**

- The hypothesis testing performed for the primary endpoint of change in frequency of migraine days.
- The null hypothesis is that the change in migraine days for patients in the ALD403 treatment arm will equal the change in migraine days for patients receiving placebo.
- The change from baseline is expected to be negative as migraines are being reduced. Clinically relevant results require a larger reduction of migraines on the ALD403 treatment arms.

- o ANCOVA model will be used to test for a difference between treatment arms, with treatment and the stratification variables of baseline migraine days and prophylactic medication use will be the independent variables.
- Secondary Efficacy Analyses

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- o Testing will be performed for the key secondary endpoints and the change in acute migraine medication days endpoint
- o Will be stratified by the randomization stratification factor
- o Change in acute migraine medication days will be tested using an ANCOVA model
- o Key secondary endpoints will be tested using a CMH/extended CMH test.
- o Time to first migraine will be summarized using Kaplan-Meier methods
- o Summary statistics including confidence interval for the treatment differences will be used to summarize results of the remaining secondary endpoints

### **Multiplicity Adjustment**

A multiplicity procedure will be used to account for multiplicity of dose levels for the primary endpoint and the key secondary endpoints. The procedure will start with the 300 mg vs. placebo comparison for the primary endpoint. If statistically significant, testing will continue to key secondary endpoints for 300 mg. The procedure will then move on to the 100 mg group for the primary and subsequent key secondary endpoints. Statistical testing will be conducted to maintain a study-wide two-sided 5% alpha level.

***Reviewer's comments: The final version of the SAP had some deviations from the protocol, including that the SAP identified the HIT-6 and Acute Migraine Medication usage endpoints as key secondary endpoints for the 300 mg dose group only, because they were included in the testing algorithm to control for errors of multiplicity. The SAP also included an exploratory endpoint of migraine-free days as it was felt it may be clinically meaningful way of viewing the treatment benefit.***

### **Handling of Missing Data**

Missing data will be handled in the same way as in Study 006 (See Section 6.1.1 above).

### **Sample Size Determination**

The planned sample size is 1050 randomized and treated patients, allocated into 3 treatment groups in a 1:1:1 ratio. Pair-wise testing of each ALD403 group vs. placebo was performed, to provide at least 90% power for the primary endpoint, assuming a treatment effect of at least 1 day and a common standard deviation of 4 days or less. For the key secondary endpoints, 90% power would be achieved, assuming a placebo responder rate of 20% and an ALD403 responder rate of 31%.

### **Protocol Amendments**

The original protocol was dated August 17, 2016. Three amendments were made to the original protocol, which are summarized below in Table 21.

**Table 21 Summary of Major Protocol Amendments, Study 011**

| Amendment Number | Date            | Major Changes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                | 24 October 2016 | <ul style="list-style-type: none"> <li>The original protocol (August 17, 2016) was never submitted to health authorities or ethics committee so this was the original version under which the study was initiated.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 2                | 20 March 2017   | <ul style="list-style-type: none"> <li>Clarified the number of days needed for eDiary compliance as 24 out of 28 days</li> <li>Dosing windows and period of observations updated based on preliminary review of safety data from other studies</li> <li>Clarified exclusion criteria for temporomandibular disorders, atypical migraine subtypes and added autoimmune disorders and active, progressive or unstable cardiovascular, neurological, and autoimmune disorders were excluded</li> <li>Added discontinuation criteria for pregnancy or suicidal ideation</li> </ul>                                                                                                                                                                |
| 3                | 31 August 2017  | <ul style="list-style-type: none"> <li>Updated the key secondary endpoints to included 50% migraine responder rate, percentage of subjects with migraine on the day after dosing, and reduction in migraine prevalence from baseline to Week 4 to ensure consistency across development program</li> <li>A change was made to sample size section to clarify 350 subjects per group provides at least 90% power for the primary endpoint, and not for the change from baseline tests</li> <li>Clarifications made to statistical section of synopsis to clarify the primary endpoint and key secondary endpoints</li> <li>Clarified that the decision rule is a multiplicity procedure for the primary and key secondary endpoints</li> </ul> |

## 6.2.2. Study Results

### Compliance with Good Clinical Practices

The applicant provided attestation that Study 011 was conducted in accordance with standards of Good Clinical Practice (GCP) as defined by the International Council for Harmonisation (ICH) and all application federal and local regulations.

### Financial Disclosure

Please see Appendix 13.2.

### Patient Disposition

There were 2263 patients screened for Study 011, with a total of 1121 patients randomized, and 1072 patients treated in the study. They were equally distributed amongst the treatment arms (Table 22).

**Table 22 Patient Disposition for Study 011**

|                                |      |             |
|--------------------------------|------|-------------|
| Screened Population            |      | <b>2263</b> |
| Screen Failures                | 1142 |             |
| Randomized Population          |      | <b>1121</b> |
| ALD403 300 mg                  |      | 374         |
| ALD403 100 mg                  |      | 372         |
| Placebo                        |      | 375         |
| Treated Population             |      | <b>1072</b> |
| ALD403 300 mg                  |      | 350         |
| ALD403 100 mg                  |      | 356         |
| Placebo                        |      | 366         |
| Completed Study                |      | <b>971</b>  |
| Discontinued Study Prematurely |      | <b>101</b>  |
| Withdrawal by subject          | 63   |             |
| Lost to follow-up              | 33   |             |
| Physician decision             | 3    |             |
| Other                          | 2    |             |

Source: Reviewer adapted from Study 011 CSR Figure 2 and Table 7 (14.1.1.1)

**Table 23 Reasons for Randomized but Not Treated by Treatment Arm**

|                                               | Treatment Arm |               |          |           |
|-----------------------------------------------|---------------|---------------|----------|-----------|
|                                               | ALD403 300 mg | ALD403 100 mg | Placebo  | Total     |
| <b>Total Randomized</b>                       | 374           | 372           | 375      | 1121      |
| Randomized not Treated                        | 24 (6.4)      | 16 (4.3)      | 9 (2.4)  | 49 (4.4)  |
| <b>Reason for Discontinuation<sup>a</sup></b> |               |               |          |           |
| Withdrawal by Subject                         | 9 (37.5)      | 8 (50.0)      | 2 (22.2) | 19 (38.8) |
| Adverse Event                                 | 2 (8.3)       | 0             | 0        | 2 (4.1)   |
| Study Burden                                  | 5 (20.8)      | 3 (18.3)      | 0        | 8 (16.3)  |
| Lack of Efficacy                              | 0             | 0             | 0        | 0         |
| Worsening of study indication                 | 0             | 0             | 0        | 0         |
| Other                                         | 2 (8.3)       | 5 (31.3)      | 2 (22.2) | 9 (18.4)  |
| Randomization capped                          | 0             | 0             | 0        | 0         |
| Lost to Follow-up                             | 1 (4.2)       | 1 (6.3)       | 1 (11.1) | 3 (6.1)   |
| Death                                         | 0             | 0             | 0        | 0         |
| Study terminated by sponsor                   | 0             | 0             | 0        | 0         |
| Other                                         | 15 (58.3)     | 7 (43.8)      | 6 (66.7) | 27 (55.1) |

<sup>a</sup> Percentages based upon number of subjects randomized but not treated. These patients were not included in full analysis population

Source: Reviewer Adapted from Study 011 CSR Table 14.1.1.1

**Reviewer's comment:** There were 4.4% of patients that were randomized but not treated for a variety of reasons, largely unrelated to either treatment (never dosed) or underlying condition. There were slightly more of these patients in the 300 mg treatment arm (6.4% vs 2.4% in placebo), but not disproportionately so, and it's unlikely that this small percentage would influence the efficacy results in a large study such as this one.

**Table 24 Reasons for Early Study Discontinuation by Treatment Arm (Treated Patients)**

|                               | ALD403 300 mg<br>N = 350<br>n (%) | ALD403 100 mg<br>N = 356<br>n (%) | Placebo<br>N = 366<br>n (%) | Total<br>N = 1072<br>n (%) |
|-------------------------------|-----------------------------------|-----------------------------------|-----------------------------|----------------------------|
| Withdrawal by Subject         | 20 (5.7)                          | 20 (5.6)                          | 23 (6.3)                    | 63 (5.9)                   |
| Adverse Event                 | 4 (1.1)                           | 0                                 | 1 (< 1)                     | 5 (< 1)                    |
| Study Burden                  | 3 (< 1)                           | 4 (1.1)                           | 3 (< 1)                     | 10 (< 1)                   |
| Lack of Efficacy              | 6 (1.7)                           | 5 (1.4)                           | 10 (2.7)                    | 21 (2.0)                   |
| Worsening of study indication | 0                                 | 0                                 | 0                           | 0                          |
| Other                         | 7 (2.0)                           | 11 (3.1)                          | 9 (2.5)                     | 27 (2.5)                   |

Source: Adapted from Study 011 CSR Table 14.1.1.1, Reviewer verified

**Reviewer's comment:** Among those patients that did receive treatment and then discontinued from the study early, only a small number of patients (1%) discontinued due to an adverse event. A higher percentage of patients in the placebo arm withdrew from the study because of lack of efficacy compared to those who received eptinezumab, which correlates with a positive treatment effect. This pattern was also noted in the episodic migraine study (Study 006) as described above.

### Protocol Violations/Deviations

There were important protocol deviations reported for 277 patients (24.7%), with 51 of these patients (4.5%) having ICH/GCP deviations. The number of patients with protocol deviations was evenly distributed among the treatment arms and was similar to the protocol deviations noted in Study 006.

The most frequently reported deviations were study procedures/assessments (115 patients), and the most frequently reported ICH/GCP deviations were related to informed consent process/timing (43 patients). The informed consent deviations related mostly to the patient not being re-consented in a timely manner, or not being signed by the PI.

The deviations reported were all evaluated by the applicant and determined to have no overall impact on the safety and efficacy conclusions per the applicant. A summary of protocol deviations is presented in Table 25.

**Table 25 Summary of Important Protocol Deviations among Randomized Patients**

|                               | ALD403 300 mg<br>N = 374<br>n (%) | ALD403 100 mg<br>N = 372<br>n (%) | Placebo<br>N = 375<br>n (%) | Overall<br>N = 1121<br>n (%) |
|-------------------------------|-----------------------------------|-----------------------------------|-----------------------------|------------------------------|
| At least 1 Protocol Deviation | 95 (25.4)                         | 90 (24.2)                         | 92 (24.5)                   | 277 (24.7)                   |
| Concomitant Medication        | 18 (4.8)                          | 19 (5.1)                          | 28 (7.5)                    | 65 (5.8)                     |
| Exclusion Criteria            | 7 (1.9)                           | 5 (1.3)                           | 3 (< 1)                     | 15 (1.3)                     |
| Inclusion Criteria            | 12 (3.2)                          | 13 (3.5)                          | 5 (1.3)                     | 30 (2.7)                     |
| Study procedures/assessments  | 44 (11.8)                         | 35 (9.4)                          | 36 (9.6)                    | 115 (10.3)                   |
| Study treatment admin         | 16 (4.3)                          | 8 (2.2)                           | 13 (3.5)                    | 37 (3.3)                     |
| Visit scheduling              | 8 (2.1)                           | 7 (1.9)                           | 6 (1.6)                     | 21 (1.9)                     |
| ICH/GCP Deviations            | 16 (4.3)                          | 18 (4.8)                          | 17 (4.5)                    | 51 (4.5)                     |

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Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

|                        |          |          |          |          |
|------------------------|----------|----------|----------|----------|
| ICF process/timing     | 13 (3.5) | 16 (4.3) | 14 (3.7) | 43 (3.8) |
| Inv adequate resources | 3 (< 1)  | 2 (< 1)  | 2 (< 1)  | 7 (< 1)  |
| Other GCP deviation    | 0        | 0        | 1 (< 1)  | 1 (< 1)  |

ICH/GCP = International Council for Harmonization/Good Clinical Practice; ICF = informed consent form  
Source: Reviewer adapted from Study 011 CSR Table 14.1.1.3

***Reviewer's comment: After completion of a clinical site visit, it was determined that there may have been possible unblinding events that were not reported in the CSR. Upon further information provided by the applicant, there were actually 6 patients in Study 011 who were unblinded during the study. As detailed below, a sensitivity analysis which removed these patients from the primary efficacy analysis did not alter the results.***

#### Table of Demographic Characteristics

A total of 1121 patients were randomized, and of those, 1072 patients received treatment and were included in the safety population and full analysis population. As noted above in Table 23, 49 patients were randomized but never treated and are not included in the analysis populations. Overall the demographics were generally well-balanced between the treatment arms as noted in Table 26.

**Table 26 Demographic characteristics of the primary efficacy analysis population**

| Demographic Parameters                                        | Treatment Group                   |                                   |                             | Overall<br>N = 1072<br>n (%) |
|---------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------|------------------------------|
|                                                               | ALD403 300 mg<br>N = 350<br>n (%) | ALD403 100 mg<br>N = 356<br>n (%) | Placebo<br>N = 366<br>n (%) |                              |
| <b>Sex</b>                                                    |                                   |                                   |                             |                              |
| Male                                                          | 36 (10.3)                         | 49 (13.8)                         | 41 (11.2)                   | 126 (11.8)                   |
| Female                                                        | 314 (89.7)                        | 307 (86.2)                        | 325 (88.8)                  | 946 (88.3)                   |
| <b>Age</b>                                                    |                                   |                                   |                             |                              |
| Mean years (SD)                                               | 41.0 (10.4)                       | 41.0 (11.7)                       | 39.6 (11.3)                 | 40.5 (11.1)                  |
| Median (years)                                                | 40.5                              | 41                                | 40                          | 41                           |
| Min, max (years)                                              | 18, 65                            | 18, 65                            | 18, 65                      | 18, 65                       |
| <b>Age Group</b>                                              |                                   |                                   |                             |                              |
| ≤ 35 years                                                    | 114 (32.6)                        | 113 (31.7)                        | 141 (38.5)                  | 368 (34.3)                   |
| > 35 years                                                    | 236 (67.4)                        | 243 (68.3)                        | 225 (61.5)                  | 704 (65.7)                   |
| <b>Race</b>                                                   |                                   |                                   |                             |                              |
| White                                                         | 322 (92.0)                        | 332 (93.3)                        | 321 (87.7)                  | 975 (91.0)                   |
| Black or African American                                     | 23 (6.6)                          | 21 (5.9)                          | 38 (10.4)                   | 82 (7.7)                     |
| Other                                                         | 5 (1.4)                           | 3 (0.8)                           | 7 (1.9)                     | 15 (1.4)                     |
| <b>Ethnicity</b>                                              |                                   |                                   |                             |                              |
| Hispanic or Latino                                            | 18 (5.1)                          | 33 (9.3)                          | 35 (9.6)                    | 86 (8.0)                     |
| Not Hispanic or Latino                                        | 332 (94.9)                        | 323 (90.7)                        | 331 (90.4)                  | 986 (92.0)                   |
| <b>Region</b>                                                 |                                   |                                   |                             |                              |
| United States                                                 | 195 (55.7)                        | 198 (55.6)                        | 232 (63.4)                  | 625 (58.3)                   |
| European Union <sup>1</sup>                                   | 53 (15.1)                         | 50 (14.0)                         | 51 (13.9)                   | 154 (14.4)                   |
| Other <sup>2</sup>                                            | 102 (29.1)                        | 108 (30.3)                        | 83 (22.7)                   | 293 (27.3)                   |
| <b>BMI (kg/m<sup>2</sup>)</b>                                 |                                   |                                   |                             |                              |
| Mean (SD)                                                     | 26.3 (5.0)                        | 26.4 (5.0)                        | 27.0 (5.6)                  | 26.6 (5.2)                   |
| Median                                                        | 25.2                              | 25.9                              | 26.1                        | 25.8                         |
| Min, max                                                      | 15.9, 38.9                        | 16.7, 38.8                        | 17.3, 39                    | 15.9, 39                     |
| <b>Baseline Migraine Days, n (%)<sup>3</sup></b>              |                                   |                                   |                             |                              |
| < 17 days                                                     | 193 (55.1)                        | 192 (53.9)                        | 204 (55.7)                  | 589 (54.9)                   |
| ≥ 17 days                                                     | 157 (44.9)                        | 164 (46.1)                        | 162 (44.3)                  | 483 (45.1)                   |
| <b>Baseline prophylactic medication use (y/n)<sup>3</sup></b> |                                   |                                   |                             |                              |
| YES                                                           | 130 (37.1)                        | 132 (37.1)                        | 135 (36.9)                  | 397 (37.0)                   |
| NO                                                            | 220 (62.9)                        | 224 (62.3)                        | 231 (63.1)                  | 675 (63.0)                   |

<sup>1</sup> European Union includes patients from Belize, Czech Republic, Germany, Denmark, Spain, Hungary, Italy, Slovakia and Great Britain

<sup>2</sup> Other includes patients from Republic of Georgia, Ukraine, and Russia

<sup>3</sup> As entered at randomization by the site

Source: Clinical reviewer's analysis of Study 011 ADSL dataset

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Migraine history is summarized below based on age of migraine diagnosis, years of migraine suffering (including prior to diagnosis) and average number of headaches and migraines per 28-day period both in the 3 months prior to screening and as recorded in the eDiary during the baseline screening period. Overall, the migraine and headache characteristics and the mean baseline number of migraine days were similar across treatment groups.

**Table 27 Migraine History Characteristics**

| Demographic Parameters                                   | Treatment Group                   |                                   |                             | Overall<br>N = 1072<br>n (%) |
|----------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------|------------------------------|
|                                                          | ALD403 300 mg<br>N = 350<br>n (%) | ALD403 100 mg<br>N = 356<br>n (%) | Placebo<br>N = 366<br>n (%) |                              |
| <b>Duration since diagnosis (years)- Migraine</b>        |                                   |                                   |                             |                              |
| Mean years (SD)                                          | 19.0 (11.5)                       | 18.3 (12.22)                      | 17 (11.6)                   | 18.1 (11.8)                  |
| Median (years)                                           | 17                                | 16                                | 15                          | 16                           |
| Min, max                                                 | 0, 55                             | 0, 59                             | 0, 59                       | 0, 59                        |
| <b>Disease duration/suffering (years)</b>                |                                   |                                   |                             |                              |
| Mean years (SD)                                          | 12.4 (11.1)                       | 11.6 (11.7)                       | 11.6 (10.9)                 | 11.8 (11.2)                  |
| Median                                                   | 10                                | 6                                 | 8                           | 8                            |
| Min, max                                                 | 1, 55                             | 1, 57                             | 1, 59                       | 1, 59                        |
| <b>Prior Average Number of Migraine Days<sup>1</sup></b> |                                   |                                   |                             |                              |
| Mean (SD)                                                | 14.9 (4.5)                        | 14.5 (4.3)                        | 15.1 (4.4)                  | 14.8 (4.4)                   |
| <b>Prior Average Number of Headache Days<sup>1</sup></b> |                                   |                                   |                             |                              |
| Mean (SD)                                                | 20.1 (3.3)                        | 20.1 (3.3)                        | 20.0 (3.4)                  | 20.1 (3.3)                   |
| <b>Medication Overuse Headache Diagnosis</b>             |                                   |                                   |                             |                              |
| Yes                                                      | 147 (42.))                        | 139 (39.0)                        | 145 (39.6)                  | 431 (40.2)                   |
| No                                                       | 203 (58.0)                        | 217 (61.0)                        | 221 (60.4)                  | 641 (59.8)                   |
| <b>Baseline Migraine days (eDiary)</b>                   |                                   |                                   |                             |                              |
| Mean (SD)                                                | 16.1 (4.8)                        | 16.1 (4.6)                        | 16.2 (4.5)                  | 16.1 (4.6)                   |
| <b>Baseline Headache Days (eDiary)</b>                   |                                   |                                   |                             |                              |
| Mean (SD)                                                | 20.4 (3.2)                        | 20.4 (3.1)                        | 20.6 (3.0)                  | 20.5 (3.1)                   |

<sup>1</sup>Average number per 28-day period in the 3 months prior to screening (reported)

Source: Clinical reviewer's analysis of Study 011 ADSL dataset

**Reviewer's comment:** There are patients that report shorter disease duration since time of diagnosis then number of years they have suffered with migraines. It is likely that this discrepancy is including years of migraines prior to receiving a diagnosis of migraines, and may be affected by recall bias. However, both descriptions of "disease duration" are similar between the treatment arms, although there is a trend towards slightly longer disease durations in the ALD403 300 mg arm, but only by an average of one year. There is no indication that a disease duration of one year longer would have any impact on the ability of the study to detect a treatment effect.

The average number of migraine and headache days in the table above are as reported by the patient over the 3-month period prior to screening. The baseline headache/migraine days

**over the 28-day screening as reported in the eDiary were very similar to those reported in the 3-months prior, although there was an average of one extra migraine day in each treatment arm.**

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance for treatment administration was not measured throughout the study as the treatments were administered intravenously at the site visits. However, compliance with recording daily in the eDiary was monitored and patients were counseled on completing the diary at every visit.

Concomitant medications were also evaluated at baseline. The most frequently used concomitant acute medications for headache in > 10% of patients included ibuprofen (35.7%), sumatriptan (35.6%), paracetamol (15.5%) and rizatriptan (12.4%). The most frequently reported prophylactic concomitant headache medication in > 10% of patients was topiramate (14.5%). The usage of acute medications was similar among the treatment arms, as outlined in Table 28. A formal analysis regarding any reduction in the use of acute migraine medications is outlined below in Efficacy Results – Secondary Endpoints.

**Table 28 Percent of Days with Any Headache Medication Usage (Baseline)**

| Medication Category                                                   | Treatment Group                   |                                   | Placebo<br>N = 366<br>n (%) | Overall<br>N = 1072<br>n (%) |
|-----------------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------|------------------------------|
|                                                                       | ALD403 300 mg<br>N = 350<br>n (%) | ALD403 100 mg<br>N = 356<br>n (%) |                             |                              |
| <b>Any Acute Medications at Baseline (% of days used)<sup>1</sup></b> | N = 349                           | N = 354                           | N = 365                     | N = 1068                     |
| Mean (SD)                                                             | 52.5 (24.1)                       | 41.1 (24.1)                       | 49.9 (25.9)                 | 41.1 (24.7)                  |
| Median                                                                | 54.6                              | 53.9                              | 52.0                        | 53.9                         |
| Min, Max                                                              | 0, 100                            | 0, 100                            | 0, 100                      | 0, 100                       |
| <b>Ergotamine Usage</b>                                               |                                   |                                   |                             |                              |
| Mean (SD)                                                             | 1.0 (7.5)                         | 0.3 (2.4)                         | 0.6 (3.9)                   | 0.6 (5.1)                    |
| <b>Triptan Usage</b>                                                  |                                   |                                   |                             |                              |
| Mean (SD)                                                             | 24.5 (23.3)                       | 24.4 (25.8)                       | 22.9 (24.1)                 | 23.4 (24.7)                  |
| ≥ 33% of days                                                         | 125 (35.7)                        | 124 (34.8)                        | 116 (31.7)                  | 365 (34.0)                   |
| < 33% of days                                                         | 225 (64.3)                        | 231 (64.9)                        | 250 (68.3)                  | 706 (65.9)                   |
| <b>Simple Analgesic Usage</b>                                         |                                   |                                   |                             |                              |
| Mean (SD)                                                             | 21.2 (24.2)                       | 22.0 (23.6)                       | 23.3 (24.9)                 | 22.2 (24.3)                  |
| <b>Opioid Usage</b>                                                   |                                   |                                   |                             |                              |
| Mean (SD)                                                             | 0.4 (2.1)                         | 0.9 (5.9)                         | 0.5 (2.2)                   | 0.6 (3.8)                    |
| <b>Combination Analgesic Usage</b>                                    |                                   |                                   |                             |                              |
| Mean (SD)                                                             | 15.8 (23.1)                       | 13.8 (20.7)                       | 11.1 (19.3)                 | 13.5 (21.1)                  |

<sup>1</sup> Denominator is the number of days with a non-missing evening report for the selected interval. Only patients who completed the evening report at least half the time for the selected interval are included

Source: Adapted from Study 011 CSR 14.1.4.2, reviewer verified

Concomitant cardiovascular medications were reported in 22.9% of the study population. Most patients who had cardiovascular risk factors were excluded from the study, as in Study 006 described above.

