# CLINICAL REVIEW

| | |
|---|---|
| Application Type | sBLA |
| Application Number(s) | 761089 – s31 |
| Priority or Standard | Priority |
| Submit Date(s) | February 5, 2025 |
| Received Date(s) | February 5, 2025 |
| PDUFA Goal Date | August 5, 2025 |
| Division/Office | Division of Neurology 2 |
| Reviewer Name(s) | Patricia Scripko |
| Review Completion Date | August 5, 2025 |
| Established/Proper Name | Fremanezumab |
| (Proposed) Trade Name | Ajovy |
| Applicant | Teva |
| Dosage Form(s) | subcutaneous |
| Applicant Proposed Dosing Regimen(s) | 225 mg monthly |
| Applicant Proposed Indication(s)/Population(s) | Pediatric patients with episodic migraine, aged 6-17 years weighing at least 45 kg |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) (if applicable) | Pediatric patients with episodic migraine 6-17 years of age who weigh 45 kg or more |

Table of Contents

Table of Tables

Tables:


Figures:

## Glossary

| | |
|---|---|
| AC | advisory committee |
| ADA | anti-drug antibody |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AR | adverse reaction |
| AST | aspartate aminotransferase |
| BLA | biologics license application |
| BP | blood pressure |
| 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 |
| CFR | Code of Federal Regulations |
| CM | chronic migraine |
| CMC | chemistry, manufacturing, and controls |
| CGRP | calcitonin gene-related peptide |
| CK | creatine kinase |
| 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 |
| DBTP | double-blind treatment period |
| DBPC | double-blind placebo-controlled |
| DMC | data monitoring committee |
| EBV | Epstein barr virus |
| ECG | electrocardiogram |
| EM | episodic migraine |
| eCTD | electronic common technical document |
| 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 |
| FRMP | fremanezumab |
| GCP | good clinical practice |
| GRMP | good review management practice |
| HTN | hypertension |
| ICH | International Council for Harmonization |
| ICHD-3 | International Classification of Headache Disorders, version 3 |
| IMP | Investigational medical product |
| IND | Investigational New Drug Application |
| iPSP | initial pediatric study plan |
| IRT | Interactive report technology |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| LFT | liver function test |
| LS | least squares |
| LSM | least squares mean |
| LSMD | least squares mean difference |
| MAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| MMD | monthly migraine day |
| 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 |
| OL | open label |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PedMIDAS | pediatric migraine disability assessment |
| PedsQL | pediatric quality of life inventory TM |
| 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 |
| PSUR | Periodic Safety Update report |
| PT | preferred term |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SD | standard deviation |
| SE | standard error |
| SGE | special government employee |
| SOC | system organ class |
| SPA | special protocol assessment |
| TEAE | treatment emergent adverse event |
| WK | week |

Clinical Review
Patricia Scripko
sBLA 761089-31
Fremanezumab

# 1. Executive Summary

## 1.1. Product Introduction

Fremanezumab (Ajovy) is a monoclonal antibody (mAb) that binds to the calcitonin gene-related peptide (CGRP) receptor ligand, which is implicated in the pathophysiology of migraine. Fremenazumab was approved for the preventive treatment of migraine in adults in September 2018. This supplemental BLA (sBLA) is for the proposed indication of the preventive treatment of episodic migraine (EM) in pediatric patients aged 6-17 years weighing at least 45kg.