**Table 29 Use of Concomitant Cardiovascular Medications**

| Demographic Parameters    | Treatment Group                   |                                   | Placebo<br>N = 366<br>n (%) | Overall<br>N = 1072<br>n (%) |
|---------------------------|-----------------------------------|-----------------------------------|-----------------------------|------------------------------|
|                           | ALD403 300 mg<br>N = 350<br>n (%) | ALD403 100 mg<br>N = 356<br>n (%) |                             |                              |
| Cardiovascular Medication | 80 (22.9)                         | 85 (23.9)                         | 80 (21.9)                   | 245 (22.9)                   |

Source: Adapted from Study 011 CSR, Table 14.1.4.1

## Efficacy Results – Primary Endpoint

The primary endpoint for this study is the change from baseline in frequency of migraine days for Weeks 1-12. The primary endpoint was calculated as the number of monthly migraine days within 4-week intervals that were then averaged up to Week 12. The difference of this estimate from baseline was calculated as the change from baseline in frequency of monthly migraine days over Weeks 1-12 (See Table 30). The primary endpoint was statistically significant for the ALD403 300 mg and 100 mg treatment groups.

**Table 30 Analysis of Migraine Days by 12-Week Interval and Treatment Effect**

| Interval                     | Treatment Group             |                             | Placebo<br>N = 366 |
|------------------------------|-----------------------------|-----------------------------|--------------------|
|                              | ALD403<br>300 mg<br>N = 350 | ALD403<br>100 mg<br>N = 356 |                    |
| <b>Baseline</b>              |                             |                             |                    |
| Mean (SD)                    | 16.1 (4.8)                  | 16.1 (4.6)                  | 16.2 (4.6)         |
| <b>Weeks 1-12</b>            |                             |                             |                    |
| Estimated Mean               | 7.9                         | 8.5                         | 10.5               |
| Mean difference from placebo | -2.59                       | -2.03                       |                    |
| 95% CI                       | (-3.45, -1.74)              | (-2.88, -1.18)              |                    |
| <b>Change from baseline</b>  |                             |                             |                    |
| Estimated Mean               | -8.2                        | -7.7                        | -5.6               |
| Mean difference from placebo | -2.59                       | -2.03                       |                    |
| 95% CI                       | (-3.45, -1.74)              | (-2.88, -1.17)              |                    |
| p-value                      | < 0.0001                    | < 0.0001                    |                    |

CI = Confidence interval

Migraine days over 12 week periods were all monthly migraine days

Change from baseline was the difference in migraine days between baseline and the selected Week 1-12 interval

Source: Reviewer's analysis of ADEFFCE dataset and adapted from Study 011 CSR Table 16

**Reviewer's comment: The primary endpoint is statistically significant and indicates a clinically meaningful decrease in monthly migraine days. There is a trend towards a greater effect**

***(larger difference from placebo) with the 300 mg dose compared to the 100 mg dose. The treatment effect, while modest, is similar in magnitude to the treatment effect of other previously approved anti-CGRP monoclonal antibodies that were approved in 2018.***

The applicant performed sensitivity analyses based on a modified missing data imputation rule and modified definition of baseline, both of which support the primary efficacy endpoint analysis. They also calculated sensitivity analyses with change from baseline in migraine days over Weeks 1-24 as well as Weeks 1-12, which also supported the primary efficacy treatment effect. See Dr. Bai's statistical review for more detailed analyses.

### **Data Quality and Integrity**

There were no major identified concerns with regard to data quality or integrity. The OSI site inspections did uncover a few examples of unblinding and many cases of possible unblinding. There were 6 patients at 4 sites in Study 011 [REDACTED] (b) (6) [REDACTED] that had unblinding events. A sensitivity analysis was conducted with removal of these patients which showed no impact on the primary endpoint. The treatment effect was maintained at -2.52 for the 300 mg arm, and -1.98 for the 100 mg arm (See Table 38). See OSI review for complete details.

### **Efficacy Results – Secondary and other relevant endpoints**

Based on the applicant's decision rule to adjust for multiplicity, the results for the primary endpoint and all the key secondary endpoints for all dose groups were statistically significant. The endpoints and p-values are described below in Table 31. All endpoints were tested with an alpha of 5% as per the pre-specified multiple testing procedure that was a combination of gate-keeping and the Holm's procedure.

Key secondary endpoints are described above in Section 6.2.1. The results of these analyses are summarized in the following tables.

**Table 31 Key Secondary Efficacy Endpoint Analysis**

|                                      | ALD403 300 mg<br>N = 350 | ALD403 100 mg<br>N = 356 | Placebo<br>N = 366 |
|--------------------------------------|--------------------------|--------------------------|--------------------|
| <b>75% responder rate Weeks 1-4</b>  |                          |                          |                    |
| n (%)                                | 129 (36.9)               | 110 (30.9)               | 57 (15.6)          |
| Diff from placebo (%)                | 21.3                     | 15.3                     |                    |
| 95% CI                               | (15.0, 27.6)             | (9.3, 21.4)              |                    |
| p-value                              | < 0.0001                 | < 0.0001                 |                    |
| <b>75% responder rate Weeks 1-12</b> |                          |                          |                    |
| n (%)                                | 116 (33.1)               | 95 (26.7)                | 55 (15.0)          |
| Diff from placebo (%)                | 18.1                     | 11.7                     |                    |
| 95% CI                               | (12.0, 24.3)             | (5.8, 17.5)              |                    |
| p-value                              | < 0.0001                 | 0.0001                   |                    |
| <b>50% responder rate Weeks 1-12</b> |                          |                          |                    |
| n (%)                                | 215 (61.4)               | 205 (57.6)               | 144 (39.3)         |
| Diff from placebo (%)                | 22.1                     | 18.2                     |                    |
| 95% CI                               | (14.9, 29.2)             | (11.1, 25.4)             |                    |
| p-value                              | < 0.0001                 | < 0.0001                 |                    |

Source: Adapted from Study 011 CSR Table 17, 18, 19; reviewer verified

#### Percentage of Patients with Migraine on Day after Dosing (Day 1)

As in Study 006, the applicant summarized the percentage of patients who had a migraine on the day after dosing, where Day 0 is the day the treatment is administered, and Day 1 is the first day after dosing. To calculate the baseline migraine prevalence rate, the applicant used the daily migraine prevalence, where on average 58% of patients had a migraine on any given day during the 28-day screening period, based on eDiary entries (Table 32).

When comparing migraine prevalence on the day of dosing and on the day after dosing (Day 1) in the treatment arms compared to placebo, the percentage of patients with a migraine on Day 1 in the ALD403 300 mg and ALD403 100 mg treatment groups were both statistically significantly lower than the placebo arm.

As in Study 006, the Division also requested the applicant provide subgroup analyses to look specifically at the incidence of migraine on Day 1, separated by those patients who had a migraine on Day 0, and those patients who did not have a migraine on Day 0. The two subgroup analyses presented below vary by how a “migraine on the day of dosing” was defined. For the initial subgroup analysis, migraine on day of dosing includes any migraine present at any time on Day 0, and migraine on Day 1 is defined as migraine present at any time on Day 1. For the alternate subgroup analysis, migraine on day of dosing includes only those patients who had a migraine ongoing at the start of the treatment, and migraine on Day 1, includes only those patients who had a new migraine starting between the end of infusion on Day 0 and the end of Day 1.

**Table 32 Percentage of Patients with a Migraine at Baseline and on Day 1**

|                                                   | ALD403 300 mg | ALD403 100 mg | Placebo |
|---------------------------------------------------|---------------|---------------|---------|
| Percentage of Patients with a Migraine            | N = 350       | N = 356       | N = 366 |
| Baseline <sup>1</sup> (daily migraine prevalence) | 57.4          | 57.5          | 58.0    |
| Day 0                                             | 33.1          | 40.0          | 45.3    |
| Day 1                                             | 27.8          | 28.6          | 42.3    |
| p-value <sup>2</sup>                              | < 0.0001      | < 0.0001      |         |
| <b>Subgroup analysis<sup>3</sup></b>              |               |               |         |
| Yes Migraine on Day of Dosing (day 0)             | N = 112       | N = 139       | N = 160 |
| Day 1 Migraine                                    | 51.9          | 51.2          | 69.2    |
| p-value*                                          | 0.0005        | 0.0011        |         |
| No Migraine on Day of Dosing (day 0)              | N = 228       | N = 214       | N = 189 |
| Day 1 Migraine                                    | 16.1          | 13.4          | 20.3    |
| p-value*                                          | 0.0779        | 0.2591        |         |
| <b>Alternate Analysis<sup>4</sup></b>             |               |               |         |
| Yes Migraine on Day of Dosing (Day 0)             | N = 61        | N = 74        | N = 77  |
| Day-1 Migraine                                    | 22.4          | 29.3          | 33.6    |
| p-value*                                          | 0.596         | 0.1880        |         |
| No Migraine on Day of Dosing (day 0)              | N = 276       | N = 265       | N = 270 |
| Day 1 Migraine                                    | 25.2          | 26.0          | 38.7    |
| p-value*                                          | 0.0016        | 0.0005        |         |

<sup>1</sup> Baseline was the average daily migraine prevalence over the 28-day screening period prior to treatment as recorded in eDiary, Day 0 is first day of treatment;

<sup>2</sup> p-values were obtained from an extended Cochran-Mantel-Haenszel test stratified by randomized baseline migraine days and prophylactic medication use and were statistically significant

<sup>3</sup> Migraine on day of dosing includes any migraine present at any time during Day 0, and Migraine on Day 1 defined as migraine present at any time on Day 1

<sup>4</sup> Migraine on Day of Dosing includes only those patients who had a migraine that was ongoing at the start of treatment and Migraine on Day 1 includes only those that were new migraines starting between the infusion on Day 0 and the end of Day 1

\*p-values not reliable for these subgroup analyses given the small number of patients in each group

Source: Reviewer verified and adapted from Study 011 CSR Table 20 (14.2.2.4.2) and tables 14.2.2.4.1a and 14.2.2.4.1c

**Reviewer's comment: The above analyses demonstrate that the overall migraine prevalence on Day 1 was lower in the treatment arms than in the placebo arm, and this difference was statistically significant.**

**The two subgroup analyses demonstrate that amongst only those patients who had a migraine on Day 0, they were more likely to also have a migraine on Day 1 in the placebo arm than if they received treatment. For those patients who had a migraine ongoing during the infusion (alternate subgroup analysis), they were also more likely to have a migraine on Day 1 if they received placebo rather than treatment. However, of those patients who did not have a migraine at the time of infusion, the percent of patients who had a Day 1 migraine after receiving placebo was much higher (38.7%) than those patients who had a migraine on Day 1 after receiving treatment (25-26%). Although this is a post-hoc analysis on a small subgroup, the data appears to demonstrate that there is a trend towards decreased migraines in the**

***treatment group starting as early as day one. In the chronic migraine study, patients had to have an average of 15 migraine days per month. Therefore, if they did not have a migraine on the day they received the infusion, the likelihood of having one the next day would be quite high (on average). Therefore, there is evidence that the data supports a decrease in migraine prevalence that begins on the day after dosing.***

(b) (4)

(b) (4)

***Upon further discussion and analysis of the data, I interpreted the percentage of with a migraine on the day after dosing not as a clinically meaningful endpoint by itself, but rather as the ability to demonstrate an early onset of efficacy (as determined by the primary endpoint). (See also discussion in Section 7.1.5).***

The applicant also analyzed the average daily migraine prevalence and the reduction from baseline over Weeks 1-4, as seen below in Table 33. The mean difference in average daily migraine prevalence over weeks 1-4 was -11.0 for the 300 mg treatment arm, and -8.26 for the 100 mg treatment arm, both of which were statistically significant compared to placebo.

**Table 33 Analysis of Reduction in Migraine Prevalence by Weeks 1-4**

|                              | ALD403 300 mg<br>N = 350 | ALD403 100 mg<br>N = 356 | Placebo<br>N = 366 |
|------------------------------|--------------------------|--------------------------|--------------------|
| <b>Migraine Prevalence</b>   |                          |                          |                    |
| Baseline                     | 57.4                     | 57.5                     | 58.0               |
| Overall Weeks 1-4            |                          |                          |                    |
| Estimated Mean               | 27.9                     | 30.6                     | 38.9               |
| Mean difference from placebo | -11.0                    | -8.26                    |                    |
| 95% CI                       | (-14.2, -7.8)            | (-11.5, -5.1)            |                    |
| Change from baseline         |                          |                          |                    |
| Estimated Mean               | -29.8                    | -27.1                    | -18.8              |
| Mean difference from placebo | -11.0                    | -8.26                    |                    |

|         |               |               |  |
|---------|---------------|---------------|--|
| 95% CI  | (-14.2, -7.8) | (-11.5, -5.1) |  |
| p-value | <0.0001       | <0.0001       |  |

*Change from baseline is the model-estimated difference in migraine prevalence between baseline and the selected interval*

*P-values are obtained from a repeated measure model including group, visit (Weeks 1, 2, 3 and 4), baseline migraine prevalence and treatment group-by-visit interaction*

*Source: Table 14.2.2.4.3a, reviewer-verified*

### Change in acute migraine medication usage

The statistical comparison for change in acute migraine medication usage was only pre-specified for the 300 mg treatment arm versus placebo. The applicant provided data for the change from baseline in acute migraine medication usage for ALD403 300 mg for Weeks 1-12. An “acute migraine medication day” was a day with any triptan or ergotamine as recorded in the eDiary. Mean acute migraine medications days was low at baseline and reduced over Weeks 1-12 in all treatment groups. The reductions were numerically greater in both ALD403 groups compared to placebo, with a statistically significant reduction of -1.4 days in the ALD403 300 mg group ( $p < 0.0001$ ). The reduction in the ALD403 100 mg group compared with placebo was nominally significant with a p-value of  $< 0.0001$ .

**Table 34 Analysis of Change in Acute Migraine Medication Days for Weeks 1-12 (Full Analysis Population)**

|                                       | ALD403 300 mg<br>N = 350 | ALD403 100 mg<br>N = 356 | Placebo<br>N = 366 |
|---------------------------------------|--------------------------|--------------------------|--------------------|
| <b>Acute Migraine Medication Days</b> |                          |                          |                    |
| Baseline Mean (SD)                    | 6.7 (6.48)               | 6.6 (6.93)               | 6.2 (6.70)         |
| Weeks 1-12                            |                          |                          |                    |
| Mean (SD)                             | 3.2 (4.71)               | 3.3 (4.84)               | 4.3 (5.67)         |
| Change from baseline                  |                          |                          |                    |
| Mean (SD)                             | -3.5 (4.62)              | -3.3 (4.89)              | -1.9 (4.18)        |
| Mean difference from placebo          | -1.4                     | -1.1                     |                    |
| 95% CI                                | (-1.88, -0.87)           | (-1.66, -0.65)           |                    |
| p-value                               | < 0.0001                 | < 0.0001*                |                    |

*Source: Study 011 CSR Table 23, Table 14.2.2.3.2 and Table 14.2.2.3.2a*

*\*not a pre-specified statistical comparison*

***Reviewer’s comment: The use of acute migraine medications (triptans and ergotamine) was low at baseline, but similar across treatment arms in the chronic migraine population, with approximately 6 acute migraine medication days per month. The lower-than-expected rate of acute migraine medication use may be due to more frequent use of over-the counter products such as NSAIDs which were not included in this calculation. The observed reduction in migraine days was also consistent with a reduction in acute migraine medication use, as demonstrated above. The reduction in use of acute migraine medications was only pre-specified for the 300 mg treatment arm, and it was statistically significant. The reduction of***

**acute migraine medications days was nominally significant for the 100 mg treatment arm.**

#### Headache Impact Test (HIT-6)

A statistical comparison for the final key secondary endpoint of the Headache Impact Test (HIT-6) was only pre-specified for the ALD403 300 mg treatment arm versus placebo. The mean difference in score over Weeks 9-12 and the change from baseline were analyzed for each treatment arm (Table 34).

**Table 35 Summary and Analysis of Headache Impact Test Scores**

|                                       | ALD403 300 mg<br>N = 350 | ALD403 100 mg<br>N = 356 | Placebo<br>N = 366 |
|---------------------------------------|--------------------------|--------------------------|--------------------|
| <b>Acute Migraine Medication Days</b> |                          |                          |                    |
| Baseline Mean (SD)                    | 65.1 (4.99)              | 65.0 (4.94)              | 64.8 (5.46)        |
| Weeks 9-12                            |                          |                          |                    |
| Mean                                  | 57.6                     | 58.8                     | 60.5               |
| Change from baseline                  |                          |                          |                    |
| Mean                                  | -7.5                     | -6.2                     | -4.5               |
| Mean difference from placebo          | -2.88                    | -1.73                    |                    |
| 95% CI                                | (-3.91, -1.84)           | (-2.76, -0.70)           |                    |
| p-value                               | < 0.0001                 | 0.0010*                  |                    |

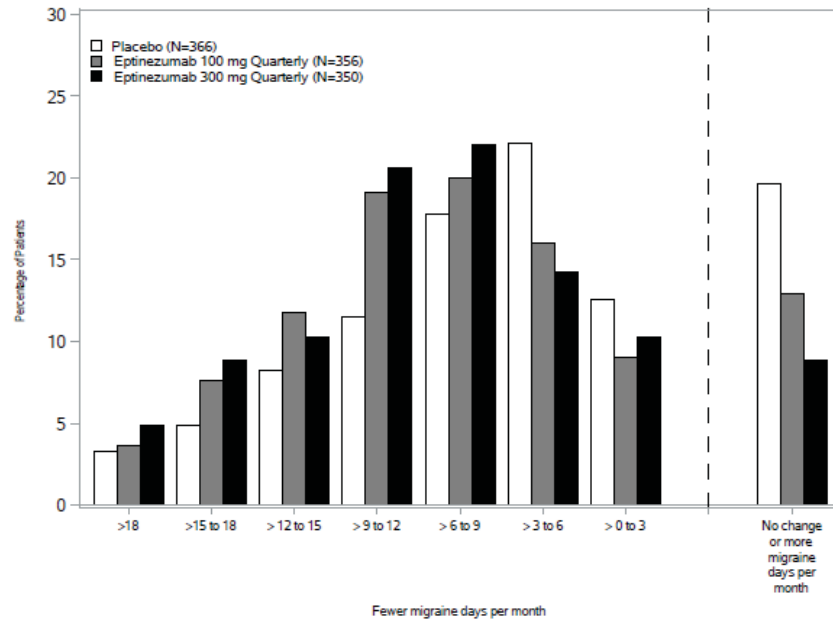
Source: Study 011 CSR Table 14.2.3.5.1, reviewer-verified

**Reviewer's comment:** *The applicant demonstrated improvement in the HIT-6 scores in the treatment groups, with the improvement being statistically significant for the 300 mg treatment arm, which was a pre-specified key secondary endpoint. However, there are several flaws with the HIT-6 (b) (4). The key concerns are that it was designed in a general headache, not migraine, population, and has been validated in the general headache population. There are other symptoms to consider in the migraine population, so that an improvement in headaches does not always equate to overall improvement in quality of life, etc. Please see the COA review for further details (b) (4).*

#### Dose/Dose Response

Overall, the doses demonstrated similar efficacy over placebo at all doses tested. Figure 7 demonstrates the distribution of change from baseline in mean monthly migraine days over Months 1-3 by treatment arm.

**Figure 7 Study 011: Distribution of Change from Baseline in Mean Monthly Migraine Days over Months 1-3**



Source: Applicant-provided Figure 14.2.2.8.2 (Integrated Summary of Efficacy)

### Migraine Freedom

There were some patients who achieved 100% reduction in migraine days and became migraine-free for the entire primary treatment period, or for any given 4-week interval. The 100% responder rate was greater in the 300 mg treatment arm and the 100 mg treatment arm compared to placebo for every 4 week interval, with more responders in the 300 mg treatment arm.

**Table 36 100% Responder Rate by 4-week Intervals and Treatment Arm During Primary Efficacy Treatment Period**

| 100% responder rates<br>Interval | ALD403 300 mg<br>N = 350<br>(%) | ALD403 100 mg<br>N = 356<br>(%) | Placebo<br>N = 366<br>(%) |
|----------------------------------|---------------------------------|---------------------------------|---------------------------|
| Weeks 1-4                        | 13.4                            | 7.9                             | 2.7                       |
| Weeks 5-8                        | 14.9                            | 13.5                            | 6.3                       |
| Weeks 9-12                       | 17.1                            | 11.2                            | 6.3                       |
| Weeks 1-12                       | 15.1                            | 10.8                            | 5.1                       |

100% migraine responder was a patient who achieved a 100% reduction in migraine days (i.e. migraine free) for that interval of time

Source: Study ALD403 CSR, Table 25 (14.2.2.2.1 and 14.2.2.2.2)

### Persistence of Effect/ Durability of Response

This reviewer also evaluated the mean change from baseline in monthly migraine days over Weeks 1-24 to look for sustained treatment effect, which is summarized below in Table 37. Migraine responder rates over Weeks 1-24 were also similar to those seen over Weeks 1-12, demonstrating a durability of response. There appeared to be a trend toward a more sustained response in the 300 mg group compared to 100 mg treatment arm.

**Table 37 Study 011 Mean Change from Baseline in Monthly Migraine Days Through Week 24 (Full Analysis Population)**

| Interval                             | Treatment Group             |                             | Placebo<br>N = 366 |
|--------------------------------------|-----------------------------|-----------------------------|--------------------|
|                                      | ALD403<br>300 mg<br>N = 350 | ALD403<br>100 mg<br>N = 356 |                    |
| <b>Baseline</b>                      |                             |                             |                    |
| Mean (SD)                            | 16.1 (4.8)                  | 16.1 (4.6)                  | 16.2 (4.6)         |
| <b>Weeks 1-24</b>                    |                             |                             |                    |
| Estimated Mean Monthly Migraine Days | 7.6                         | 8.2                         | 10.2               |
| Mean difference from placebo         | -2.6                        | -2.0                        |                    |
| Change from baseline (mean)          | -8.5                        | -7.9                        | -5.9               |
| Mean difference from placebo         | -2.6                        | -2.0                        |                    |
| <b>Weeks 13-24</b>                   |                             |                             |                    |
| Estimated Mean Monthly Migraine Days | 7.3                         | 8.0                         | 10.0               |
| Mean difference from placebo         | -2.7                        | -2.0                        |                    |
| Change from baseline (mean)          | -8.8                        | -8.2                        | -6.2               |
| Mean difference from placebo         | -2.7                        | -2.0                        |                    |

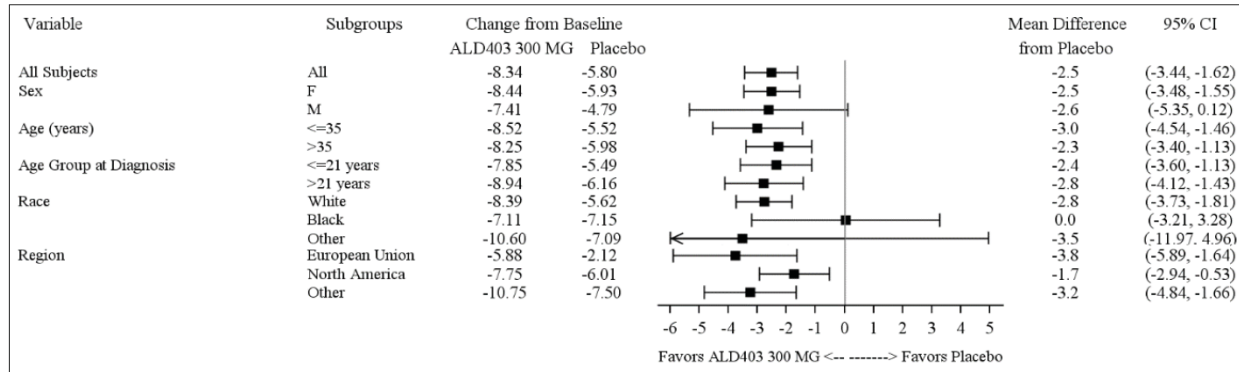
Source: Reviewer analysis of ADEFFCE dataset, adapted from Study 011 CSR Table 14.2.1.2.1b)

### Additional Analyses Conducted on the Individual Trial

#### Subgroup analyses

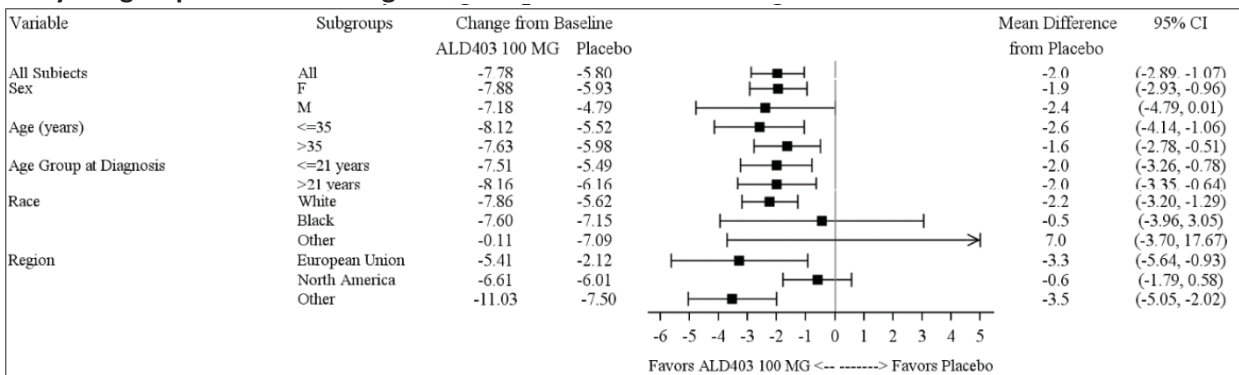
The following figures present a forest plot of difference from placebo in migraine days change from baseline over Weeks 1-12 (primary endpoint) by subgroup for the 300 mg arm (Figure 8) and 100 mg arm (Figure 9). The ALD403 300 mg treatment arm showed consistent reductions from baseline in monthly migraine days when compared with placebo across all clinically important subgroups. The reductions from baseline in the 300 mg group were more robust and consistent across the analyzed subgroups compared to the 100-mg group.

**Figure 8 Forest Plot of Differences from Placebo in Migraine Days Change from Baseline Over Weeks 1-12 by Subgroups – ALD403 300 mg**



Source: Dr. Bai's statistical Review Figure 4-3

**Figure 9 Forest Plot of Difference from Placebo in Migraine Days Change from Baseline Over Weeks 1-12 by Subgroup- ALD403 100 mg**

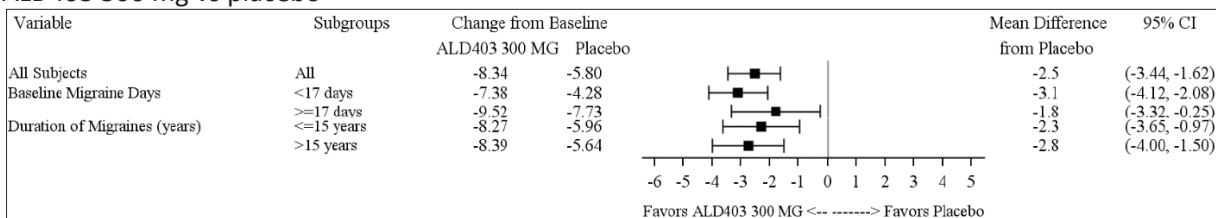


Source: Dr. Bai's statistical Review Figure 4-4

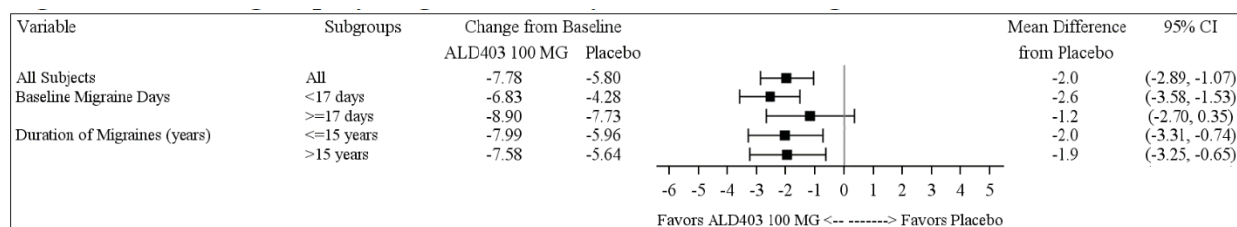
The applicant also looked at subgroup analyses by patient's baseline migraine days (<= 17 days or > 17 days) and migraine history (<= 15 years or > 15 years). These subgroups numerically favor the ALD403 300 mg and ALD403 100 mg treatments over placebo (Figure 10).

**Figure 10 Forest Plot of Subgroup Analyses by Migraine History**

#### ALD403 300 mg vs placebo



#### ALD403 100 mg vs. placebo



Source: Adapted from Study 011 CSR Figure 9, 10 and Dr. Bai's Statistical Review

## Sensitivity analyses (See above)

As noted above, the performed sensitivity analyses based upon modified missing data imputation rule supported the primary endpoint analysis. There was also a sensitivity analysis performed with removal of the 6 patients that were unblinded during the study. The treatment effect remained nearly the same with removal of these patients in the primary efficacy endpoint analysis.

**Table 38 Sensitivity Analysis of Primary Endpoint with Removal of Unblinded Patients**

|                                          | 300 mg | 100 mg |
|------------------------------------------|--------|--------|
| Primary Endpoint Difference from Placebo | -2.5   | -2.0   |
| After removal of patients                | -2.52  | -1.98  |

Source: Reviewer-created table of statistician's analysis of primary endpoint with removal of 6 unblinded patients from primary analysis

## 7. Integrated Review of Effectiveness

### 7.1. Assessment of Efficacy Across Trials

#### 7.1.1. Primary Endpoints

The two pivotal studies were conducted in distinct populations (episodic migraine and chronic migraine) and there was no formal pooling of the study populations or efficacy data. However, given the similarities in trial design and endpoints, some of the results are considered collectively in this section. The primary endpoint across both pivotal studies was the change from baseline in mean monthly migraine days over weeks 1-12. Eptinezumab administered every 3 months resulted in a statistically significant reduction in monthly migraine days as demonstrated by the primary efficacy analyses for Study 006 in episodic migraine, and Study 011 in chronic migraine (Table 39).

The primary endpoint was significant for the 100 mg and 300 mg treatment arms in both studies. It was nominally significant for the 30 mg dose in Study 006, but was not statistically significant because of the applicant's serial, fixed-sequence procedure to adjust for multiplicity,

which required them to spend their alpha prior to testing the 30 mg dose. However, the treatment effect for the 30 mg dose was numerically similar, and even slightly better than, the treatment effect seen for the 100 mg dose.

***Reviewer's comment: The primary endpoint of reduction in mean monthly migraine days over weeks 1-12 compared to placebo is the same primary endpoint used in the recent approvals for the other CGRP antagonists approved in 2018. It is also similar to the primary endpoint used in other approved preventive treatments for episodic and chronic migraine. Although the treatment effect is modest, especially in the episodic migraine study, it is similar to other approved therapies, and likely represents a clinically meaningful reduction in migraine days for patients.***

***The 30 mg dose appears to be as effective as the 100 mg and 300 mg dose when comparing the treatment effects. However, the dose-response curve is relatively flat, and the 30 mg dose was not tested in Study 011, so there is no experience with the 30 mg dose in the preventive treatment of chronic migraine.***

**Table 39 Summary of Primary and Key Secondary Efficacy Endpoints**

| Primary Efficacy Endpoint                     | STUDY ALD403-CLIN-006        |                              |                               |                    | STUDY ALD403-CLIN-011       |                             |                    |
|-----------------------------------------------|------------------------------|------------------------------|-------------------------------|--------------------|-----------------------------|-----------------------------|--------------------|
|                                               | Treatment Group              |                              |                               | Placebo<br>N = 222 | Treatment Group             |                             | Placebo<br>N = 366 |
|                                               | ALD403<br>300 mg<br>N = 222  | ALD403<br>100 mg<br>N = 221  | ALD403<br>30 mg<br>N = 223    |                    | ALD403<br>300 mg<br>N = 350 | ALD403<br>100 mg<br>N = 356 |                    |
| Change from baseline in Monthly Migraine Days | -4.29                        | -3.88                        | -4.01                         | -3.19              | -8.2                        | -7.7                        | -5.6               |
| Treatment effect <sup>^</sup>                 | -1.11<br>(p-value = 0.0001)  | -0.69<br>(p-value = 0.0181)  | -0.82<br>(p-value = 0.0046)** |                    | -2.59<br>(p-value < 0.0001) | -2.03<br>(p-value < 0.0001) |                    |
| <b>Key Secondary Endpoints</b>                |                              |                              |                               |                    |                             |                             |                    |
| 75% Responder Rate Weeks 1-4 (%)              | 31.5                         | 30.8                         | 30.0                          | 20.3               | 36.9                        | 30.9                        | 15.6               |
| Treatment effect <sup>^</sup>                 | 11.3<br>(p-value = 0.006)    | 10.5<br>(p-value = 0.0112)   | 9.8<br>(p-value = 0.017)**    |                    | 21.3<br>(p-value < 0.0001)  | 15.3<br>(p-value < 0.0001)  |                    |
| 75% Responder Rate Weeks 1-12 (%)             | 29.7                         | 22.2                         | 24.7                          | 16.2               | 33.1                        | 26.7                        | 15.0               |
| Treatment effect <sup>^</sup>                 | 13.5<br>(p-value = 0.0007)   | 6.0<br>(p-value = 0.113)*    | 8.4<br>(p-value = 0.027)**    |                    | 18.1<br>(p-value < 0.0001)  | 11.7<br>(p-value = 0.0001)  |                    |
| 50% Responder Rate Weeks 1-12 (%)             | 56.3                         | 49.8                         | 50.2                          | 37.4               | 61.4                        | 57.6                        | 39.3               |
| Treatment effect <sup>^</sup>                 | 18.9<br>(p-value = 0.0001)   | 12.4<br>(p-value = 0.0085)** | 12.8<br>(p-value = 0.0065)**  |                    | 22.1<br>(p-value < 0.0001)  | 18.2<br>(p-value < 0.0001)  |                    |
| Percentage of Pts with Migraine on Day 1      | 13.9                         | 14.8                         | 17.3                          | 22.5               | 27.8                        | 28.6                        | 42.3               |
| Treatment effect <sup>^</sup>                 | -8.6<br>(p-value = 0.0159)** | -7.7<br>(p-value = 0.0312)** | -5.2<br>(p-value = 0.1539)*   |                    | -13.9<br>(p-value < 0.0001) | -13.2<br>(p-value < 0.0001) |                    |
| Migraine Prevalence Reduction Weeks 1-4       | n/a                          | n/a                          | n/a                           |                    | -29.8                       | -27.1                       | -18.8              |
| Treatment effect <sup>^</sup>                 |                              |                              |                               |                    | -11.0<br>(p-value < 0.0001) | -8.26<br>(p-value < 0.0001) |                    |
| HIT-6 Change Over Weeks 9-12                  | n/a                          | n/a                          | n/a                           |                    | -7.5                        | n/a                         | -4.3               |
| Treatment effect <sup>^</sup>                 |                              |                              |                               |                    | -2.88<br>(p-value < 0.0001) |                             |                    |
| Acute Migraine Med Reduced Weeks 1-12         | n/a                          | n/a                          | n/a                           |                    | -3.5                        | n/a                         | -1.9               |
| Treatment effect <sup>^</sup>                 |                              |                              |                               |                    | -14<br>(p-value < 0.0001)   |                             |                    |

<sup>^</sup>Treatment effect = difference from placebo; n/a – not pre-specified, \* not significant, \*\* nominally significant

### 7.1.2. Secondary and Other Endpoints

The analyses of the key secondary endpoints are included above in Table 39. The studies were consistent with their responses on key secondary endpoints, which includes a likely clinically meaningful result on the 50% and 75% responder analyses outlined above. The other secondary endpoints are supportive of the primary endpoint, including the reduction in acute migraine medication and a reduction in daily migraine prevalence.

There is some data supporting that the percentage of patients with a migraine on day 1 after

dosing is decreased in the treatment groups compared to placebo.

(b) (4)

(b) (4)

### 7.1.3. Subpopulations

The efficacy results were similar across subpopulations by age, gender, and race. However, it should be noted that the majority of the patients in both studies were white, female, and between the ages of 18 and 65 years. There were no major differences based on migraine history. Treatment effects were similar in both studies among different subpopulations, but were not pooled given the different indications of episodic and chronic migraine.

### 7.1.4. Dose and Dose-Response

For both studies, the 100 mg and 300 mg doses of eptinezumab demonstrated similar efficacy over placebo, with a trend towards a slightly higher treatment effect in the 300 mg treatment arm. Both groups demonstrated highly statistically significant reduction in monthly migraine days over weeks 1-12 compared with placebo. In the responder analyses, the two treatment groups had higher response rates overall for the responder endpoints than placebo up to Week 12 in both episodic and chronic migraines. There was no clear dose response trend. The patients in the 300 mg treatment arm had a numerically greater magnitude of therapeutic effect than ALD403 100 mg but 100 mg was still significant, and the difference was minimal with overlapping confidence intervals. Migraine reductions were rapid and maintained in both treatment groups. As noted above, in Study 006, the 30 mg dose was nominally significant, and numerically better than the 100 mg dose, but not statistically significant. The 30 mg dose was not included as a treatment arm in Study 011 in patients with chronic migraine.

Study 005, a Phase 2 study in chronic migraine, also looked at dose-response over a range of doses including 10, 30, 100, 300 mg and placebo. In that study the primary endpoint was a 75% responder analysis and not the mean change from baseline in monthly migraine frequency.

However, the treatment effect of decrease in monthly migraine days from baseline, compared to placebo was included as a secondary endpoint. In that study, the treatment effect in the 30 mg, 100 mg, and 300 mg treatment arms were similar after a single dose. The 30 mg dose did not differ significantly in treatment effect from the 100 mg dose (Table 40).

**Table 40 Study 005 Dose-response Analysis of Decrease in Monthly Migraine Days over Weeks 1-12**

|                                                  | ALD403<br>10 mg | ALD403<br>30 mg | ALD403<br>100 mg | ALD403<br>300 mg | Placebo |
|--------------------------------------------------|-----------------|-----------------|------------------|------------------|---------|
| N                                                | 130             | 122             | 122              | 121              | 122     |
| Baseline Monthly Migraine Frequency (Weeks 1-12) | 16.4            | 16.2            | 16.9             | 16.5             | 16.4    |
| Change from Baseline                             | -6.7            | -7.9            | -7.7             | -8.2             | -5.6    |
| Treatment effect (Difference from Placebo)       | -1.2            | <b>-2.4</b>     | <b>-2.1</b>      | <b>-2.7</b>      |         |
| p-value                                          | 0.1802          | <b>0.0054</b>   | <b>0.0178</b>    | <b>0.0034</b>    |         |

Source: Reviewer-verified and adapted table from study 005 ADAEFF dataset, on modified full analysis population (removal of Site 165), Study 005 CSR Table 14.2.2.3.2

**Reviewer's comment: It appears from the Phase 2 dose-range study and primary efficacy analysis from Study 006 that the 30 mg dose is likely as effective as the 100 mg dose in the treatment of episodic migraine, and may have demonstrated effectiveness had it been studied in the pivotal study for patients with chronic migraine. However, the 30 mg dose was not studied in a pivotal study of chronic migraine and was nominally but not statistically significant in the treatment of episodic migraine. In general, the 30 mg dose and 100 mg dose demonstrated similar efficacy and the 300 mg dose had a trend towards slightly higher effectiveness; however overall the dose-response curve was very flat. There are likely to be some patients who may respond to lower doses, and some patients that will require higher doses, particularly for the more difficult-to-treat chronic migraine condition, and therefore we agree with the approval of a low dose (100 mg) and high dose (300 mg) for treatment of both episodic and chronic migraine.**

#### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

The applicant performed an ad-hoc analysis evaluating the onset of efficacy by examining the reduction in mean monthly migraine days in progressively smaller time windows, starting with Weeks 1-12 down to day 1 alone. The analysis examined the efficacy of the 100 mg and 300 mg doses over placebo over increasing narrow intervals as listed below:

- Weeks 1-12, weeks 1-8, weeks 1-4, weeks 1-3, weeks 1-2, week 1, days 1-6, days 1-5, days 1-4, days 1-3, days 1-2, and day 1.

Testing was to be stopped at the first result that failed to achieve statistical significance at the 5% level. The applicant proposed that at the end of this procedure, it could be concluded that efficacy (i.e., a difference from placebo) had been demonstrated for each "successful" time interval, and that it can be used to determine onset of efficacy. (b) (4)

(b) (4) In both studies and for both doses, all tests achieved nominal significance at each time point tested.

**Table 41 Closed Testing Approach To Evaluate Onset of Effect (PSS)**

| Primary Efficacy Endpoint               | STUDY ALD403-CLIN-006       |                             |                    | STUDY ALD403-CLIN-011       |                             |                    |
|-----------------------------------------|-----------------------------|-----------------------------|--------------------|-----------------------------|-----------------------------|--------------------|
|                                         | Treatment Group             |                             | Placebo<br>N = 222 | Treatment Group             |                             | Placebo<br>N = 366 |
|                                         | ALD403<br>300 mg<br>N = 222 | ALD403<br>100 mg<br>N = 221 |                    | ALD403<br>300 mg<br>N = 350 | ALD403<br>100 mg<br>N = 356 |                    |
| <b>Weeks 1-12 Change from baseline*</b> |                             |                             |                    |                             |                             |                    |
| Estimated mean                          | -4.3                        | -3.9                        | -3.2               | -8.2                        | -7.7                        | -5.6               |
| Difference from placebo                 | -1.1                        | -0.7                        |                    | -2.6                        | -2.0                        |                    |
| p-value                                 | 0.0001                      | 0.0182                      |                    | <0.0001                     | <0.0001                     |                    |
| <b>Weeks 1-4 Change from baseline*</b>  |                             |                             |                    |                             |                             |                    |
| Estimated mean                          | -4.1                        | -4.0                        | -2.8               | -8.2                        | -7.5                        | -5.2               |
| Difference from placebo                 | -1.4                        | -1.2                        |                    | -3.1                        | -2.3                        |                    |
| p-value                                 | <0.0001                     | 0.0004                      |                    | <0.0001                     | <0.0001                     |                    |
| <b>Week 1 Change from baseline*</b>     |                             |                             |                    |                             |                             |                    |
| Estimated mean                          | -4.5                        | -4.1                        | -2.9               | -7.9                        | -7.2                        | -4.6               |
| Difference from placebo                 | -1.7                        | -1.3                        |                    | -3.3                        | -2.6                        |                    |
| p-value                                 | 0.006                       | 0.0092                      |                    | <0.0001                     | <0.0001                     |                    |
| <b>Days 1-3 Change from baseline*</b>   |                             |                             |                    |                             |                             |                    |
| Estimated mean                          | -4.9                        | -4.9                        | -3.0               | -8.2                        | -7.9                        | -5.4               |
| Difference from placebo                 | -1.9                        | -1.9                        |                    | -2.8                        | -2.5                        |                    |
| p-value                                 | 0.0037                      | 0.0036                      |                    | <0.0001                     | 0.0002                      |                    |
| <b>Day 1 Change from baseline*</b>      |                             |                             |                    |                             |                             |                    |
| Estimated mean                          | -4.7                        | -4.5                        | -2.2               | -8.2                        | -8.0                        | -4.3               |
| Difference from placebo                 | -2.5                        | -2.2                        |                    | -4.0                        | -3.8                        |                    |
| p-value                                 | 0.0102                      | 0.0206                      |                    | <0.0001                     | <0.0001                     |                    |

\*Change from baseline is the difference in migraine days between baseline and selected interval  
Source: Reviewer-adapted table from Summary of Clinical Efficacy Table 30 (ISE 14.4.1.1.4)

**Reviewer's comment: The clinical meaningfulness of the onset of effect is questionable. As outlined above, preventive treatment of migraine is measured by reduction in migraine headaches over time. This analysis does demonstrate that the reduction of migraines may be measurable as early as 1 week after dosing which is likely beneficial information for patients and prescribers.**

**In combination with established efficacy as determined by the primary efficacy endpoint and supported by the key secondary endpoints, it appears that it would be meaningful to know that the treatment benefit may begin soon dosing, in contrast to older preventive treatments that required long periods of titration and had delayed onset of efficacy, sometimes taking several weeks prior to showing any effect. The applicant was able to demonstrate that the percentage of patients with a migraine on the day after dosing was higher for patients who received placebo compared to those patients who received treatment. This was a pre-specified endpoint that was nominally significant in the episodic migraine study (Study 006), and statistically significant in the chronic migraine study (Study 011). As noted above, it is**