The proposed dose is 225 mg given subcutaneously (SC) once every month for patients who weigh 45kg or more, using a prefilled syringe or autoinjector. The product can be administered by a healthcare provider, patients 13 years or older, and/or caregivers with instruction.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness to support approval for the indication of preventive treatment of episodic migraine in pediatric patients aged 6-17 years based on an adequate and well-controlled study and confirmatory evidence from efficacy established for the preventive treatment of migraine in the adult population. The primary endpoint of change from baseline in mean monthly migraine days (MMD) across the 12-week double-blind treatment period (DBTP) met statistical significance, as did the three secondary endpoints of change from baseline in mean monthly headache days of at least moderate severity across the 12-week DBTP, the proportion of subjects with at least a 50% reduction in mean MMDs across the 12-week DBTP, and change from baseline in mean monthly acute medication use days across the 12-week DBTP. Chemistry manufacturing, and controls (CMC) information to support the 120 mg dose for patients who weigh less than 45 kg was not provided. Therefore, this reviewer recommends approval of fremanezumab 225 mg monthly SC for the preventive treatment of episodic migraine in pediatric patients 6-17 years of age who weigh 45kg or more.

## 1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Fremanezumab (Ajovy) is a monoclonal antibody (mAb) that binds to the calcitonin gene-related peptide (CGRP) receptor ligand. Fremanezumab was approved for the preventive treatment of migraine in adults in September 2018. The Applicant is proposing the indication of fremenazumab 225 mg given subcutaneously (SC) monthly for the preventive treatment of

episodic migraine in pediatric patients aged 6-17 years weighing at least 45 kg.

Migraine is a common neurological disease characterized by attacks of moderate to severe headache with associated hypersensitivity to environmental stimuli and a variety of symptoms such as nausea, fatigue, and cognitive impairment. Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives. For school-aged children, having migraine may result in absence from school-related activities and affect performance (1). Given its high prevalence and its severity, migraine is one of the most disabling neurologic conditions worldwide and is the most disabling neurologic condition in children and adolescents (2). There are no approved therapies for the preventive treatment of episodic migraine in pediatric patients aged 6-11 years, and only one approved product for pediatric patients 12-17 years of age, despite the high prevalence of migraine in the pediatric population.

This document reviews the efficacy and safety profile of fremanezumab in the pediatric episodic migraine population based on a pivotal efficacy trial including a 12-week double-blind, placebo-controlled (DBPC) trial and an open label (OL) safety trial for up to 9 months of treatment.

Efficacy was demonstrated by an adequate and well-controlled randomized, DBPC trial with a 12-week treatment period. In this trial, subjects had approximately 8 monthly migraine days at baseline. Fremanezumab reduced monthly migraine days (MMDs) by 1.0 day compared to placebo. Fremanezumab also reduced monthly moderate to severe headache days and acute headache medication use days each by 1.1 day compared to placebo. Finally, fremanezumab increased the odds of having at least a 50% reduction in average monthly migraine days by 2.5 times compared to placebo, with 27% of subjects in the placebo cohort compared to 47% of subjects in the fremanezumab cohort achieving at least a 50% reduction in monthly migraine days. All these endpoints were deemed clinically meaningful. Substantial evidence of effectiveness is provided by this single study with confirmatory evidence from the preventive treatment of migraine in adults.

The fremanezumab safety profile in adults includes risks of hypertension, Raynaud's phenomenon, hypersensitivity reactions and injection site reactions. The overall safety in the pediatric trials supporting this sBLA is similar to the known safety profile established for the adult migraine population.
The pediatric trials supporting safety in this sBLA include the DBPC trial as well as an open label long-term safety trial of up to 9 months. Risks observed in our review of the pediatric trials included:

- Injection site reactions, which occurred in 16% of the fremanezumab cohort compared to 13% in the placebo cohort in the controlled trial with no increase in injection site reactions observed with drug exposure duration.
- Hypersensitivity reactions (not including local injection site reactions), which occurred in approximately 5-6% of fremanezumab-treated subjects versus 1-2% placebo-treated subjects in the controlled trial. No cases of severe hypersensitivity reactions or anaphylaxis were observed and there was no increase in hypersensitivity reactions observed with drug exposure duration.

A potential risk of increased blood pressure was also observed with an outlier analysis showing an imbalance in this occurrence in fremanezumab-treated subjects compared to placebo-treated subjects, but no adverse events (AEs) of hypertension were reported in the controlled trial and no trends in mean blood pressure change by visit were observed in the fremanezumab cohort compared to the placebo cohort.