*difficult to draw conclusions from this endpoint alone. Further analysis of the data of the percent of patients with a migraine in each treatment arm compared to placebo daily for the first month demonstrates that this effect is sustained throughout the first month. This analysis, combined with the ad-hoc testing above, supports the conclusion that the treatment effect may begin as early as day one for some patients. The following figures demonstrating the percentage of patients with a migraine on the day prior to dosing (Day -1) through Day 7 for Study 006 and Study 011.*

**Figure 11 Percentage of Patients with a Migraine, Day -1 to Day 7 (Study 006)**

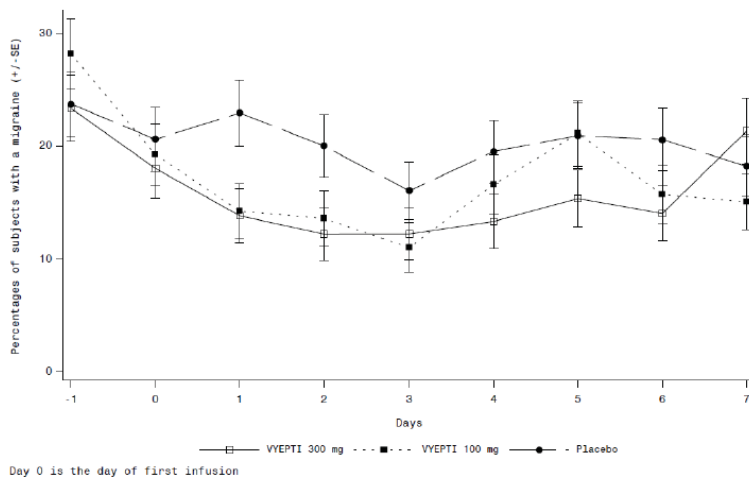
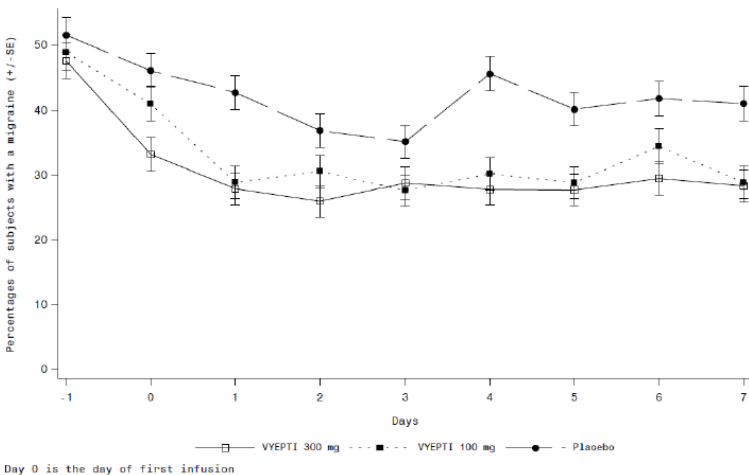


**Figure 12 Percentage of Patients with a Migraine, Day -1 to Day 7 (Study 011)**



## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

Eptinezumab would be the first CGRP-antagonist that is administered by intravenous infusion rather than injection for the preventive treatment of migraine. There are some benefits to having a treatment that is available for infusion. The treatment will be particularly beneficial to those patients who are hesitant to inject themselves monthly, or even every 3 months. The treatment may also benefit those who have trouble remembering to take their injections on the prescribed schedule, as the treatments will be scheduled in advance for infusion at an infusion center or doctor's office, which may increase overall compliance. Intravenous administration may also be beneficial for patients who are in the hospital for other conditions, or a small number of patients who receive infusions for other therapies and already have indwelling catheters placed. There is also a benefit to an early onset of efficacy, without the need for a slow titration of dose, or the delayed onset of older approved therapies.

Given the applicant's analyses that demonstrate that the treatment may start to be effective on the day after infusion, the treatment may ultimately be studied or used as an off-label treatment for who have "status migranosis" or transformed migraines that are persistent and refractory to other outpatient treatment options. There is a current need for studies in this acute migraine patient population who have limited treatment options once the migraine has been present for several days without relief and can no longer rely on the traditional abortive migraine treatments.

It is important to note that the treatment may also be used by patients who are older, have more cardiovascular risk factors that were excluded from these studies, or have more comorbid conditions, especially if is used in inpatient settings. However, these factors are more likely to impact the safety of the drug, rather than have any substantial impact on efficacy.

In general, given the infusion schedule and the need to be administered in a medical setting, there is very little risk for alterations in the dose, administration, or dosing schedule. Patients will not be self-administering the medication, and will not be able to use it more frequently than it is scheduled by their treating prescriber.

#### **7.2.2. Other Relevant Benefits**

As noted, the benefit of having an intravenous drug for prevention of migraines may be to improve compliance with patients, because they have to have an appointment to receive the infusion. It may also provide benefit for patients who have difficulty remembering to take a daily oral medication, or patients who are hesitant to give themselves a monthly injection.

The medication will be difficult to abuse or result in overdose given it will only be administered in a controlled fashion, either in an infusion center, doctor's office, or hospital setting.

### **7.3. Integrated Assessment of Effectiveness**

Overall, the applicant has provided sufficient evidence of effectiveness in the preventive treatment of episodic and chronic migraine. Treatment with eptinezumab reduces the mean monthly migraine days for each dose and population studied. The treatment effects were robust and clinically meaningful. There were no differences based on race, sex, or age. The treatment effect was supported by key secondary endpoints. Although the HIT-6 demonstrated improvement in patients on treatment compared to placebo, there are concerns detailed above

(b) (4)

The evidence for effectiveness across doses was substantial and statistically significant. It appears that the treatment effect is therapeutically similar to previously approved biologic therapies that also act on the CGRP pathway, but is the product available by intravenous infusion rather than a subcutaneous injection. This may offer benefit to patients who are reluctant to give themselves an injection at home, or who may forget to take their next dose. It is also given every 3 months rather than daily or monthly, which may also help with compliance.

## 8. Review of Safety

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### 8.1. Safety Review Approach

The majority of the safety analyses were conducted on the population of patients from Studies 006 and Study 011, which is the pivotal study population (PSS) as outlined in the Integrated Summary of Safety (ISS). Some of the analyses also included Study 005, a Phase 2 study that also contained a double-blind period treatment period following a single dose, and also included the 30 mg dose. Finally, there are additional analyses which were done on the overall eptinezumab (OE) population which includes the open-label extension study, Study 013, as well as Study 002, a single-dose phase 2 study of a supratherapeutic dose (1000 mg).

Safety data from the applicant was summarized for 3 pools of studies:

Pivotal Studies pool (PS): patients from Studies 006 and 011.

Overall Eptinezumab Pool (OE): patients from Studies 002, 005, 006, 011, and 013 (primary treatment phase only)

Placebo-controlled (PC) pool: patients from Studies 002, 005, 006, and 011

Because of minor differences in study design, there can be bias introduced by looking at the incidence of adverse events in patients receiving the 30 mg dose. The 30 mg dose was only included in Study 006 in the PS pool, and there were differences in study design, in that Study 006 was a 48 week study, and Study 011 was a 24 week study. Therefore a smaller number of

patients received 30 mg for a longer period of time, thus increasing the likelihood that there may be a higher number of TEAEs. These findings will be interpreted with caution. There is also a 30 mg dose group in the Phase 2 Study 005 which may be included in some analyses for supportive information.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

**Table 42 Overall Size of the Safety Database**

| Safety Database<br>Individuals exposed to any treatment in this development program for migraine |                      |                  |
|--------------------------------------------------------------------------------------------------|----------------------|------------------|
| Clinical Trial Groups                                                                            | Eptinezumab<br>(n= ) | Placebo<br>(n= ) |
| Healthy volunteers                                                                               | 371                  | 99               |
| Controlled trials conducted for this indication <sup>1</sup>                                     |                      |                  |
| ALD403-CLIN-005                                                                                  | 495                  | 121              |
| ALD403-CLIN-006                                                                                  | 666                  | 222              |
| ALD403-CLIN-011                                                                                  | 706                  | 366              |
| ALD403-CLIN-002                                                                                  | 81                   | 82               |
| Total                                                                                            | 1948                 | 787              |
| All other trials conducted for this indication                                                   |                      |                  |
| ALD401-CLIN-013                                                                                  | 111 <sup>2</sup>     | n/a              |

<sup>1</sup> Studies 002, 005, 006, 011 which are the PC population

<sup>2</sup> Excludes 16 patients who received eptinezumab in Study 005 and one patient who received eptinezumab in Study 002 who were later enrolled in Study 013

Source: Reviewer verified from Applicant provided Summary of Clinical Safety Table 3 and Table 6

**Table 43 Summary of Eptinezumab Exposure**

| Dosage                        | Number of patients exposed to the study drug: |            |             |
|-------------------------------|-----------------------------------------------|------------|-------------|
|                               | >= 1 dose                                     | >=6 months | >=12 months |
| Any dose (all studies)        | N = 2076                                      | N = 1872   | N = 991     |
| Any dose (pivotal studies)    | N = 1372                                      | N = 1252   | N = 536     |
| 300 mg dose (pivotal studies) | N = 574                                       | N = 531    | N = 177     |
|                               | *823 total                                    |            |             |

Source: Reviewer-created table from Summary of Clinical Safety

### Disposition

Overall, there were low numbers in the pivotal studies population who discontinued the treatment or discontinued from the study, and the numbers were similar in the eptinezumab population (12.4%) and in the placebo arm (13.3%). This indicates that the tolerability to the drug was overall acceptable. The dispositions by study are noted above in Section 6.1.2 and 6.2.2.

The below table summarizes the disposition by dose for all pivotal studies. Of note, the 30 mg dose was only included in Study 006, and therefore has smaller treatment arm in a longer study. Overall, this may skew some of the 30 mg safety studies to appear as if the 30 mg dose has more safety concerns than the higher doses.

**Table 44 Patient Disposition for Pivotal Studies Safety Population by Treatment Group**

|                                        | Epti 30 mg<br>n (%) | Epti 100 mg<br>n (%) | Epti 300 mg<br>n (%) | Placebo<br>n (%) | All Epti Pivotal<br>n (%) |
|----------------------------------------|---------------------|----------------------|----------------------|------------------|---------------------------|
| Safety Population                      | 219                 | 579                  | 574                  | 588              | 1372                      |
| Discontinued Treatment Early           | 49 (22.4)           | 62 (10.7)            | 59 (10.3)            | 78 (13.3)        | 170 (12.4)                |
| Discontinued Study Early               | 51 (23.3)           | 82 (14.2)            | 82 (14.3)            | 98 (16.7)        | 215 (15.7)                |
| Reason for Treatment Discontinuation   |                     |                      |                      |                  |                           |
| Adverse Event                          | 11 (5.0)            | 8 (1.4)              | 13 (2.3)             | 9 (1.5)          | 32 (2.3)                  |
| Withdrew Informed Consent              | 23 (10.5)           | 27 (4.7)             | 28 (4.9)             | 46 (7.8)         | 78 (5.7)                  |
| Investigator Decision                  | 2 (0.9)             | 1 (0.2)              | 1 (0.2)              | 0                | 4 (0.3)                   |
| Lost to Follow-Up                      | 7 (3.2)             | 15 (2.6)             | 13 (2.3)             | 18 (3.1)         | 35 (2.6)                  |
| Other                                  | 6 (2.7)             | 11 (1.9)             | 4 (0.7)              | 5 (0.9)          | 21 (1.5)                  |
| Reason for Early Study Discontinuation |                     |                      |                      |                  |                           |
| Withdrawal by Patient                  | 35 (15.9)           | 49 (8.5)             | 50 (8.7)             | 62 (10.5)        | 134 (9.8)                 |
| Adverse Event                          | 2 (0.9)             | 3 (0.5)              | 7 (1.2)              | 2 (0.3)          | 12 (0.9)                  |
| Study Burden                           | 24 (10.9)           | 19 (3.2)             | 13 (2.3)             | 24 (4.1)         | 44 (3.2)                  |
| Lack of Efficacy                       | 18 (8.2)            | 8 (1.4)              | 8 (1.4)              | 18 (3.1)         | 18 (1.3)                  |
| Other                                  | 18 (8.2)            | 19 (3.2)             | 22 (3.8)             | 18 (3.1)         | 60 (4.4)                  |
| Investigator Decision                  | 3 (1.4)             | 3 (0.5)              | 1 (0.2)              | 1 (0.2)          | 7 (0.5)                   |
| Lost to Follow-Up                      | 12 (5.5)            | 25 (4.3)             | 30 (5.2)             | 33 (5.6)         | 67 (4.9)                  |
| Other                                  | 1 (0.5)             | 5 (0.9)              | 1 (0.2)              | 2 (0.3)          | 7 (0.5)                   |

Source: Applicant-provided Summary of Clinical Safety Table 7; reviewer-verified

### 8.2.2. Relevant characteristics of the safety population:

**Table 45 Demographics and Baseline Characteristics of Safety Population (Pivotal Studies)**

| Demographic Parameters               | Treatment Group                   |                                   |                                  | Placebo<br>N = 588<br>n (%) | Overall<br>N = 1960<br>n (%) |
|--------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------|------------------------------|
|                                      | ALD403 300 mg<br>N = 574<br>n (%) | ALD403 100 mg<br>N = 579<br>n (%) | ALD403 30 mg<br>N = 219<br>n (%) |                             |                              |
| <b>Sex</b>                           |                                   |                                   |                                  |                             |                              |
| Male                                 | 61 (10.6)                         | 93 (16.1)                         | 34 (15.5)                        | 77 (13.1)                   | 265 (13.5)                   |
| Female                               | 513 (89.4)                        | 486 (83.9)                        | 185 (84.5)                       | 511 (86.9)                  | 1695 (86.5)                  |
| <b>Age (years)</b>                   |                                   |                                   |                                  |                             |                              |
| Mean years (SD)                      | 40.7 (10.9)                       | 40.6 (11.3)                       | 39.1 (11.5)                      | 40.2 (11.3)                 | 40.2 (11.3)                  |
| Median (years)                       | 40                                | 41                                | 37                               | 40                          | 40                           |
| Min, max (years)                     | 18, 71                            | 18, 68                            | 18, 69                           | 18, 71                      | 18, 71                       |
| <b>Age Group</b>                     |                                   |                                   |                                  |                             |                              |
| ≤ 35 years                           | 203 (35.4)                        | 186 (32.1)                        | 93 (42.5)                        | 229 (39.0)                  | 711 (36.3)                   |
| > 35 years and < 65 years            | 364 (63.4)                        | 390 (67.4)                        | 122 (55.7)                       | 350 (59.5)                  | 1226 (62.5)                  |
| ≥ 65 years                           | 7 (1.2)                           | 3 (0.5)                           | 4 (1.8)                          | 9 (1.5)                     | 23 (1.2)                     |
| <b>Race</b>                          |                                   |                                   |                                  |                             |                              |
| White                                | 509 (88.7)                        | 528 (91.2)                        | 180 (82.2)                       | 502 (85.4)                  | 1719 (87.7)                  |
| Black or African American            | 50 (8.7)                          | 38 (6.6)                          | 31 (14.2)                        | 68 (11.6)                   | 187 (9.5)                    |
| Other                                | 15 (2.6)                          | 13 (2.2)                          | 8 (3.6)                          | 18 (3.0)                    | 54 (2.8)                     |
| <b>Ethnicity</b>                     |                                   |                                   |                                  |                             |                              |
| Hispanic or Latino                   | 58 (10.1)                         | 75 (13.0)                         | 45 (20.6)                        | 69 (11.7)                   | 247 (12.6)                   |
| Not Hispanic or Latino               | 516 (89.9)                        | 504 (87.0)                        | 174 (79.4)                       | 519 (88.3)                  | 1713 (87.4)                  |
| <b>Region/Country</b>                |                                   |                                   |                                  |                             |                              |
| United States                        | 381 (66.4)                        | 382 (66.0)                        | 194 (88.6)                       | 417 (70.9)                  | 1374 (70.1)                  |
| Rest of World <sup>1</sup>           | 140 (24.4)                        | 147 (25.4)                        | 25 (11.4)                        | 120 (20.4)                  | 432 (22.0)                   |
| European Union                       | 53 (9.2)                          | 50 (8.6)                          | 0                                | 51 (8.7)                    | 154 (7.9)                    |
| <b>BMI (kg/m<sup>2</sup>)</b>        |                                   |                                   |                                  |                             |                              |
| Mean (SD)                            | 27.3 (6.1)                        | 27.6 (6.3)                        | 29.9 (8.3)                       | 27.9 (6.6)                  | 27.9 (6.6)                   |
| Median                               | 26                                | 26.5                              | 28.2                             | 26.6                        | 26.6                         |
| Min, max                             | 15.9, 49.8                        | 15.6, 59.3                        | 17.8, 67.5                       | 15.6, 67.5                  | 15.6, 67.5                   |
| <b>Baseline Migraine Days (days)</b> |                                   |                                   |                                  |                             |                              |
| Mean (SD)                            | 12.8 (5.4)                        | 12.9 (5.3)                        | 8.3 (2.9)                        | 12.4 (5.3)                  | 12.4 (5.3)                   |
| Median (days)                        | 12                                | 12                                | 8                                | 12                          | 12                           |
| Min, Max (days)                      | 4, 26                             | 4, 28                             | 4, 14                            | 3, 28                       | 3, 28                        |

<sup>1</sup>Includes Republic of Georgia, Russia, and the Ukraine

Source: Reviewer's analysis of ISS PSS population ADL dataset

Overall, the demographics of the treatment arms were similar. There were more women than men in each arm, which is consistent with the known increased prevalence of migraine in women rather than men. However, there was a considerably higher ratio of women to men in these studies (6.4:1) than the ratio of women to men in the general population with migraine which is more like 4-5 to 1. The baseline migraine days were similar in all treatment arms, other than the 30 mg arm which was only studied in the episodic migraine study, so by definition had to have less than 15 migraine days a month.

***Reviewer's comment: Overall, the population appears generalizable to the United States migraine population. There are only a small number of patients (1.2%) over the age of 65 years, so the elderly population is not well represented and that is one of the limitations for the overall evaluation of safety.***

### **8.2.3. Adequacy of the safety database:**

The safety database is adequate in size and exposure, despite the small numbers of patients over age 65 years as noted above. Otherwise, the safety database has demographics that are similar amongst the treatment arms and overall generalizable to the US population of patients with migraines since the majority of the patients (77%) in all studies were from the United States. There is not enough variation in race or ethnicity to make any substantial conclusions on safety by race. There is only a small percent (1.2%) of patients over age 65 which makes any conclusions difficult to make on safety in older patients.

## **8.3. Adequacy of Applicant's Clinical Safety Assessments**

### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

There are no issues with regard to data integrity or quality. There were no major errors found within the datasets and the analyses performed by the applicant were easily reproducible. The JumpStart team within the Office of Computational Science assessed the datasets for quality and integrity and did not find any major issues.

### **8.3.2. Categorization of Adverse Events**

The applicant used standard definitions of adverse events (AEs), treatment-emergent AEs (TEAEs), and serious AEs (SAEs). An AE was defined per ICH E6 as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal product. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.

SAEs were defined as any adverse event that results in:

- Death
- Is life threatening
- Inpatient hospitalization or prolonged existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or required hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Treatment-emergent AEs (TEAEs) were defined as all AEs with a start date and time on or after the date and time of the first infusion of the study drug. All AEs were monitored until resolution, stabilization in the judgment of the Investigator, or if the patient was lost to follow-up or withdrew from the study. Patients were followed for 20 weeks after drug discontinuation, which would be the equivalent of approximately 5 half-lives.

Severity of AEs were graded based on the following scale:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADLs)
- Grade 3: Severe or medically significant but not immediately life threatening; hospitalizations or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

AEs of special interest included those in the following sections:

- Hypersensitivity and Anaphylactic Events  
The subset of AEs with MedDRA-coded SOC of immune system disorders, and PTs of hypersensitivity, anaphylactic reaction, and anaphylactoid reaction.
- Events associated with C-SSRS/Suicidality  
The subset of AEs with MedDRA-coded SOC of psychiatric disorders and PTs of suicidal behavior, suicidal ideation, suicidal attempt, and self-injurious behavior.
- Cardiovascular Events  
The subset of AEs with one of the following:
  - MedDRA-coded SOC of cardiac disorders and PTs of atrial fibrillation, bradycardia, chest pressure, palpitations, sinus bradycardia, sinus tachycardia, and tachycardia,
  - MedDRA-coded SOC of investigations and PTs of blood pressure

increase, blood pressure systolic increase, elevated blood pressure, heart rate increased, heart rate decreased, heart rate irregular, electrocardiogram abnormal, electrocardiogram Q wave abnormal, electrocardiogram QT interval abnormal, and electrocardiogram QT prolonged,

- MedDRA-coded SOC of nervous system disorders and PTs of seizure and syncope,
- MedDRA-coded SOC of vascular disorders and PTs of flushing, hot flush, hypertension, hypotension, and ischemia.

- Hepatic Events

A subset of AEs with MedDRA-coded SOC of investigations and PTs of alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased.

- Events Associated with Study Drug Infusion

Subset of AEs within 1 week of dosing with a MedDRA-coded SOC of skin and subcutaneous tissue disorders and PTs of dermatitis bullous, pruritis, pruritis generalized rash, rash, rash macular, rash macular-papular, rash papular, rash pruritic, and urticaria OR a MedDRA-coded SOC of General disorders and administration site conditions and PTs of Infusion site erythema, infusion site extravasation, infusion site pain, infusion site paresthesia, infusion site pruritis, infusion site rash, infusion site reaction, and infusion site swelling.

The coding of verbatim terms to preferred terms appeared appropriate for the most part. The applicant appropriately coded verbatim terms related to “hypersensitivity”, including allergic infusion reaction, itching, rash, angioedema, allergic reaction in throat, allergic reaction urticaria and related terms. They separated these from other reactions such as “allergic reaction to pineapple”, which was simply coded to “allergic reaction other”. There was a patient that was coded as Depression suicidal for the verbatim term “worsening of depression with suicidal ideation”. This was recoded as two separate TEAEs, one for depression and one for suicidal ideation. Another patient had the verbatim term “head injury due to a fall” that was recoded as two TEAEs, one for “head injury” and one for “fall”.

There were also a few terms that were recoded by this reviewer to avoid any splitting of terms and for ease of review, which are outlined below in Table 46.

**Table 46 Recoded AE Terms to Group Similar Terms**

| Original Coded Term                                                                                                                                                                                         | Recoded Terms               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper                                                                                                                            | Abdominal pain              |
| Acute sinusitis, sinusitis                                                                                                                                                                                  | Sinusitis                   |
| Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test increased, transaminases increased                                                  | Hepatic enzyme increased    |
| Anticipatory anxiety, anxiety, anxiety disorder                                                                                                                                                             | Anxiety                     |
| Conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis, conjunctivitis allergic                                                                                                                  | Conjunctivitis              |
| Depressed mood, depression, major depression                                                                                                                                                                | Depression                  |
| Dizziness postural, dizziness                                                                                                                                                                               | Dizziness                   |
| Gastritis, gastritis erosive                                                                                                                                                                                | Gastritis                   |
| Gastroduodenitis, gastroenteritis, gastroenteritis viral, gastrointestinal infection                                                                                                                        | Gastroenteritis             |
| Lower respiratory tract infection, respiratory tract infection, respiratory tract congestion, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection | Respiratory Tract infection |
| Migraine, migraine with aura                                                                                                                                                                                | Migraine                    |
| Oropharyngeal pain, pharyngitis, pharyngitis streptococcal, viral pharyngitis,                                                                                                                              | Pharyngitis                 |
|                                                                                                                                                                                                             |                             |

### 8.3.3. Routine Clinical Tests

Please refer to the Schedule of Assessments for Study 006 (Table 3) and Study 011 (Table 20) for timing and schedule of routine clinical tests.

The included clinical laboratory tests including hematology, serum chemistry, and serology included albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen, calcium, bicarbonate, creatinine, globulin, glucose, phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, triglycerides, magnesium, and uric acids. Hematology tests included hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differentials, and other associated CBC values. Pregnancy testing and testing for ALD403 -antibodies were also performed per the schedule of assessments.

All clinical laboratory values were measured by a central laboratory. Summary statistics for actual values and changes from baseline were tabulated for each laboratory result by scheduled visit. Patients with any clinical laboratory values outside of the normal reference range at any post-baseline assessment were summarized, and shifts from baseline values were tabulated.

Vital signs (including blood pressure and pulse) were measured and recorded along with 12-lead ECGs at screening and baseline, and on the day of infusion just prior to infusion and 4 hours after infusion. They were also checked routinely at most visits per the Schedule of Assessments. The observed data at baseline and change from baseline for each measurement day were summarized with descriptive statistics.

***Reviewer's comment: Timing and adequacy of clinical tests appeared adequate given the study design, patient population, and known safety profile from previously approved drugs in the same class (CGRP-antagonists). Of note, the infusion was given over 30 minutes for Study 011, except if needed to be given over 1 hour at the decision of the Investigator. Out of 1,072 patients who received 2,092 infusions, 33 patients required the dose to be given for longer than 30 minutes, some of which were planned to be given over an hour and some of which had a dose interruption due to IV infiltration or something similar.***

## 8.4. Safety Results

### 8.4.1. Deaths

There were no deaths reported during the eptinezumab development program.

### 8.4.2. Serious Adverse Events

In the pivotal studies population there were 41 SAEs in 27 patients, for a total of 1.3% of the eptinezumab population, and 1.5% of the placebo population. The only SAEs to occur in more than one patient receiving eptinezumab were two patients with suicidal ideation, both receiving 100 mg eptinezumab, and two patients with suicide attempts, one who received 100 mg (same as patient above) and one who received 300 mg eptinezumab. This results in a total of 3 patients with a suicide-related SAEs which are outlined in more detail in the narratives below.

There were also 3 patients who had SAEs of migraine, 2 on treatment (100 mg and 300 mg) and 1 who received placebo. There were 3 patients who had an SAE of syncope (1 who received eptinezumab, and two patients who received placebo) and 2 patients had nephrolithiasis (1 patient in 30 mg arm and 1 patient in placebo arm).

Four patients receiving eptinezumab had SAEs that resulted in study drug discontinuation. These were acute kidney injury, stomal hernia, rhabdomyolysis, and seizure. The first three occurred in patients receiving 30 mg, and the seizure occurred in a patient who received 300 mg. They are also outlined in the narratives below.

#### Suicide-related narratives (SAEs)

- (b) (6), *suicide ideation and suicide attempt*  
45-year-old black male who received 3 doses of 100 mg IV q3 months with first dose on (b) (6) and last dose on (b) (6). On (b) (6), 1 month after the first dose, he was admitted to the hospital with suicidal ideation with plan, and auditory hallucinations telling him to kill himself. He had specific triggers related to a prior diagnosis of PTSD and prior sexual assault. He was again hospitalized (b) (6), 11 days after the 2<sup>nd</sup> dose, for suicidal ideation and worsening depression, also with PTSD-related triggers. On (b) (6), 2.5 months after the 2<sup>nd</sup> dose, he had a suicide attempt reportedly due to stress with his roommate in his residential treatment program, and again had auditory hallucinations. In (b) (6) his blood pressure was found to be high, 163/90, so he did not receive the final dose due to elevated blood pressure. He discontinued from the study due to study burden and did not return for the final follow-up visit. He answered no on all C-SSRS questions at each visit.
- (b) (6), *suicide ideation*  
54-year-old black female received 2 doses of 100 mg IV q3 months on (b) (6) and (b) (6). She had previously admitted to feelings of suicidal ideation on screening but without plan or intent. She was admitted to hospital on (b) (6), almost 3 months after the 2<sup>nd</sup> dose of treatment, for worsening depression with suicidal ideation and plan. Of note, while in the inpatient psychiatric unit, she also had syncope which resulted in fall and leg fracture requiring surgery. The syncope was felt to be a side effect from prazosin for PTSD, and she was discharged in (b) (6). Of note, she had history of depression, alcohol abuse, prior suicidal ideation, suicide attempts, PTSD, and anxiety.
- (b) (6), *suicide attempt*  
18-year-old white female who received 2 doses of 300 mg eptinezumab IV q3 months on (b) (6) and (b) (6). On her initial C-SSRS, she answered no to all questions. She was seen by her counselor on (b) (6), 6 weeks after the 2<sup>nd</sup> dose of treatment. At that visit, her counselor continued her Zoloft and recommended Adderall, which was never filled. On that same day, she subsequently took 40+ tabs of acetaminophen and was admitted to hospital for suicide attempt. She reported she was upset about a family relationship and wanted to hurt herself and die; she also revealed prior self-injury (cutting). She had prior history of major depressive disorder and anxiety, which were reportedly stable at the time of study. She also had history of prior overdose on acetaminophen/diphenhydramine 5 years prior to the study. She denied drug use or allergies.

***Reviewer's comment: There were 3 patients out of 1,372 patients in the PSS who received eptinezumab who had suicide-related SAEs, compared to zero patients who received placebo. However, all three of the patients had a prior history of depression and what appear to be significant social stressors that were reported to have triggered these events. At least two of***

***them also had prior suicide attempts, so it is unclear if there could be any relationship between the study treatment and the suicidal thoughts/attempts. Further discussion of suicidality is included in Section 8.5.2.***

***Of note, the initial patient described above did have elevated blood pressure leading to discontinuation of the study drug (See Section 8.4.3 below).***

SAEs resulting in study discontinuation

- (b) (6), ***acute kidney injury***  
31-year-old multiple-race female patient received 30 mg eptinezumab IV on (b) (6) and had a study drug interruption for infusion site extravasation. On (b) (6), 6 weeks after the initial treatment, she underwent hysteroscopy, D&C, and Mirena replacement due to abnormal uterine bleeding, without complications. On (b) (6) she presented to the emergency room with intractable nausea/vomiting and hematemesis. Patient was receiving multiple concomitant medications, and she was found to have bilateral hypoperfusion to both kidneys possibly due to a septic phenomenon which occurred from the D&C. The final diagnosis was acute kidney injury of unknown etiology.

***Reviewer's comment: There is no indication that the acute kidney injury is related to the eptinezumab. It is most likely secondary to the sepsis, which was related to an unrelated medical procedure.***

- (b) (6) ***stomal hernia***  
53-year-old white female with a past history of colostomy, pelvic abscess surgery, abdominal and pelvic adhesions, and hiatus hernia, received 30 mg eptinezumab IV on (b) (6). On (b) (6), 15 days after initial dose, patient presented to the hospital for reversal of her colostomy, but was noted to have a paracolostomy hernia requiring repair. She underwent a complete paracolostomy hernia repair, placement of bilateral ureteral stents, complete total hysterectomy, and lysis of extensive intraabdominal and pelvic adhesions. Hospital stay was complicated by UTI and sigmoid colon diverticulitis that were present on day prior to hospitalization, as well as post-operative anemia requiring blood transfusion. She was withdrawn from the study due to the parastomal hernia, and completed visits through Week 20 prior to being lost-to-follow up.

***Reviewer's comment: There is no indication that the stomal hernia was related to study drug, as the patient was already planned for colostomy repair prior to drug treatment. There lacks sufficient information to determine if diverticulitis or presence of paracolostomy hernia were related to study treatment.***

- (b) (6), ***rhabdomyolysis***  
34-year-old black female received 3 doses of 30 mg IV eptinezumab q3 months on (b) (6) and (b) (6), and (b) (6). On (b) (6), 120 days after the last dose of treatment, she presented to the emergency room with moderate flank pain to the right side x 5 days, localized muscle pain in the back, with difficulty voiding. Labs

revealed a creatine kinase (CK) of approximately 1000 and patient was diagnosed with rhabdomyolysis, given hydration and was informed that there was no damage to the kidneys. Rhabdomyolysis was mild and resolved with hydration. On further review, the case was felt to have been elevated CK secondary to excessive exercise in dry heat of Nevada, not a case of rhabdomyolysis. She also was diagnosed with cellulitis of skin at the same time.

***Reviewer's comment: The sole case of elevated CK in the setting of vigorous exercise, almost 3 months after the last dose of study drug is unlikely related to the eptinezumab dose.***

- (b) (6), seizure

47-year old-white female received one dose of 300 mg eptinezumab IV on (b) (6). Two days later she had an adverse event of a mild rash. On (b) (6), almost 2 months after the first dose, the patient had a generalized seizure at the beach with her daughter, and was subsequently hospitalized. The seizure resulted in a fall and she sustained multiple thoracic compression fractures as a result of the fall. An EEG showed mild diffuse encephalopathy, the neurologist believed that the etiology may have been toxic-metabolic in etiology and no anti-seizure medications were necessary. She received a TLSO brace, pain medication and walker for the compression fractures. She was given a diagnosis of possible underlying osteoporosis that contributed to the compression fractures.

***Reviewer's comment: This patient had a seizure that was believed to be toxic-metabolic by the treating neurologist. There are not sufficient details to reach that conclusion, so a possible link to the study drug cannot be fully excluded.***

***Reviewer's comment: There are no safety signals identified in the reported SAEs among the pivotal studies population. Other than suicidality, which is discussed in detail later, there were no other SAEs that appeared more prevalent in the treatment group than placebo. The SAEs that resulted in discontinuation only occurred in one patient each, and none of them is concerning for a treatment-related SAE.***

When analyzing the total ISS "overall eptinezumab" population (OE pool), 46 patients had SAEs, 35 who received eptinezumab (1.7%) and 11 patients in the placebo arm (1.4%). The incidence of SAEs was about equal in both populations and similar to the pivotal studies. These SAEs include the patients outlined above and the findings are consistent with the findings in the pivotal studies population. There were no new safety signals identified in the remainder of the ISS population.

The additional SAEs that were reported in more than 1 additional eptinezumab patient were uterine leiomyoma (3), conversion disorder (2) and seizure (2). The narratives of the conversion disorder and seizures are detailed below. The three patients with uterine leiomyomas required hysterectomy during the study period. However, this condition is common in this patient population and does not appear related to the study drug.

SAEs of Conversion Disorder and/or Seizures

- (b) (6), *conversion disorder*

48-year-old white female received a single dose of 1000 mg study drug intravenously on (b) (6). She completed the study through 24 weeks. On (b) (6), 1 month after treatment, she had reported TEAEs of transient ischemic attack (TIA) and conversion disorder requiring hospitalization. She reported right facial weakness, left facial hypoesthesia, right body hypoesthesia, right sided occipital head/neck pain, nausea, and unsteadiness on her feed. She reported right upper and lower extremity heaviness x 1 month. She had a normal CT scan, MRI and MRA brain were normal, and doppler ultrasound of carotid and vertebral arteries were normal also. Symptoms resolved the next day and she was ultimately determined to have conversion disorder. She subsequently also had AEs of ECG Q wave abnormal (mild), and an AESI of chest pain with dyspnea requiring hospitalization, with normal work-up and concern for possible lateral ischemia on EKG with no evidence of acute myocardial ischemia.

- (b) (6), *conversion disorder with seizures*

43-year-old white female who received 300 mg study drug intravenously on (b) (6) and (b) (6). The second dose was interrupted because of an AE of allergic reaction and pruritis generalized. She received intramuscular Benadryl and infusion was restarted. She subsequently had study drug discontinued due to the AE of allergic reaction consistent with hypersensitivity. She continued in study for follow-up visits until (b) (6) when she withdrew because of study burden. However, she had a second adverse event on (b) (6), 3.5 months after the last dose of study drug, with a complex narrative that was initially thought to be complicated migraine vs. acute psychosis vs. temporal lobe seizures vs. botulinum toxin overdose, and was ultimately diagnosed as conversion disorder with non-epileptic seizures. She began having intermittent spells of confusion, lasting 15-20 minutes, associated with hallucinations, disorientation, and time loss. She also reported episodic slurred speech, chills, shortness of breath, drowsiness, nausea, vomiting, diarrhea, headache, and a metallic taste in her mouth. Then she reported a new type of "spells" where she would feel lost. She would remain conscious but be unable to recognize her husband, her house, or her environment. These occurred daily, lasting 2 minutes up to 30 minutes. Her husband had videos of the events, sometimes with left sided tremors. They were ultimately captured on Video EEG which showed a normal alpha rhythm throughout the event, and were determined to be non-epileptic seizures. She was diagnosed with conversion disorder secondary to excessive family stressors and was treated with cognitive behavioral therapy.

- (b) (6), *seizure*

28-year-old white female received a single dose of 300 mg study drug intravenously on (b) (6). She completed visits through Week 16 and then withdrew from study/lost-

to-follow-up. On (b) (6), 4 months after treatment, she experienced a seizure. On (b) (6) she experienced another seizure and was admitted to hospital. The seizure activity lasted 30 seconds with an associated feeling of déjà vu, no other aura. There was 10 minutes of post-ictal confusion. She had another seizure witnessed in the emergency department. There was a family history of focal seizure activity in her brother. She received loading dose of levetiracetam and had normal evaluation including vital signs, physical exam, complete blood count, and basic metabolic panel. She had normal CT head, urine drug screen, and a normal MRI of the head without contrast. EEG was normal with no epileptiform features identified. She continued on levetiracetam and had a second normal EEG with no epileptiform features. She was diagnosed with a seizure disorder.

***Reviewer's comment: These two episodes of reported seizure activity are unlikely related to the study drug treatment and do not raise concern for a new safety signal. The initial case was a case of conversion disorder with psychosocial triggers and non-epileptic seizures, and the second case was new-onset seizure disorder in a patient with a family history of focal seizures. Although it is unclear if the medication could have lowered the seizure threshold in this patient, there are not sufficient cases to consider this treatment-related at this time.***

There were also an additional two patients who reported SAEs of suicidal ideation in the Phase 2 study (Study 005), one who received placebo, and one patient who received 10 mg eptinezumab. Both of these patients had a history of depression and reported triggers for their suicidal ideation without attempt. The patient who received placebo threatened to “put a gun to his head and pull the trigger” due to unresolved migraine pain, and the patient who received a single 10 mg IV dose had a history of depression and thought about killing herself with a plan after being fired.

***Reviewer's comment: There is an additional patient who received eptinezumab who reported an SAE of suicidal ideation, in the setting of a history of depression and the social stressor of being fired. Further discussion of suicidality is below in Section 8.5.2.***

I also reviewed additional SAEs that were submitted to the 120-day safety update that are not included in the original ISS. There were 2 additional SAEs reported after the initial data cut-off. One patient had uncontrolled diabetes mellitus leading to hospitalization (Day 560 of study), and another patient had worsening osteoarthritis leading to hospitalization and surgical procedure (Day 348 of study).

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the PSS, there were 42 patients who had the study drug withdrawn due to adverse events, 34 (2.5%) patients who were receiving eptinezumab, and 8 patients receiving placebo (1.4%).

The only TEAEs leading to study drug withdrawal that occurred in more than 1 patient were hypersensitivity in 13 patients, and hypertension and/or blood pressure increased in 3 patients. Of the 34 AEs leading to discontinuation in the eptinezumab treatment groups, there were 4 AEs that were SAEs and were already detailed above.

The details related to hypersensitivity are detailed in Section 8.5.4 below. Despite resulting in discontinuation from the study, none of the events were serious or severe. There were no cases of anaphylaxis in the pivotal studies. There was one report of angioedema that was mild.

Further details on the patients who discontinued for hypertension/blood pressure increased are outlined below:

- (b) (6), blood pressure increased (see also SAE narrative above for suicidal ideation)  
45-year-old male who received 100 mg eptinezumab intravenously x3 doses before discontinuing from the study drug because of elevated blood pressure. His blood pressure at screening was 140/80, with subsequent recordings of 135/73 (Day 0 pre-dose), 138/76 (Day 0 post-dose), 135/84 (Week 4), 136/74 (Week 8), 140/85 (Week 12), 138/93 (Week 16), 136/88 (Week 20), 137/87 (Week 24), 161/90 (Week 28), and 163/90 (Week 36 pre-dose). The investigator decided to discontinue treatment due to the increased blood pressure, which began at Week 28. Of note, he did have positive urine screen for cocaine at the time of his suicide attempt on Week 24).
- (b) (6), hypertension  
49 year-old male who received 100 mg eptinezumab intravenously on (b) (6), with subsequent doses on (b) (6) and (b) (6) before discontinuing from study for worsening hypertension, which was rated Grade 2/moderate. At screening his initial blood pressure was 134/86, with subsequent recordings of 126/81 (Day 0 pre-dose), 124/82 (Day 0 post-dose), 128/97 (Week 4), 128/88 (Week 8), 141/94 (Week 12 pre-dose), 138/92 (Week 12 post-dose), 135/90 (Week 16), 135/90 (Week 20), 135/85 (Week 24 pre-dose), 135/85 (Week 24 post-dose), 126/84 (Week 28) and 133/84 (ET visit). Decision to discontinue study drug was made at Week 28 visit and patient was started on metoprolol at Week 15, and increased at Week 28. The maximum increase from baseline was 7 points in systolic blood pressure and 8 points in diastolic blood pressure. He did have medical history of hypertension, hyperlipidemia, prediabetes, sinus tachycardia, among other conditions. His concomitant medications included sumatriptan, excedrin migraine, naproxen, cyclobenzaprine, doxazosin, metoprolol, methocarbamol, bismuth subsalicylate, multivitamins, and aspirin.
- (b) (6), hypertension  
43-year-old male who received 30 mg eptinezumab intravenously on (b) (6)

before discontinuing from the study for Grade 2 hypertension for which he was started on lisinopril. He withdrew from the study due to the need for medication for hypertension. His baseline blood pressure was 134/72, with subsequent blood pressures of 122/88 (Day 0 pre-dose), 140/99 (Day 0 post-dose), 144/100 (unscheduled visit (b) (6)), 142/107 (Week 4), and 127/98 (ET visit). The maximum increase from baseline after the first dose was 20 points in systolic blood pressure and 35 diastolic blood pressure increase. He was started on lisinopril and hypertension had not resolved at time of study completion. He was on concomitant medications with elk antler velvet, sumatriptan, naproxen, multivitamins and magnesium.

***Reviewer's comment: The above two patients discontinued from the study for Grade 2 hypertension. There is not enough information provided to know if the worsening of the hypertension was treatment-related, although it cannot be excluded based on the available details. The first patient above had pre-existent hypertension and there was a very modest increase in blood pressure, which is not concerning. The second patient had a more significant increase in blood pressure, however, the highest recorded BP of 144/100 was initially noted 4 days prior to dosing, making it less likely drug-related. It then decreased on Day 0, and increased again immediately after dosing. No alternate etiology is provided. The third patient was discontinued from the study as an "Investigator decision" due to blood pressure increased. This patient's medical history was complicated by psychiatric comorbidities and cocaine use; however his blood pressure did increase significantly after starting the drug to a maximum 163/91. None of these events were serious, but warrant further monitoring. See further discussion of hypertension below in Section 8.5.1.***

In the open-label extension Study 013, an additional 6 patients discontinued secondary to an adverse event. Three of these 6 were due to hypersensitivity reactions, with one patient reporting an SAE of anaphylactic reaction (see details below). The other AEs resulting in study discontinuation were infusion site erythema, complex regional pain syndrome and DVT in the same patient, and palpitations.

- (b) (6), anaphylactic reaction  
58-year-old white male received study drug on (b) (6) at 10:28 am, and the infusion was stopped at 10:40 am due to erythema, pruritis, nasal congestion and hives across body. At 10:35 am, initially noted erythema of neck and nasal stuffiness and infusion rate was decreased. After the Investigator evaluated patient, the infusion was stopped. Received 30 mL of drug total. Normal vitals were maintained throughout. Patient was given 50 mg diphenhydramine orally with 0.3 mg epinephrine. Continued to have hives, facial flushing, slight facial edema. There was no throat constriction, mucosal swelling or shortness of breath. He then received 50 mg IV diphenhydramine at 11:42 am with immediate response with reduction in itching, nasal congestion and flushing. Mild urticaria

and erythema continued for 7 days. ECGs remained normal. Vitals pre-dose 126/84, hr 74. Postdose 2 hours later 130/88 and hr 66. He did have a history of an allergy to sulfites (reported as more severe). Had also previously participated in an anti-CGRP mAB study more than 6 months prior. Medical history significant for h/o chronic migraines, asthma, sulfite allergy, environmental allergies, insomnia, vertigo, depression and septoplasty.

***Reviewer's comment: The above reaction is consistent with an allergic/hypersensitivity reaction to the drug, and consistent with patients' history of prior drug allergy (sulfites) and prior exposure to CGRP monoclonal antibodies. However, as assessed by the applicant, the patient did not meet the clinical diagnostic criteria for an anaphylactic adverse reaction because there were no clinical signs of respiratory or cardiovascular manifestations, per the "Second symposium on the definition and management of anaphylaxis: Summary Report"<sup>8</sup>. The applicant proposes this event falls under allergic reaction and infusion reaction of grade 2 moderate severity.***

***There were very few TEAEs that led to discontinuation from the study, however the rate was double amongst those patients receiving treatment compared to those receiving placebo. Almost 40% of these TEAEs leading to discontinuation were related to hypersensitivity. The number of patients with hypersensitivity leading to discontinuation was less than 1% of the total population, and the reason for many of these discontinuations was protocol-driven; however, there does appear to be a true risk for a hypersensitivity reaction after infusion. The risk may have been underestimated due to these patients discontinuing from the study after initial mild or moderate reactions. Furthermore, hypersensitivity is a known risk with monoclonal antibodies, and has been described as a warning in the label for the other approved CGRP-mAb antagonists. Therefore, it seems reasonable to include hypersensitivity as a warning in the prescribing information. See further discussion in Section 8.5.4.***

#### 8.4.4. Significant Adverse Events

In the pivotal studies population, 48 patients reported 70 TEAEs of severe intensity. Of these 48 patients, 18 patients were in the placebo arm (3%) and 30 patients were receiving eptinezumab (2.2%). The only severe TEAEs that occurred in more than one patient receiving eptinezumab were migraine (2) and ECG T wave inversion (2, both on 300 mg). Of note, there were 4 patients in the placebo arm who also reported a severe TEAE of migraine.