Safety and efficacy have been established for the indication of preventive treatment of episodic migraine in patients 6-17 years of age. However, the proposed indication from the Applicant is limited to those weighing 45 kg or more given the unavailability of a product-delivery device for the dose studied for subjects weighing <45 kg (120 mg).

This reviewer recommends approval of fremanezumab 225 mg SC monthly for the preventive treatment of episodic migraine in patients 6-17 years of age who weigh 45 kg or more. Because the 120 mg dose strength is not available for marketing, PMR 3485-3 is considered only partially fulfilled.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Migraine is a common, chronic, neurologic disorder that often presents in childhood with equal prevalence in males and females before puberty with a transition to increased prevalence in females compared to males beginning around early adolescence, when menarche occurs.<br>• Migraine is characterized by recurrent, moderate to severe headaches worsened with activity, and associated with nausea, vomiting, and sensitivity to external stimuli with photophobia and phonophobia.<br>• Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives. For school-aged children, having migraine may result in absence from school-related activities and affect performance.<br>• Given its prevalence and severity, migraine is the most disabling neurologic condition in school-aged children and adolescents world-wide. | Migraine is a common disorder in childhood and adolescence and can be disabling with significant impact on this population's quality of life. |
| Current Treatment Options | • There is only one FDA approved treatment option for the preventive treatment of migraine in pediatric patients, which is topiramate, approved for adolescents aged 12-17 years.<br>• There are several therapies used off-label for the preventive treatment of episodic migraine in pediatric patients, although the benefit of these therapies over placebo is unclear. | Fremanezumab would be the second approved treatment for the preventive treatment of episodic migraine in pediatric patients, and the first available to a subset of pediatric patients aged 6-11 |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | | years. |
| Benefit | • Efficacy of fremenazumb for the preventive treatment of episodic migraine in pediatric patients 6 to 17 years of age was demonstrated in a randomized, double-blind, placebo-controlled trial. The primary endpoint was the change from baseline in mean MMDs across a 12-week DBTP. There was a decrease of 2.5 MMDs from baseline in fremanezumab-treated subjects, compared to a decrease of 1.4 MMDs from baseline in placebo-treated subjects. The primary endpoint analysis was statistically significant (p=0.021) and clinically meaningful.<br>• Secondary endpoints controlled for multiplicity also demonstrated statistical significance of fremanezumab compared to placebo as follows:<br>1. mean change from baseline in monthly average number of headache days of at least moderate severity during the 12-week DBTP with fremanezumab reducing these monthly headache days by 1.1 day compared to placebo<br>2. proportion of subjects reaching at least 50% reduction in the monthly average number of migraine days during the 12-week DBTP with fremanezumab increasing the odds of having at least a 50% reduction in MMDs by 2.5 fold compared to placebo, with 27% in the placebo cohort compared to 47% in the fremanezumab cohort achieving at | Fremanezumab is effective for the preventive treatment of episodic migraine in patients aged 6-17 years weighing at least 45kg based on a single, adequate and well-controlled trial. Subjects weighing 45 kg or more received 225 mg monthly, while those weighing less than 45 kg received 120 mg monthly.<br><br>Compared to placebo-treated subjects, fremanezumab-treated subjects are likely to experience a greater decrease in mean |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | least a 50% reduction in monthly migraine days.<br>3. mean change from baseline in the monthly average number of days of use of acute headache medications during the 12-week DBTP with fremanezumab reducing monthly acute headache medication use days by 1.1 days compared to placebo | MMDs, monthly average headache days of at least moderate severity, monthly average acute headache medication use days, as well as be more likely to experience at least a 50% reduction in MMDs.<br><br>The pediatric episodic migraine indication will be limited by weight since the 120 mg dose preparation is not available for marketing. |
| Risk and Risk Management | • The fremanezumab safety database includes a 12-week DBPC trial with an optional open-label safety study with up to 9months of additional treatment.<br>• The fremanezumab safety profile in adults includes risks of hypertension, Raynaud's phenomenon, hypersensitivity reactions and injection site reactions.<br>• In pediatric subjects 6-17 years of age, the overall risk of having at least one AE in the placebo-controlled trial was 55% for fremanezumab-treated subjects and 49% for placebo-treated subjects. Adverse drug reactions included injection site reactions (16% | Overall, the safety profile in pediatrics appears acceptable and similar to the previous findings in the pivotal adult trials and postmarket safety experience in adults. No new safety signals were observed in the |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | in fremanezumab cohort and 13% in placebo cohort).There was no increase in injection site reactions observed with drug exposure duration across studies.<br>• There is a Warning and Precaution in the current label for hypersensitivity. Hypersensitivity reactions were also observed in the pediatric trials, with approximately 5-6% of subjects experiencing a possible hypersensitivity reaction in the fremanezumab cohort compared to approximately 1-2% in the placebo cohort in the controlled trial, and approximately 3% of subjects experiencing a possible hypersensitivity reaction in the open label trial. No cases of severe hypersensitivity reactions or anaphylaxis were observed and there was no increase in hypersensitivity reactions observed with drug exposure duration.<br>• There is a Warning and Precaution in the current label for hypertension. In the pediatric controlled trial, outlier analyses for blood pressure effects suggested a risk of elevated blood pressure with use of fremanezumab. No treatment emergent adverse events of hypertension or overall patterns or trends in mean blood pressure changes by visit were observed in the fremanezumab cohort compared to the placebo cohort in the controlled trial. | pediatric population. |