***Reviewer's comment: Analysis of TEAEs of severe intensity did not reveal any new concerning***

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<sup>8</sup> Sampson HA et al., Second symposium on the definition and management of anaphylaxis: Summary Report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117:391-7.

***safety signals, and the incidence of severe TEAEs was greater in the placebo treatment arm than then eptinezumab treatment arms. There were 2 patients who had a severe TEAE of T wave inversion on ECG. Further discussion of ECG related changes are detailed below, but the verbatim terms for these two cases were nonspecific and not associated with other clinical signs or TEAEs. Therefore, they were not considered adverse drug reactions at this time.***

Among the PSS, there were 30 patients who reported 35 TEAEs that resulted in interruption of the drug infusion, but none of these TEAEs were severe or serious. Of the 30 patients, 17 infusions were interrupted due to infusion site extravasation, 8 for hypersensitivity reactions, and 3 for infusion site pain.

I also evaluated the database for Designated Medical Events (DME) and the following terms were not found in any patients in the database: acute respiratory failure, amyotrophic lateral sclerosis, aplastic anemia, colitis ischaemic, congenital anomalies, disseminated intravascular coagulation, endotoxic shock, haemolysis, hemolytic anemia, liver failure, liver necrosis, liver transplant, neuroleptic malignant syndrome, pancytopenia, progressive multifocal leukoencephalopathy, product infectious disease transmission, pulmonary fibrosis, pulmonary hypertension, Stevens-Johnson syndrome, sudden death, suicide, Torsade de pointes, toxic epidermal necrolysis, and thrombotic thrombocytopenic purpura.

In the OE population, there were a few DME terms identified. There were 2 cases of seizure, 1 case of rhabdomyolysis, and one case of acute kidney injury that were also SAEs and are detailed above in Section 8.4.2. There is also a single case of potential anaphylaxis that is described in detail above in Section 8.4.3.

There was 1 report each of bilateral deafness, night blindness, systemic lupus erythematosus, serotonin syndrome, and 3 reports of agranulocytosis (neutropenia). There are detailed in narratives below.

- (b) (6), *neutropenia*  
34-year-old White female received a single dose of eptinezumab 100 mg IV on (b) (6). She completed the remainder of the study visits for this single-dose study. On (b) (6), 346 days after study drug administration, she experienced neutropenia with a WBC count of  $3.2 \times 10^3/\mu\text{L}$ , and a neutrophil count of  $1.36 \times 10^3/\mu\text{L}$ . Her levels were normal 1 month later. She did have bronchitis and leukopenia at the same time.
- (b) (6), *neutropenia*  
53-year-old white female received 300 mg eptinezumab IV every 12 weeks x 2 doses on (b) (6) and (b) (6). She completed the study. On (b) (6) at the time of the second dose, she was noted to have neutropenia, with a neutrophil count of  $1.45 \times 10^3/\mu\text{L}$ , and WBC count was  $3.00 \times 10^3/\mu\text{L}$ . Her cell counts normalized on (b) (6). There

was no treatment given for the neutropenia and it resolved on its own.

- (b) (6), *neutropenia*

52-year-old white female received 100 mg eptinezumab every 12 weeks x 2 doses on (b) (6), and (b) (6). She completed the study. She had neutropenia on initial screening visit, prior to treatment. They then were reportedly normal at an additional screening visit prior to the first treatment dose. For the remainder of the study, her neutrophil and WBC counts fluctuated between normal and low, without treatment.

**Reviewer's comment: There are three TEAEs of neutropenia in the OE treatment population. However, the third patient had pre-existent neutropenia prior to receiving study drug, and the levels fluctuated throughout the study. The initial case also had an alternative explanation with a likely viral-induced leukopenia. These cases do not raise a safety signal for the drug, but further analysis will be provided in Section 8.4.6 below.**

- (b) (6), *deafness bilateral*

36-year-old white female who received 30 mg eptinezumab IV every 12 weeks x 4 doses, on (b) (6), and (b) (6). She completed the study. On (b) (6), approximately 7 months after the initial dose, she experienced bilateral hearing loss, which was graded as mild/grade 1 in severity. She had a simultaneous sinus infection and bilateral ear infection 2 months prior to the hearing loss.

**Reviewer's comment: Given the preceding bilateral ear infections, it is much more likely that the ear infections were the cause of the hearing loss rather than the study drug. This single event of hearing loss does not raise concern for a safety signal.**

- (b) (6), *systemic lupus erythematosus*

42-year-old white female received eptinezumab 300 mg IV every 12 weeks x 2 doses on (b) (6) and (b) (6). She completed the study. On (b) (6), 1.5 months after last dose of drug, she experienced an event of lupus, requiring treatment with steroids, azathioprine, and esomeprazole. The event was graded severe (grade 3) in severity. She also had additional AEs of myalgia and arthralgia, reported in (b) (6), prior to the event of lupus. She had no prior relevant medical history other than migraine.

**Reviewer's comment: There is no indication that the event of SLE was related to the study drug, and it was the sole case reported.**

- (b) (6), *serotonin syndrome*

23-year-old patient received a single dose of eptinezumab 300 mg IV on (b) (6). On (b) (6), 41 weeks after the dose, the patient was hospitalized with tremors, hyperreflexia, diaphoresis, flushed skin, and tachycardia that began one hour after taking tramadol. She was diagnosed with serotonin syndrome, as she was taking concomitant bupropion and escitalopram. The medications were stopped, and her symptoms improved.

**Reviewer's comment: This patient has a clear alternate etiology for her serotonin syndrome**

**with the combination of tramadol, bupropion and escitalopram, all of which have a risk of serotonin syndrome. The single dose of eptinezumab 10 months earlier is unlikely related to the event.**

- (b) (6), night blindness  
22-year-old White female received a single dose of eptinezumab 300 mg IV on (b) (6), and then completed the remaining study visits for Study 005. On (b) (6) after 109 days, she experienced night blindness of grade 2/moderate severity that was resolving. She also was experiencing concomitant neck strain treated with Percocet, ibuprofen, and cyclobenzaprine at the time of the night blindness. It was not felt to be related to the study drug by the investigator.

**Reviewer's comment: There is not enough detail provided in this narrative to draw any significant conclusions regarding causality. However, as a single case without any pathophysiologic mechanism, it is unlikely that this event was related to the study drug.**

#### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs occurring in the ISS database in the pivotal study population in more than 1% of the treated patients and greater than placebo are included below in Table 47. The AEs that were  $\geq 2\%$  more than placebo are in bold. Using the below standard queries, there were no common TEAEs that occurred in more than 2% of population and  $\geq 2\%$  more than placebo, except for all infections, including nasopharyngitis. The sponsor proposed an AE table for labeling that included (b) (4) nasopharyngitis.

**Table 47 TEAEs in the ISS Pivotal Studies Population which occurred in  $\geq 1\%$  of treatment group and greater than placebo ( $\geq 2\%$  than placebo in bold)**

| Adverse Event                                                     | All Eptinezumab Treated Patients |                       |                       |                           | Placebo<br><br>N = 588 (%) |
|-------------------------------------------------------------------|----------------------------------|-----------------------|-----------------------|---------------------------|----------------------------|
|                                                                   | 30 mg<br>N = 219 (%)             | 100 mg<br>N = 579 (%) | 300 mg<br>N = 574 (%) | All Doses<br>N = 1372 (%) |                            |
| <b>Infection, all</b>                                             | <b>34</b>                        | <b>26</b>             | <b>29</b>             | <b>29</b>                 | <b>27</b>                  |
| URI, cold, rhinitis, upper resp tract infection, flu-like illness | 23                               | 18                    | 21                    | 20                        | 19                         |
| Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff  | 4                                | 3                     | 4                     | 4                         | 3                          |
| Fall, dizziness, balance disorder                                 | 4                                | 3                     | 3                     | 3                         | 2                          |
| Asthenia, fatigue, malaise, weakness, narcolepsy                  | 2                                | 3                     | 3                     | 3                         | 2                          |
| Abdominal pain, distension, bloating, spasm, IBS, megacolon       | 4                                | 2                     | 3                     | 3                         | 2                          |
| Somnolence, fatigue, sedation                                     | 2                                | 3                     | 3                     | 3                         | 2                          |
| Dizziness, light-headedness                                       | 4                                | 3                     | 2                     | 3                         | 2                          |
| Cough                                                             | 0                                | 2                     | 2                     | 2                         | 1                          |
| Allergic reaction, hypersensitivity                               | 2                                | 2                     | 2                     | 2                         | 1                          |
| Depression                                                        | 1                                | 1                     | 2                     | 2                         | 1                          |
| <b>Anxiety, nervousness, panic attacks</b>                        | <b>2</b>                         | <b>1</b>              | <b>2</b>              | <b>2</b>                  | <b>0</b>                   |

|                                                   |   |   |   |   |   |
|---------------------------------------------------|---|---|---|---|---|
| Constipation                                      | 1 | 1 | 1 | 1 | 0 |
| Weight gain                                       | 1 | 1 | 1 | 1 | 0 |
| Pruritis                                          | 1 | 1 | 1 | 1 | 0 |
| Arrhythmia                                        | 2 | 1 | 1 | 1 | 0 |
| Reflux, GERD                                      | 1 | 0 | 1 | 1 | 0 |
| Solid neoplasia, ALL (benign, malignant, unknown) | 0 | 1 | 1 | 1 | 0 |
| Tachycardia                                       | 1 | 0 | 1 | 1 | 0 |
| Wheeze, bronchospasm, asthma                      | 0 | 1 | 1 | 1 | 0 |
| Infection, bacterial                              | 1 | 1 | 0 | 1 | 0 |
| Edema, non-pulmonary, fluid retention, overload   | 1 | 1 | 0 | 1 | 0 |

Source: Reviewer created table from ISS Pivotal Studies Population ADAE dataset, utilizing ODE-1 safety queries

Anxiety, nervousness and panic attacks also occurred in more than 2% than the placebo arm, but the overall incidence was low, even in the treatment arms at only 2% (rounded). The population of young, female patients with migraines often have co-morbid anxiety, especially with chronic migraines. There is no indication from the above significant AEs, SAEs, or AEs leading to discontinuation that anxiety is drug-related.

The following table summarizes the common TEAEs by Preferred Term that demonstrated a risk difference between any treatment arm and placebo of  $\geq 1\%$  (Table 48).

**Table 48 Common TEAEs that Occurred in  $\geq 1\%$  of treatment population and  $\geq 1\%$  greater than placebo in any treatment arm ( $\geq 2\%$  than placebo in bold)**

| Adverse Event                         | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) | Greatest<br>Risk<br>Difference |
|---------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|--------------------------------|
|                                       | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |                                |
| <b>Infections and infestations</b>    |                                  |                          |                          |                              |                           |                                |
| Nasopharyngitis                       | 6                                | 6                        | 8                        | 7                            | 6                         | 2                              |
| Respiratory Tract infection^          | 12                               | 7                        | 9                        | 9                            | 8                         | 5                              |
| Urinary Tract Infection               | 2                                | 2                        | 3                        | 2                            | 2                         | 1                              |
| Diarrhoea                             | 2                                | 1                        | 2                        | 2                            | 1                         | 1                              |
| Influenza                             | 2                                | 1                        | 3                        | 2                            | 2                         | 1                              |
| Rhinorrhoea                           | 0                                | 1                        | 1                        | 1                            | 0                         | 1                              |
| <b>Nervous System Disorders</b>       |                                  |                          |                          |                              |                           |                                |
| Dizziness                             | 4                                | 3                        | 2                        | 3                            | 2                         | 2                              |
| Fatigue                               | 2                                | 3                        | 2                        | 3                            | 1                         | 2                              |
| Anxiety                               | 2                                | 1                        | 1                        | 1                            | 0                         | 1                              |
| <b>Immune System Disorders</b>        |                                  |                          |                          |                              |                           |                                |
| Hypersensitivity reactions*           | 3                                | 1                        | 2                        | 2                            | 0                         | 3                              |
| Food Allergy                          | 1                                | 0                        | 0                        | 0                            | 0                         | 1                              |
| <b>Gastrointestinal Disorders</b>     |                                  |                          |                          |                              |                           |                                |
| Nausea                                | 4                                | 2                        | 3                        | 3                            | 3                         | 1                              |
| Cholelithiasis                        | 0                                | 1                        | 0                        | 1                            | 0                         | 1                              |
| Constipation                          | 1                                | 1                        | 1                        | 1                            | 0                         | 1                              |
| <b>General and Systemic Disorders</b> |                                  |                          |                          |                              |                           |                                |

|                          |          |          |          |          |          |          |
|--------------------------|----------|----------|----------|----------|----------|----------|
| Weight Increased         | 1        | 1        | 1        | 1        | 0        | 1        |
| Joint Pain               | 2        | 2        | 3        | 2        | 2        | 1        |
| <b>Pain in Extremity</b> | <b>2</b> | <b>1</b> | <b>1</b> | <b>1</b> | <b>0</b> | <b>2</b> |
| Muscle Strain            | 1        | 1        | 0        | 1        | 0        | 1        |
| Contusion                | 1        | 1        | 0        | 1        | 0        | 1        |

<sup>a</sup>Includes multiple preferred terms including upper, lower, viral, acute, and viral upper respiratory tract infections

<sup>\*</sup>Includes the Preferred Terms: Hypersensitivity, as well as pruritus and flushing/hot flush that occurred only on day of dosing

Source: Reviewer's analysis of ISS ADAE dataset (PSS population)

**Reviewer's comment:** *There are very few common TEAEs that are convincingly related to the study drug to be declared common adverse drug reactions. However, hypersensitivity did lead to discontinuation in 13 patients, which were largely protocol-driven, but it is also a known class effect, a common concern with all biologic treatments, and should be considered for inclusion in the label as a warning/precaution. When grouped with flushing and pruritus that occurred on the day of dosing, hypersensitivity reactions would meet the  $\geq 2\%$  and  $>2\%$  greater than placebo, which is the commonly used cut-off for common AEs to be included in labeling that has been used for the other in-class CGRP antibodies indicated for preventive treatment of migraine. Fatigue almost meets the 2% cut-off and could be included in the AE table, although it is less clear if it may be drug-related and is actually only a 1.4% risk difference if calculated with the raw, not rounded percentages.*

*Respiratory tract infections would also meet the 2% cutoff if the 30 mg dose was included in the table, and dizziness and pain in extremity could meet the 2% cutoff, but again would not be  $\geq 2\%$  if using the raw, not rounded percentages. For all of these adverse events, the lack of a dose response also makes them less likely to be drug-related.*

*Nasopharyngitis was present in 8% of the 300 mg treatment arm, and only 6% of the placebo arm, but these numbers are not concerning for relatedness to the drug. Also, anxiety is borderline for being a possible adverse drug reaction. However, the overall percentage of patients with anxiety and fatigue are low (1% in total pool, no more than 3% in any treatment arm), and these are symptoms that are common in the migraine population, so it is difficult to confirm anxiety and fatigue as drug-related. For this reason, if the 100 mg and 300 mg are approved doses, then the only AEs to be included in the common AE table would be nasopharyngitis, hypersensitivity reactions, and possibly fatigue.*

#### 8.4.6. Laboratory Findings

There were few TEAEs related to laboratory findings, and they occurred in  $< 0.3\%$  of the eptinezumab patients, and in similar proportion in placebo patients. There were no serious AEs related to laboratory values, and there were no findings to suggest that eptinezumab was associated with any liver or renal toxicity.

Review of the laboratory findings did not show any significant changes from baseline in laboratory values. Shift tables demonstrated that among the patients whose laboratory results shifted from normal to abnormal were similar between eptinezumab-treated patients and placebo-treated patients. The shift tables for liver function tests and hematology tests are included below.

There were no patients in any of the 5 studies who met criteria for Hy's law for signs of drug-induced liver injury. In both the eptinezumab and placebo arms, there were infrequent reports of elevated liver enzymes or bilirubin. There were no trends over time or dose-related trends in the laboratory values or changes from baseline in the pivotal studies. Given the 3 reports of neutropenia in the safety database, hematology labs were also analyzed with no notable differences between treatment and placebo.

**Table 49 Shift Table for Liver Function Tests in Pivotal Studies Population (PSS)**

| Laboratory parameter and shift              | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|---------------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                             | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>Alanine Aminotransferase (ALT)</b>       |                                  |                          |                          |                              |                           |
| Normal to High                              | 18                               | 8                        | 10                       | 10                           | 10                        |
| Normal to High (> 3x ULN)                   | 1                                | 1                        | 1                        | 1                            | 0                         |
| <b>Aspartate Aminotransferase (AST)</b>     |                                  |                          |                          |                              |                           |
| Normal to High                              | 9                                | 7                        | 6                        | 7                            | 5                         |
| Normal to High (> 3x ULN)                   | 0                                | 0                        | 0                        | 0                            | 0                         |
| <b>Bilirubin</b>                            |                                  |                          |                          |                              |                           |
| Normal to High                              | 3                                | 2                        | 2                        | 2                            | 1                         |
| Number of patients n (%) with Bili > 2x ULN | 1 (0)                            | 1 (0)                    | 1 (0)                    | 3 (0)                        | 1 (0)                     |

Source: Reviewer analysis of ISS dataset ADLB, \*all patients had high bilirubin at baseline and went up from there

**Reviewer's comment:** There were no cases that met Hy's law for drug-induced liver injury. The number of patients with elevated transaminases was similar between the treatment arm and placebo. There was no relationship with dose.

**Table 50 Shift Table for Hematology Labs in Pivotal Studies Population (PSS)**

| Laboratory parameter and shift | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|--------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>Hemoglobin</b>              |                                  |                          |                          |                              |                           |
| Normal to Low                  | 4                                | 6                        | 4                        | 5                            | 6                         |
| Normal to High                 | 3                                | 1                        | 1                        | 1                            | 1                         |
| <b>Platelets</b>               |                                  |                          |                          |                              |                           |
| Normal to Low                  | 1                                | 1                        | 1                        | 1                            | 0                         |

|                                     |                     |   |   |   |   |   |
|-------------------------------------|---------------------|---|---|---|---|---|
|                                     | Normal to High      | 5 | 4 | 3 | 4 | 5 |
| <b>White Blood Cell Count (WBC)</b> |                     |   |   |   |   |   |
|                                     | Normal to Low       | 3 | 5 | 5 | 5 | 4 |
| <b>Neutrophils</b>                  |                     |   |   |   |   |   |
|                                     | Normal to Low shift | 4 | 3 | 5 | 4 | 3 |

Source: Reviewer's analysis of ISS dataset ADLB

**Reviewer's comment: The hematology labs did not reveal any concerning findings with the incidence of any shifts from normal similar in the eptinezumab and placebo treatment arms. Despite the 3 TEAEs of neutropenia detailed above, there does not seem to be a relevant safety signal for neutropenia or bone marrow suppression with treatment.**

#### 8.4.7. Vital Signs

Overall, the mean vital signs were comparable at baseline for the eptinezumab and placebo treatment arms. The post-baseline vital signs were also comparable, with no significant differences between eptinezumab and placebo patients, and no dose-related changes noted. Attention was given specifically to certain vital signs. There were only a few TEAEs related to vital signs, which are discussed above (i.e., hypertension). Weight increased was also reported as a TEAE in 13 treatment patients and 2 placebo patients.

This reviewer analyzed the mean change from baseline in systolic blood pressure (SBP), and diastolic blood pressure (DBP) and found no dose-related treatment effect was noted. The incidence of certain increases in BP and BMI were also calculated and illustrated in the table below (See Table 51).

**Table 51 Incidence of Specific Vital Signs Changes from Baseline by Treatment Arm (PSS)**

| Vitals Signs                                  | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|-----------------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                               | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| Blood Pressure                                |                                  |                          |                          |                              |                           |
| Systolic BP ≥ 10 mm Hg increase from baseline | 53                               | 55                       | 58                       | 56                           | 56                        |
| Systolic BP ≥ 20 mmHg increase from baseline  | 16                               | 20                       | 18                       | 19                           | 21                        |
| Systolic BP > 140 mmHg                        | 12                               | 13                       | 10                       | 12                           | 11                        |
| Diastolic BP ≥ 10 mmHg increase from baseline | 45                               | 42                       | 38                       | 41                           | 38                        |
| Diastolic BP ≥ 20 mmHg increase from baseline | 10                               | 7                        | 6                        | 7                            | 6                         |
| Diastolic BP > 90 mm Hg                       | 21                               | 15                       | 14                       | 15                           | 15                        |
| Weight/BMI                                    |                                  |                          |                          |                              |                           |
| Weight increase ≥ 7%                          | 15                               | 10                       | 9                        | 11                           | 9                         |
| BMI increase ≥ 1                              | 40                               | 14                       | 15                       | 18                           | 12                        |
| BMI increase ≥ 2                              | 16                               | 7                        | 5                        | 8                            | 4                         |
| Heart Rate                                    |                                  |                          |                          |                              |                           |
| HR ≥ 10 bpm decrease from baseline            | 49                               | 46                       | 46                       | 47                           | 46                        |

|                                         |    |    |    |    |    |
|-----------------------------------------|----|----|----|----|----|
| HR $\geq$ 20 bpm decrease from baseline | 14 | 12 | 11 | 12 | 12 |
| HR $\geq$ 10 bpm increase from baseline | 57 | 55 | 51 | 54 | 53 |
| HR $\geq$ 20 bpm increase from baseline | 24 | 16 | 17 | 18 | 15 |
| HR < 60 bpm                             | 30 | 29 | 28 | 28 | 29 |
| HR > 100 bpm                            | 9  | 5  | 5  | 6  | 7  |

Source: Reviewer's analysis of ISS ADVS dataset for PSS pool

There were also no significant differences in the treatment arms in the incidence of heart rate < 60 bpm, or frequency of HR > 100 bpm. There were no dose-related trends or differences in HR noted amongst the treatment arms. The overall mean weight change from baseline was low in all treatment arms (approximately 0.3-0.5 kg). The mean change from baseline in BMI was similar amongst treatment arms (0.1-0.3).

Including the open-label extension study, there was no significant difference in the number of patients who had Systolic BP > 140 or Diastolic BP > 90 at any point in the study, including the screening/baseline BP, between the placebo and treatment arms.

**Reviewer's comment: There were no apparent treatment effects of eptinezumab on any vital signs including blood pressure compared to placebo. There is a trend toward increasing BMI which is greater in the treatment group than in placebo, although the overall percent of patients who increased their weight > 7% is not significantly different between treatment and placebo, so the overall changes in BMI may have been driven by a few outliers.**

#### 8.4.8. Electrocardiograms (ECGs)

In the PSS population, the means for the ECG parameters were comparable between treatment arms and placebo at baseline and at all post-baseline evaluations. The mean changes from baseline were small and similar amongst treatment arms. There were no dose-related trends. Similar proportions of patients who received eptinezumab (0.4%) and patients who received placebo (0.4%) had a shift in any post-baseline ECG from normal to abnormal clinically significant, and one patient each in treatment and placebo groups shifted from abnormal not clinically significant to abnormal clinically significant. There was no noted dose-response relationship.

There were 3 TEAEs of T-wave inversion that occurred in 3 patients receiving 300 mg eptinezumab. The other ECG-related TEAEs occurred in one patient each and included Q wave abnormal (100 mg), ST segment depression (100 mg and placebo), ST-T segment elevation (30 mg). Three placebo patients also had ECG-related changes including T wave amplitude decreased (2 patients) and T wave abnormal (1 patient).

**Reviewer's comment: The incidence of ECG abnormalities that were clinically significant or related to an adverse event was low, and occurred in similar frequency in patients on**

***eptinezumab and on placebo. There is no ECG-related safety signal identified.***

#### 8.4.9. QT

This is a biologic, monoclonal antibody and thus a thorough QTc study was not performed. The applicant provided summary statistics for the QTcF which are summarized below.

No patient in the PSS population had a QTcF interval that was > 500 msec. The incidence of QTcF intervals >450 and ≤ 480 msec was similar in the eptinezumab and placebo groups. There were 2 patients in the treatment arm that had a QTcF > 480 msec and ≤ 500 msec.

The largest mean increase from baseline in QTcF was 4 msec. There were similar proportions of patients amongst the treatment arms and placebo who had an increase from baseline of QTcF > 30 ms or > 60 ms (See Table 52). There was no dose-response noted, and the incidence was low overall.

In the Overall Eptinezumab population, there was a similar incidence of 8% of QTcF increase from baseline > 30 msec, and 0.4% incidence of QTcF increase from baseline > 60 msec.

**Table 52 Analysis of QTcF Intervals for the Pivotal Studies Population**

| QTcF Intervals                     | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                    | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>QTcF (msec)</b>                 |                                  |                          |                          |                              |                           |
| >450 to < 480 msec                 | 7                                | 6                        | 6                        | 6                            | 6                         |
| >480 to < 500 msec (n, (%))        | 0                                | 1 (0)                    | 1 (0)                    | 2 (0)                        | 0                         |
| <b>QTcF Increase from Baseline</b> |                                  |                          |                          |                              |                           |
| >30 msec                           | 12                               | 9                        | 7                        | 9                            | 8                         |
| >60 msec (n, (%))                  | 3 (1)                            | 1 (0)                    | 2 (0)                    | 6 (0)                        | 2 (0)                     |

Source: Reviewer adapted from Summary of Clinical Safety Table 38/ (ISS 14.3.4.3.3.1)

***Reviewer's comment: Eptinezumab does not appear to have any notable effect on the QTc.***

#### 8.4.10. Immunogenicity

Immunogenicity is a concern with all monoclonal antibodies because of the potential for formation of antibodies to the biologic therapy. The applicant provided an analysis of the eptinezumab-induced anti-drug antibody (ADA) response throughout the clinical studies and the effects on the safety and efficacy analyses. The applicant tested for anti-drug antibodies using a cell-based assay. Samples that were positive for binding antibodies were then tested for neutralizing activity. Potential consequences of immunogenicity include allergic-type hypersensitivity reactions and anaphylaxis, immune complex-related hypersensitivity, reduced pharmacodynamic response and altered pharmacokinetics (with subsequent decreased

efficacy), compromise of subsequent treatment with related products and uncertain long-term clinical impact. If considered to be immunogenic, administration via intravenous infusion may be associated with higher risk of immune complex formation in the systemic circulation and acute systemic hypersensitivity reactions.

A total of 2,076 subjects were treated with eptinezumab in the clinical development program, and ADA results were available for 2,074 patients. The overall incidence of treatment-emergent ADA in the studies was 15.9%, which was similar across studies. The onset of detectable ADA occurred at 8 weeks, and maximal ADA frequency and ADA titer was detected at the 24-week time-point, regardless of dose level or total number of doses. The incidence of development of neutralizing antibody (Nab) was 6.2% across all studies. The prevalence of pre-existing ADA was less than 1%. Table 53 demonstrates the percent of patients with “ever-positive” ADA results by dose and study.

**Table 53 Incidence of Eptinezumab-Induced Anti-Drug Antibody (ADA) and Neutralizing Antibody (Nab)**

|                          | Study 006        |         |         | Study 011        |         |
|--------------------------|------------------|---------|---------|------------------|---------|
|                          | Eptinezumab Dose |         |         | Eptinezumab Dose |         |
|                          | 300 mg           | 100 mg  | 30 mg   | 300 mg           | 100 mg  |
| ADA results              | N = 224          | N = 223 | N = 219 | N = 350          | N = 356 |
| Ever-positive, n (%)     | 47 (21)          | 45 (20) | 27 (12) | 69 (20)          | 60 (17) |
| NAb results              |                  |         |         |                  |         |
| Ever-positive, n (%)     | 16 (7)           | 22 (10) | 14 (6)  | 19 (5)           | 26 (7)  |
| At Sampling Time-Points* |                  |         |         |                  |         |
| Day 0 (pre-treatment)    | n/a              | n/a     | n/a     | 4 (1)            | 2 (< 1) |
| Week 4                   | 0                | 1 (< 1) | 4 (2)   | 4 (1)            | 3 (< 1) |
| Week 12                  | 24 (11)          | 20 (10) | 14 (7)  | 33 (10)          | 26 (8)  |
| Week 24                  | 34 (18)          | 35 (19) | 18 (10) | 56 (17)          | 56 (17) |
| Week 36                  | 22 (12)          | 29 (16) | 16 (9)  | 29 (9)           | 37 (11) |
| Week 56                  | 7 (4)            | 12 (7)  | 10 (6)  | n/a              | n/a     |

\*The number of evaluable ADA results differs at each time point, so the “N” used is different for each Week’s percentage calculation, Time-points varied slightly between studies

ADA = anti-drug antibody, Nab = Neutralizing antibody, N = total number of subjects, n/a = not available

Source: Reviewer-derived table from Applicant’s Integrated Summary of Immunogenicity Tables 65, 66, (ISI TLF 14.2.1.6) and Table 80 and 81 (ISI TLF 14.2.1.11)

The above table demonstrates an increase and then subsequent decrease in the percentage of patients who tested positive for ADA at each time-point with a peak at Week 24. There did not appear to be a dose-response in either study.

For evaluation of safety, the incidence of TEAEs by ADA category were calculated, including patients who tested positive for ADA at any time point in the study (“ever-positive”), and patients who tested positive for ADA prior to the dose associated with that particular TEAE

“coincident-positive”). There was no increase in incidence of TEAEs among patients who were ADA positive compared to those who were ADA-negative for either study.

**Table 54 Subgroup Analysis of TEAE Incidence among patients with and without Anti-Drug Antibodies**

| Study 006                | Number (%) of patients with TEAE |                            |                           |                                |                             |
|--------------------------|----------------------------------|----------------------------|---------------------------|--------------------------------|-----------------------------|
|                          | 300 mg<br>N = 224<br>n (%)       | 100 mg<br>N = 223<br>n (%) | 30 mg<br>N = 219<br>n (%) | Total Epti<br>N = 666<br>n (%) | Placebo<br>N = 222<br>n (%) |
| Any TEAE                 | 129 (58)                         | 141 (63)                   | 128 (58)                  | 398 (60)                       | 132 (60)                    |
| <b>Ever-positive ADA</b> | N = 47                           | N = 45                     | N = 27                    | N = 119                        |                             |
| Any TEAE                 | 31 (66)                          | 26 (58)                    | 16 (60)                   | 73 (61)                        | n/a                         |
| Coincident-Positive      | 15 (32)                          | 16 (36)                    | 11 (41)                   | 42 (35)                        | n/a                         |
| <b>Negative ADA</b>      | N = 177                          | N = 178                    | N = 192                   | N = 547                        |                             |
| Any TEAE                 | 98 (55)                          | 115 (66)                   | 112 (58)                  | 325 (59)                       | n/a                         |
| <b>Study 011</b>         | <b>N = 350</b>                   | <b>N = 356</b>             |                           | <b>N = 706</b>                 | <b>N = 366</b>              |
| Any TEAE                 | 182 (52)                         | 155 (44)                   | n/a                       | 337 (48)                       | 171 (47)                    |
| <b>Ever-positive ADA</b> | N = 69                           | N = 60                     |                           | N = 129                        |                             |
| Any TEAE                 | 33 (47)                          | 31 (52)                    | n/a                       | 64 (50)                        | n/a                         |
| Coincident-Positive      | 13 (19)                          | 7 (12)                     | n/a                       | 20 (15)                        | n/a                         |
| <b>Negative ADA</b>      | N = 281                          | N = 296                    |                           | N = 577                        |                             |
| Any TEAE                 | 149 (53)                         | 124 (42)                   | n/a                       | 273 (47)                       | n/a                         |

*Coincident-positive: confirmed ADA positive result in the sample taken just prior to dose associated with the TEAE; n/a = not applicable, N = total number of patients, TEAE = treatment-emergent adverse event*

*Source: Reviewer-verified table, adapted from ISI Table 75 (ISI TLF 14.5.1.6) and Table 89 (ISI TLF 14.5.1.11)*

As noted above, the incidence of TEAEs was similar among the general population, ADA positive population, and ADA negative population. There were no relationships noted between the ADA or Nab status and the incidence or severity of any TEAEs, SAEs, or AESIs.

In Study 006, the AEs of special interest (AESI) occurred in approximately 10 % of the treatment population. Amongst those patients with AESI, 80% occurred in patients who were ADA-negative, and 20% occurred in patients who were ADA “ever-positive”, with 10% of patients being “coincident-positive”. There were no reports of anaphylaxis or severe hypersensitivity reactions. Of the 7 patients that had mild or moderate hypersensitivity reactions, 2 were “ever-positive” ADA, 5 were negative throughout, and none were coincident positive.

In Study 011, 8% of patients had an AESI. Of these, 79% were in patients who were ADA-negative, 21% were in ADA “ever-positive” and 2 patients (3%) had coincident-positive ADA. There were no reports of anaphylaxis or severe hypersensitivity reactions. There were 6 patients with mild or moderate hypersensitivity reactions, all of whom were ADA negative. In the open-label extension Study 013, there was a patient who had a report of an anaphylactic reaction (detailed above), which was ultimately coded as a moderate hypersensitivity reaction, and was negative for ADA throughout the study.

**Reviewer's comment:** *There was no relationship between ADA status and the incidence or severity of TEAEs or AEs of special interest. The TEAEs of hypersensitivity did not occur with more frequency in patients who were ADA-positive. Immunogenicity was also examined for impact on efficacy, which is explored in more detail in the Office of Clinical Pharmacology Review by Dr. Gopichand Gottipati. Their review states that ADA status and titer levels were associated with lower  $C_{trough}$  levels, but not associated with lower efficacy. There was also a confounding effect of ADA interference with eptinezumab  $C_{trough}$  measurements, and mean  $C_{trough}$  levels were lower in the higher quartiles of mean ADA titers.*

## 8.5. Analysis of Submission-Specific Safety Issues

The AEs of special interest that were defined above included QT prolongation, liver toxicity, suicidality, cardiovascular events, infusion site reactions, neurologic events, dermatologic events, immunologic events, and infusion day TEAEs. These are outlined below by incidence and with narratives, when appropriate. Some are combined together, when appropriate.

### 8.5.1. Cardiovascular Events/QT Prolongation

There were no reported TEAEs of QT prolongation. See also Sections 8.4.8 and 8.4.9 above. There were 22 patients who reported TEAEs in the Cardiac Disorders SOC. Of these 22 patients, 4 were in the placebo arm (0.7%), and 18 were in the eptinezumab arm (1.3%). There was no apparent dose response as they were evenly distributed among the treatment arms.

The most common cardiac-related TEAEs were tachycardia (7), palpitations (5), and AV block first degree(3). The other cardiac TEAEs occurred in only 1 patient each. There were other TEAEs that were also flagged by the applicant as "cardiovascular TEAEs" that did not fall into the Cardiac Disorders SOC, but rather the Vascular or other SOC. These are noted in the below table, and also include one patient each with bradycardia and Q wave inversion.

**Table 55 Incidence of Cardiovascular System TEAEs, Pivotal Studies Population**

| Adverse Event                          | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|----------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                        | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>Cardiovascular System Disorders</b> | <b>4.6</b>                       | <b>3.1</b>               | <b>3.1</b>               | <b>3.4</b>                   | <b>2.2</b>                |
| Hypertension/Blood Pressure Increased  | 0.9                              | 1.6                      | 0.9                      | 1.2                          | 1.5                       |
| Syncope                                | 0                                | 0.5                      | 0.7                      | 0.5                          | 0.5                       |
| Flushing/hot flush/hot flashes         | 0.9                              | 0.5                      | 0.7                      | 0.7                          | 0                         |
| Tachycardia                            | 1.4                              | 0.3                      | 0.5                      | 0.6                          | 0.2                       |

|              |     |     |     |     |     |
|--------------|-----|-----|-----|-----|-----|
| Palpitations | 1.4 | 0.2 | 0.2 | 0.4 | 0.2 |
|--------------|-----|-----|-----|-----|-----|

Source: Reviewer's analysis of ISS ADAE dataset

Of the 9 patients who reported "flushing or hot flush", 5 patients reported the AE on the day of dosing, and it appears temporally-related to the infusion, and may represent an infusion reaction similar to the hypersensitivity reactions described below. The other 4 patients reported the verbatim term of increased frequency of "hot flashes" which did not occur on the day of dosing, and which is unlikely related to treatment or infusion.

In the remainder of the ISS (OE population), there were a total of 38 patients who reported TEAEs of hypertension or blood pressure increased, 27 patients on treatment and 11 patients on placebo. None of these were serious or severe. Three patients total (including the 2 patients described above in the PSS) had the drug withdrawn due to hypertension. There was no apparent dose-response noted.

**Reviewer's comment: Although there was a slightly higher incidence of cardiovascular related AEs in the treatment arm than the placebo arm, the incidence was so low that it does not rise to the level of an adverse drug reaction or safety signal. The overall incidence of hypertension, while also low, was higher in the placebo arm than any of the treatment arms. The TEAE of flushing may be related to the hypersensitivity reactions in 5 of the patients which occurred on the day of dosing, and does not appear to be a vascular safety signal. However, despite the lack of an overall safety signal for hypertension or other cardiovascular events based on the incidence rates, there are three patients that discontinued due to hypertension, and alternate explanations or etiology for their hypertension is not provided. Therefore a role of the treatment in worsening hypertension cannot be excluded, and enhanced pharmacovigilance for hypertension is recommended.**

The applicant also provided an analysis of the change in the need for or dose of cardiovascular medications, both for the pivotal studies population and the overall eptinezumab populations. The percentage of patients with new or changed dose of CV medication after receiving the first dose of eptinezumab were low and similar across treatment arms. No association with dose was observed. See Table 56 below.

**Table 56 Incidence of New or Changed dose of Cardiovascular Medication**

| New CV medications                      | All Eptinezumab Treated Patients |            |            |               |         |           | Placebo (%) |
|-----------------------------------------|----------------------------------|------------|------------|---------------|---------|-----------|-------------|
|                                         | 30 mg (%)                        | 100 mg (%) | 300 mg (%) | All Doses (%) |         |           |             |
| Pivotal Studies Safety Pool (PSS), N    | 219                              | 579        | 574        | 1372          |         |           | 588         |
| New or dose change in CV medication     | 2.3                              | 3.1        | 3.3        | 3.1           |         |           | 2.9         |
|                                         | 10 mg                            | 30 mg      | 100 mg     | 300 mg        | 1000 mg | All Doses | Placebo     |
| Overall Eptinezumab Safety Pool (OE), N | 130                              | 341        | 701        | 823           | 81      | 2076      | 791         |

|                                     |     |     |     |     |     |     |     |
|-------------------------------------|-----|-----|-----|-----|-----|-----|-----|
| New or dose change in CV medication | 5.4 | 3.8 | 3.4 | 3.5 | 3.7 | 3.7 | 3.0 |
|-------------------------------------|-----|-----|-----|-----|-----|-----|-----|

Source: Adapted from ISS Tables 14.3.2.11.3.1, 14.3.2.11.3.3

**Reviewer's comment:** *There is no identifiable trend for increased need for new or higher doses of cardiovascular medications on treatment compared to placebo. There was no association with dose and the need for new or increased dose of cardiovascular medications.*

### 8.5.2. Suicidality

The applicant assessed for the potential for suicidality and suicide-related thoughts using the Columbia-Suicide Severity Rating Scale. There were not significant numbers of abnormal reporting on the C-SSRS during the clinical development program. The suicide-related AEs that were serious are described above. In the total ISS database, there were 14 reports of suicide-related TEAEs, five of which were SAEs and were already outlined above in Section 8.4.2. Suicide-related TEAEs were reported in a total of 3 patients receiving placebo (1 serious), and 11 patients receiving eptinezumab. Four of the 11 suicide-related TEAEs on treatment are described above in the SAE section (Section 8.4.2). The remaining 7 patients had mild and self-resolving AEs, and all had a pre-existent diagnosis of anxiety and/or depression (Table 57). There was no dose-response noted, with the majority of events happening in patients who received 100 mg. All of the reported suicidal-ideations occurred in patients enrolled in the chronic migraine trials only, with the exception of one patient in Study 006 who is described above.

**Reviewer's comment:** *Within the controlled studies (Phase 2 and 3 studies), there is a slight imbalance with the number of patients reporting suicide-related TEAEs on treatment (11/1153, 0.6%) and on placebo (3/791, 0.4%). The SAEs of suicide ideation and suicide attempt were already discussed above, and occurred in 4 patients receiving drug and 1 patient receiving placebo. The remainder of the events included 7 cases on eptinezumab and 2 cases on placebo. Almost all of the patients that reported suicidal TEAEs were enrolled in chronic migraine studies, with the exception of one patient described above. It is generally known that depression and anxiety are common comorbid conditions in patients with migraine, and in particular chronic migraine. However, the majority of the events were mild and picked up only on the routine, screening C-SSRS questionnaire. The descriptions of suicidal ideation outlined below do not raise to the level of concern for a safety signal, particularly given the pre-existent anxiety and depression in all of these patients. A number of the patients reported "wishing to be dead" to stop the pain, or other similar sentiments, and none of the below patients had a suicide attempt, intent, or a plan. However, given the imbalance between the treatment arm and placebo, it may be worthwhile to have enhanced pharmacovigilance for suicide-related events.*

**Table 57 Summary of Suicide-related TEAEs Reported in the ISS (Eptinezumab-treated patients)**

| Subject ID | Dose and # of doses | Suicide related AE terms                           | Severity           | Other comments                                                                                                                                          |
|------------|---------------------|----------------------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6)    | 100 mg x 1          | Suicidal ideation/cutting/self-injurious behaviors | Grade 2 / moderate | h/o cutting/anxiety<br>Initial report at Week 8                                                                                                         |
|            | 100 mg x 1          | Suicidal ideation                                  | Grade 1 / mild     | h/o anxiety and depression<br>+ subsequent SAE of substance-induced mood disorder requiring hospitalization<br>Initial report at Week 4                 |
|            | 300 mg x 1          | Suicidal ideation                                  | Grade 1 / mild     | Initial report at Week 20                                                                                                                               |
|            | 300 mg x 1          | Suicidal ideation (brief)                          | Grade 1 / mild     | h/o prior suicide attempt<br>h/o depression<br>Initial report at Week 24                                                                                |
|            | 100 mg x 1          | Suicidal ideation (because of severe headache)     | Grade 1 / mild     | h/o anxiety<br>Initial report at Week 8<br>Stopped study drug because initiated Topiramate                                                              |
|            | 100 mg x 2          | Suicidal ideation                                  | Grade 1 / mild     | H/o depression and ADHD<br>+ Concomitant bupropion, duloxetine, lisinopril, propranolol, and amphetamine/dextroamphetamine<br>Initial report at Week 12 |
|            | 100 mg x 2          | Suicidal ideation without intent/plan              | Grade 1 / mild     | h/o depression and anxiety<br>Initial report at Week 20                                                                                                 |

Source: Reviewer-created table from review of the ISS Suicide-related Safety Narratives

## 8.5.2 Gastrointestinal Disorders and Liver Toxicity

The incidence of specific gastrointestinal disorders was reviewed. Notably, all events of constipation and abdominal pain were analyzed (see Table 58). In the pivotal studies population, the incidence of constipation in the treatment arm was more than 2x the incidence in the placebo arm. However, the overall incidence was low throughout the studies. None of the reports of constipation were serious or severe, and none led to discontinuation of treatment.

For abdominal pain, there were equal numbers of TEAEs in both the treatment arm and placebo arm, and there were no abdominal pain-related SAEs, and none led to discontinuation. There was one severe TEAE of abdominal pain reported in a patient who received placebo.

**Table 58 Incidence of Gastrointestinal Disorders TEAEs, Pivotal Studies Population**

| Adverse Event | All Eptinezumab Treated Patients |  |
|---------------|----------------------------------|--|
|---------------|----------------------------------|--|

|                                       | 30 mg<br>N = 219<br>(%) | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) | Placebo<br>N = 588<br>(%) |
|---------------------------------------|-------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
| <b>Gastrointestinal Disorders SOC</b> | <b>13.7</b>             | <b>7</b>                 | <b>11.1</b>              | <b>9.8</b>                   | <b>8.7</b>                |
| Abdominal pain, all                   | 1.8                     | 1.7                      | 1.7                      | 1.7                          | 1.4                       |
| Constipation                          | 1.4                     | 0.7                      | 1.2                      | 1.0                          | 0.3                       |

Source: Reviewer's analysis of ISS ADAE dataset, PSS population

The overall eptinezumab (OE) population was also analyzed for events of constipation that occurred outside of the pivotal studies. There were an additional 7 patients who reported constipation in addition to those outlined above. Of these 7 patients, 2 patients received placebo, and there were 5 additional cases on treatment, 1 on 100 mg, 3 on 300 mg, and 1 on 1000 mg. One of these cases occurred in the open-label extension study. None of the cases were serious, none were graded as severe, and none led to discontinuation of the drug.

***Reviewer's comment: Constipation is listed in the prescribing information as an adverse reaction for erenumab, another anti-CGRP mAb which binds to the CGRP receptor, rather than the ligand. It was recently also added as a warning after several postmarketing cases reported severe constipation. Animal studies have also suggested that blocking CGRP may induce constipation; thus, constipation was included in this review as an AE of special interest. The events of constipation, while occurring at a very low incidence of 1%, was almost 3 times more common in the treatment group than in the placebo group. However, there does not seem to be a dose-response, and there were no AEs of constipation that were serious, severe, or led to study drug discontinuation. Given the lack of severity and the low frequency of events of constipation, it does not qualify as a safety signal or adverse drug reaction in the clinical studies. However, it should continue to be monitored in the postmarketing setting and enhanced pharmacovigilance based on a potential class effect is warranted.***

Eptinezumab was also evaluated for the risk of potential liver toxicity. There were 19 patients who had a total of 21 events coded to "hepatic events" which included hepatic enzymes increased or bilirubin increased. Of these 19 patients, 6 received placebo (1%), and 13 received eptinezumab (0.9%). There was a trend towards increased events with the higher dose, but no conclusions could be made since the overall incidence was so low. None of these events led to study drug discontinuation, none were considered SAEs, and there was 1 event graded as a severe TEAE.

In the OE population, there were an additional 6 patients who had elevated hepatic enzymes or bilirubin increased, 2 on placebo and 4 on treatment. All of these patients were in the Phase 2 studies, and none were in the open-label extension period. None were reported as serious or severe, and none led to study drug discontinuation.

**Reviewer's comment:** *There is no apparent liver toxicity signal for eptinezumab based on the clinical development thus far.*

### 8.5.3. Neurologic Events

Events that were reported within the Nervous System Disorders SOC were analyzed, without any apparent safety signal in the treatment arm compared to placebo.

**Table 59 Incidence of Nervous System Disorders TEAEs, Pivotal Studies Population**

| Adverse Event                       | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|-------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                     | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>Nervous System Disorders SOC</b> | <b>4.6</b>                       | <b>7.6</b>               | <b>8.4</b>               | <b>7.4</b>                   | <b>10.7</b>               |
| Dizziness                           | 3.7                              | 2.8                      | 2.3                      | 2.7                          | 2.0                       |
| Migraine/headache                   | 0.9                              | 1.9                      | 2.6                      | 2.0                          | 3.9                       |
| Syncope/Presyncope                  | 0                                | 0.7                      | 0.9                      | 0.7                          | 1.2                       |

Source: Reviewer's analysis of ISS ADAE dataset, PSS population

**Reviewer's comment:** *In the PSS, there is no safety signal for neurologic disorders identified with eptinezumab, although dizziness was noted slightly more common with treatment (2.7%) than placebo (2%). There were 2 reported episodes of seizure that are described above in the SAEs (Section 8.4.2).*

### 8.5.4. Hypersensitivity and Infusion-related Events

Hypersensitivity reactions leading to discontinuation are outlined above in Section 8.4.3. There were 14 reported TEAEs of hypersensitivity in the treatment arm, 13 of which lead to study drug discontinuation as noted above. Many of these discontinuations were protocol-driven, and none of the hypersensitivity reactions were serious or severe. However, there were no hypersensitivity reactions in the placebo arm, making it highly likely that the events were immune-mediated reactions related to infusion of the study-drug. There were an additional 14 reports of pruritus, none of which were reported in the placebo arm. Four of these patients reported pruritus on the day of dosing, which appears consistent with infusion-related pruritus, and may be included within the spectrum of hypersensitivity reactions. An additional 5 patients reported "flushing" on the day of dosing that also may be related to an infusion reaction, or may be immune-mediated hypersensitivity reactions. Overall, there was an imbalance of hypersensitivity reactions between treatment and placebo. Further analyses were performed to look at all terms that could be associate with hypersensitivity reactions; those that appeared in the ISS pivotal study population included asthma, conjunctivitis, urticaria, hypersensitivity, rash,

flushing, dermatitis, rash pruritic, swelling face, pruritus (Table 60).

The applicant also included an analysis flag for “events associated with study drug infusion”, which included all adverse events that occurred within 7 days of infusion. There were 61 events that occurred in 61 patients within this flag. None of the events were serious, none were severe, and none led to study drug discontinuation. The most commonly reported event was infusion site extravasation, followed by rhinorrhea, pruritus, rash, and nasal congestion which occurred within 7 days of infusion. Infusion-specific terms that are unique to intravenous administration, such as “infusion-site pain, infusion site extravasation, infusion-site erythema, etc.” did not occur more commonly with treatment than with placebo (Table 60).

In the OE pool, TEAEs within the Immune System SOC occurred in 62 patients, with 23 reporting hypersensitivity. None were serious, none were severe, but 16 led to discontinuation (3 additional patients to the 13 described above in the PSS).

**Table 60 Incidence of Immune System and Infusion Related TEAEs, Pivotal Studies population**

| Adverse Event                                              | All Eptinezumab Treated Patients |                          |                          |                              | Placebo<br>N = 588<br>(%) |
|------------------------------------------------------------|----------------------------------|--------------------------|--------------------------|------------------------------|---------------------------|
|                                                            | 30 mg<br>N = 219<br>(%)          | 100 mg<br>N = 579<br>(%) | 300 mg<br>N = 574<br>(%) | All Doses<br>N = 1372<br>(%) |                           |
| <b>Infusion- related and Immune System AEs</b>             | <b>3.2</b>                       | <b>3.6</b>               | <b>4.2</b>               | <b>3.8</b>                   | <b>1.5</b>                |
| Hypersensitivity                                           | 1.8                              | 0.2                      | 1.4                      | 1.0                          | 0                         |
| Pruritus (day of dosing)*                                  | 0.5                              | 0.5                      | 0                        | 0.3                          | 0                         |
| Flushing/hot flush (on day of dosing)*                     | 0.5                              | 0.3                      | 0.3                      | 0.4                          | 0                         |
| Hypersensitivity PLUS Pruritus/Flushing on Day of Infusion | 2.7                              | 1.0                      | 1.7                      | 1.6                          | 0                         |
| Pruritus (all)                                             | 1.8                              | 1.4                      | 0.7                      | 1.2                          | 0                         |
| Urticaria**                                                | 0                                | 0.5                      | 0.2                      | 0.3                          | 0.3                       |
| Flushing/hot flush/hot flashes                             | 0.9                              | 0.5                      | 0.7                      | 0.7                          | 0                         |
| ALL HYPERSENSITIVITY-RELATED TERMS^                        | 3.7                              | 3.5                      | 4.7                      | 4.0                          | 1.5                       |
| <b>Infusion-site AEs#</b>                                  | <b>3.7</b>                       | <b>1.9</b>               | <b>1.4</b>               | <b>1.9</b>                   | <b>2.0</b>                |

Source: Reviewer’s analysis of ISS ADAE dataset, PSS population

\* Preferred terms of pruritus, flushing, and hot flush only that occurred on the day of dosing

\*\*Urticaria was not coded as a hypersensitivity reaction if it did not occur within one week of dosing

^ includes all potentially-related terms including asthma, conjunctivitis, urticaria, hypersensitivity, rash, flushing, dermatitis, rash pruritic, swelling face, pruritus

# All infusion-site related AEs including infusion-site pruritis, rash, discomfort, pain, bruising, erythema, haematoma, extravasation, and nerve damage

**Reviewer’s comment: Compared to the placebo arm, there is an imbalance of hypersensitivity-related events in patients receiving treatment. Although the events were not serious or severe, there were several cases of hypersensitivity reactions leading to discontinuation from the study. The discontinuations were primarily protocol-driven, but it is also unclear if patients would have had more serious reactions had they continued in the**

***study. Additionally, many of the hypersensitivity reactions required treatment or interruption of the drug infusion. There was one SAE of anaphylactic reaction (described above) which also required immediate treatment. It is likely that the risk of hypersensitivity may be underestimated due to the immediate access to treatment, as well as the protocol-driven discontinuation after an initial mild reaction.***

***Furthermore, if the TEAEs of hypersensitivity were combined with other immune-mediated terminology such as pruritus, urticaria, asthma, flushing, and rash, then the reactions become common in more than 2% of the eptinezumab population and greater than placebo. However, some of these terms may have had alternate explanations or were significantly removed from the timing of infusion, so it is not clear that all of these terms were drug-related. It does seem that there is a real risk for hypersensitivity reactions that was likely underestimated in these studies given the protocol-driven discontinuations. There is also known hypersensitivity risk with the other CGRP-antagonists, as well as monoclonal antibodies in general due to the risk for immunogenicity. For this reason, hypersensitivity is recommended to be included as a warning in the prescribing information and routine pharmacovigilance is recommended.***

***There were also several various infusion-site AEs that were equally frequent in the treatment arm and the placebo arm. This would indicate that these AEs are more related to placement of the IV rather than a specific infusion reaction to the drug product.***

## 8.6. Safety Analyses by Demographic Subgroups

The safety database had very few TEAEs and SAEs overall, so comparisons by subgroup are difficult. In addition, the database had a limited number of non-white patients, and only a small number of patients > 65 years of age. There were 23 patients who were treated between 65 and 74 years of age. The small number of patients over 65 years makes it difficult to discern the presence of any adverse events unique to that population.

There were 1,524 patients in the OE pool who were exposed to either the 100 mg or 300 mg doses of eptinezumab, with a median age of 40 years, 86% of whom were women. The large number of female patients in the clinical studies is reflective of the gender distribution in patients with migraine, but it is harder to make comparisons of any specific TEAEs by gender. Overall comparisons of rates of TEAEs and SAEs by subgroup are included in Table 61.

**Table 61 Rates of TEAEs and SAEs by Sex, Age, and Race in Overall Eptinezumab Pool Patients Exposed to 100 mg or 300 mg doses**

|  | Sex | Age | Race |
|--|-----|-----|------|
|--|-----|-----|------|

|       | M<br>N = 214<br>n(%) | F<br>N = 1310<br>n(%) | < median<br>age (40 y)<br>N = 744<br>n(%) | ≥ median<br>age (40 y)<br>N = 780<br>n(%) | White<br>N = 1381<br>n(%) | Black<br>N = 108<br>n(%) | Other*<br>N = 35<br>n(%) |
|-------|----------------------|-----------------------|-------------------------------------------|-------------------------------------------|---------------------------|--------------------------|--------------------------|
| TEAEs | 107<br>(50.0)        | 726<br>(55.4)         | 416<br>(55.9)                             | 417<br>(53.5)                             | 741<br>(53.7)             | 68<br>(63.0)             | 24<br>(68.6)             |
| SAEs  | 2<br>(0.9)           | 26<br>(2.0)           | 11<br>(1.5)                               | 17<br>(2.2)                               | 26<br>(1.9)               | 2<br>(1.9)               | 0                        |

\*Other races = Asian, American Indian, Native Hawaiian, Multiple, Other, or Not Reported

Source: Reviewer analysis of ISS ADSL and ADAE datasets, OE pool, exposed to 100 mg and 300 mg doses only

**Reviewer's comment: Overall, there were no significant difference in rates of AEs or SAEs by subgroup analysis of race, age, or sex. The slightly higher incidence of TEAEs among black patients is likely not significant given the small numbers of black patients enrolled in the clinical studies. The rates of SAEs did not differ by subgroup analysis in the OE population.**

## 8.7. Specific Safety Studies/Clinical Trials

No dedicated safety studies were performed for this clinical development program.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

There were no formal studies done to assess carcinogenicity. However, there were rare reports of cancer as well as tumors during clinical development. Overall, in the overall ISS database (OE pool), there were 22 patients with reported AEs in the 'neoplasms benign, malignant, and unspecified SOC'. Within those patients, 17 were in patients on treatment and 5 in patients on placebo. The majority of these were benign tumors. On treatment, there was 1 report of breast cancer, 1 squamous cell cancer, and 1 squamous cell skin cancer. All of the other tumors were benign, and were present in one patient each, with the exception of 6 reports of uterine leiomyomas, a benign condition seen frequently in this patient population. The duration of treatment was also not of significant duration to be a possible etiology of any of these tumors.

**Reviewer's comment: The above cases of largely benign tumors do not result in a safety signal for possible carcinogenicity related to eptinezumab.**

### 8.8.2. Human Reproduction and Pregnancy

During clinical development, pregnancy and breastfeeding were exclusion criteria for participation in the clinical studies. Despite the requirements for contraception, there were 31 unintended pregnancies in the development program (see Table 62). All of the 31 pregnancies

occurred in women enrolled in the studies; there were no known pregnancies in partners of male patients. Of the 31 pregnancies, 7 occurred in patients exposed to placebo, resulting in 24 pregnancies in patients exposed to eptinezumab. Of those 24 pregnancies, 9 resulted in healthy babies (8 full-term and 1 preterm at 34 weeks), 5 resulted in elective termination, 3 in spontaneous abortion, and 7 of the pregnant women withdrew consent or were lost to follow-up.

**Reviewer's comment: Review of the unintended pregnancies during clinical development does not reveal any underlying safety signals to the mom or fetus. However, the small number of patients does not allow any reliable conclusions on safety in pregnancy. Furthermore, there is no long-term follow-up of the infants after delivery to make conclusions on potential effect on the child. Therefore, a pregnancy registry will be recommended post-marketing to gather more data and draw more significant conclusions.**

**Table 62 Pregnancy Outcomes by Study and Dose**

| Subject ID              | Treatment Arm         | Pregnancy Outcome    | Additional Details        |
|-------------------------|-----------------------|----------------------|---------------------------|
| <b>Placebo patients</b> |                       |                      |                           |
| (b) (6)                 | Placebo               | Elective termination | 7 weeks EGA               |
|                         | Placebo               | Lost to follow-up    |                           |
|                         | Placebo               | FT healthy baby      | No complications          |
|                         | Placebo               | FT healthy baby      | h/o 5 prior SAs           |
|                         | Placebo               | FT healthy baby      | No complications          |
|                         | Placebo x 1           | FT healthy baby      | No complications          |
|                         | Placebo x 2           | Pending              |                           |
| <b>Phase 1 Studies</b>  | <b>Single dose</b>    |                      |                           |
| (b) (6)                 | 100 mg                | Lost to follow-up    |                           |
|                         | 300 mg                | Elective termination | 8 weeks EGA               |
|                         | 300 mg                | Lost to follow-up    | Normal at 17 weeks        |
| <b>Study 005</b>        | <b>Single dose</b>    |                      |                           |
| (b) (6)                 | 10 mg                 | FT healthy baby      | No complications          |
|                         | 100 mg                | Lost to follow-up    | Also w/ Suicidal ideation |
|                         | 100 mg                | Withdrawn            |                           |
|                         | 300 mg                | Lost to follow-up    | Normal at 6 months check  |
|                         | 300 mg                | Elective termination | 3 weeks EGA               |
|                         | 300 mg                | Lost to follow-up    | Normal 15 week US         |
|                         | 300 mg                | Elective termination | 6-8 weeks EGA             |
| <b>Study 006</b>        | <b>Dose x # doses</b> |                      |                           |
| (b) (6)                 | 30 mg IV x 4          | FT healthy baby      | 2 prior SAs               |
|                         | 30 mg IV x 4          | Spontaneous abortion | 14 weeks EGA              |
|                         | 30 mg IV x 3          | FT healthy baby      | Prior SA and 2 ETs        |
|                         | 30 mg IV x 1          | FT healthy baby      |                           |
|                         | 100 mg IV x 2         | FT healthy baby      | No complications          |
|                         | 100 mg IV x 4         | Spontaneous abortion |                           |
|                         | 100 mg IV x 1         | Withdrew consent     |                           |

|                  |               |                      |                  |
|------------------|---------------|----------------------|------------------|
| (b) (6)          | 100 mg IV x 4 | FT healthy baby      |                  |
|                  | 300 mg IV x 4 | FT healthy baby      | No complications |
| <b>Study 011</b> |               |                      |                  |
| (b) (6)          | 300 mg IV x 2 | Elective termination |                  |
|                  | 300 mg IV x 2 | FT healthy baby      | Gestational DM   |
| <b>Study 013</b> |               |                      |                  |
| (b) (6)          | 300 mg IV x 1 | Spontaneous abortion | 4 weeks EGA      |
|                  | 300 mg IV x 4 | Preterm healthy baby | 34 weeks EGA     |
|                  | 300 mg IV x 2 | Elective termination | 6 weeks EGA      |

**EGA = estimated gestational age, ET= elective termination, SA = spontaneous abortion, FT = full-term, DM = diabetes mellitus**

Source: Reviewer-created table from ISS and provided narratives

### 8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable to this review. Patients under age 18 were excluded from all studies included in this submission. The applicant has an approved iPSP and is requesting a deferral of (b) (4), as well as a pediatric waiver for patients with (b) (4) migraine under 6 years of age, (b) (4)

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

During the pre-BLA review, a consult to the controlled-substance staff (CSS) was placed and CSS did not feel that a consult would be needed for review of the BLA for the following reasons, unless a new signal was identified during the review:

- No monoclonal antibody is scheduled under the Controlled Substance Act and there have been no instances of abuse for monoclonal antibodies as a therapeutic class that are known.
- There are no structural similarities in chemical structure between eptinezumab and known drugs of abuse.
- Eptinezumab did not appear to produce any abuse-related adverse events during clinical trial development.
- Eptinezumab is not expected to cross the blood brain barrier due to its large molecular size.
- No formal assessment of abuse potential was required by the applicant.

In accordance with the Guidance for Industry “Assessment of Abuse Potential of Drugs” the database was queried for the following abuse-related terms: euphoria and related terms, terms indicative of impaired attention, cognition, and mood, psychotic terms, and other related terms of abuse including drug tolerance, habituation, seizure, overdose. There was no signal identified

for any abuse-related potential for eptinezumab. The only terms that appeared in the pivotal studies population were dizziness and somnolence, both of which are described above and were not significantly more common on treatment when compared to placebo. Furthermore, there were no cases of overdose reported in the clinical studies. The highest dose received was 1000 mg in the Phase 2 studies with no adverse events or dose-limiting toxicities noted per the applicant.

***Reviewer's comment: A review of the prior CSS consult was thorough in its discussion of reasons why eptinezumab was not anticipated to have any evidence of abuse potential. A review of the ISS database for any TEAEs related to abuse was completed, and no new safety signals were identified. There is no indication that eptinezumab would have any abuse potential once approved.***

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

This product is not yet marketed.

### 8.9.2. Expectations on Safety in the Postmarket Setting

In the clinical trials, the treatment appears relatively safe with little evidence of any concerning safety signals, other than a risk for hypersensitivity reactions. However, it is possible that further safety issues will be identified in the postmarketing setting as the drug is used more extensively, particularly in patients that are elderly, or have increased comorbid conditions, as well as potentially more cardiovascular risk factors. Furthermore, because the treatment is administered IV it may be given to inpatients who are admitted to the hospital for various reasons but also suffering from migraines, and this potentially sicker population may introduce new safety signals. However, given the overall safety profile of the drug, there are no specific safety concerns that make it likely there will be significant issues that differ from those that were identified in the clinical development program.

In the postmarketing setting, it is also possible that the drug may also be used for treatment of difficult-to-treat migraine patients in the "acute migraine" setting, i.e., for treatment of status migranosis or transformed migraine. Further studies would be needed to study the safety of administering eptinezumab for such "acute treatment" of migraine, particularly in patients who may already be receiving treatment every 3 months for preventive treatment of migraine, or who are receiving another drug in the same class. Although such studies would be required to determine safety of combining these treatments for both acute and preventive treatment, it is reassuring that the limited Phase 2 experience with doses up to 1000 mg in the Phase 2 studies did not show any significant safety concerns.

Only a small number of patients in the development program were over 65 years of age (N = 23 in the pivotal studies), and no patients were over 75 years of age. The drug may be used in elderly patients in the postmarketing setting. This is also true of patients with cardiovascular risk factors, who were largely excluded from the clinical trials. Greater exposure in patients with increased comorbid conditions in the postmarketing setting may lead to increased safety signals not identified in the clinical studies.

### **8.9.3. Additional Safety Issues From Other Disciplines**

None.

### **8.10. Integrated Assessment of Safety**

The safety of eptinezumab has been evaluated in two large pivotal studies, as well as two large Phase 2 studies and an open-label long-term extension study. My review of the data from these studies has not revealed a clear relationship to any serious safety issues.

This review closely examines the potential safety concerns that may occur with CGRP antagonism, as well as the safety findings of other recently approved biologics which also work on the CGRP pathway, with special interest to cardiovascular, gastrointestinal, immunogenicity, hepatotoxicity, hypersensitivity, and infusion reactions. There were no serious safety signals identified. However, there were several events of hypersensitivity in patients on treatment that resulted in discontinuation from the study, interruption of drug infusion, and concern for possible anaphylaxis on one occasion. There were no serious events of hypersensitivity, such as Stevens-Johnson syndrome or toxic epidermal necrolysis, and no reactions that resulted in SAEs or were graded as severe in intensity. The single case of potential anaphylaxis did not involve respiratory or cardiovascular compromise, and was more likely a moderate-severe hypersensitivity reaction. However, there is concern that had patients not discontinued from the study after the occurrence of mild events of hypersensitivity (as dictated by the protocols), more severe reactions may have been noted with subsequent doses. Given the known risk for hypersensitivity with monoclonal antibodies and the rapid rate of infusion for this intravenously-administered product, hypersensitivity should be included as a warning in the prescribing information.

There was an imbalance with the events of suicidal ideation reported in the treatment arm compared to the placebo arm. Most of these were mild, grade 1 events, with 3 patients having suicide-related SAEs. Most of the patients were being treated for chronic migraines, and had pre-existing anxiety and depression, both of which are common comorbid conditions in patients with chronic migraine. However, the imbalance between treatment and placebo makes it worthwhile to follow in the postmarketing setting. There were also three patients who

discontinued from treatment for hypertension which was significant; however, the patients had some evidence of hypertension prior to dosing as well. Although there was no signal for hypertension in an analysis of all TEAEs, the role of eptinezumab in contributing to the increased blood pressure in these patients cannot be excluded. Therefore, it is also recommended to be followed in the postmarketing setting.

Analysis of common TEAEs did not reveal any frequent safety signals that were potentially drug-related and occurred in >2 % of the population and with a risk difference  $\geq 2\%$  from placebo, so there are no common adverse drug reactions that will be included in the label.

There is not enough data to make any definitive conclusions on the safety of eptinezumab in the setting of anti-drug antibodies. There were a number of patients who developed anti-drug antibodies on treatment, but the safety profile did not differ significantly from those without anti-drug antibodies.

Overall, the safety profile of the drug was quite good and is similar to other already approved CGRP-antagonists. However, given the relatively young age and overall good health of the patient population exposed to the drug in the clinical studies, it would not be uncommon for more safety signals to appear in the postmarket setting. Enhanced pharmacovigilance for hypertension, constipation, and suicidal ideation are all warranted.

## **9. Advisory Committee Meeting and Other External Consultations**

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None planned.

## **10. Labeling Recommendations**

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### **10.1. Prescription Drug Labeling**

The label has not been finalized at the time of this review. See final approved labeling.

## **11. Risk Evaluation and Mitigation Strategies (REMS)**

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None required. No REMS is anticipated for this product.

## **12. Postmarketing Requirements and Commitments**

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Deferred nonclinical and clinical pediatric studies required under PREA. A pregnancy registry is also under consideration for BLA 761119.

## **13. Appendices**

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### **13.1. References**

See footnotes throughout.

### **13.2. Financial Disclosure**

Clinical Review  
Emily R. Freilich, MD  
BLA 761119 VYEPTI  
Eptinezumab

**Covered Clinical Study (Name and/or Number): ALD403-006, ALD403-011**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: <u>Study ALD403-006 = 518; ALD403-011 = 738</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>3</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>2</u></p> <p>Significant payments of other sorts: <u>1</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>2</u></p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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EMILY R FREILICH  
02/20/2020 08:33:59 PM

HEATHER D FITTER  
02/21/2020 01:15:35 AM