## 1.4. Patient Experience Data

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

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | |
| | | ☒ | Patient reported outcome (PRO)<br>Daily Headache Diary<br>pedMIDAS questionnaire (Pediatric Migraine Disability Assessment)<br>pedQL (Pediatric Quality of Life Inventory) | Section 6.1 |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Migraine is a common, chronic neurological disease that often phenotypically presents in childhood or adolescence. It is a primary headache disorder characterized in part by recurrent attacks of headache that are typically moderate to severe in intensity. Migraine is classified as episodic or chronic migraine based on frequency of attacks. Episodic migraine (EM) refers to migraine in individuals with headaches on fewer than 15 days per month. Chronic migraine (CM) refers to migraine in individuals with headaches on 15 or more days per month for at least 3 months with headaches having features of migraine on at least 8 days per month. Episodic migraine is more common than chronic migraine, but patients may experience both during their lifetime.

The attacks of migraine tend to involve unilateral, throbbing headaches, worsened with movement, and associated with symptoms such as nausea, vomiting, sensitivity to external sensory stimuli manifesting as phonophobia, photophobia, and osmophobia, and often involving cutaneous allodynia. Patients experiencing an attack may also experience cognitive effects, such as brain fog, mood changes, including irritability, and general fatigue. Approximately one-third of patients with migraine have aura (3). A typical migraine headache lasts longer than 2 hours in patients less than 18 years of age, as opposed to at least 4 hours in adults, and is more likely to be bilateral than in the adult population. An adult pattern of migraine is often established in late adolescence.

In large U.S. population-based studies of adolescents and adults, the one-year prevalence of migraine is approximately 17-18% in females, 6-7% in males, and 12% overall (4, 5). An increased frequency in females compared to males begins around early adolescence, when menarche occurs, and continues through adulthood, with prevalence in both sexes being estimated near 5% at age 10, then increasing in females by late adolescence/early adulthood to near 20% (6).

Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives. For school-aged children, having migraine may result in absence from school-related activities and affect performance (1). Given its high prevalence and its severity, migraine is the most disabling neurologic condition is children and adolescents aged 5-19 years (2).

## 2.2. Analysis of Current Treatment Options

There are several off-label treatments offered to pediatric migraine patients for preventive

therapy, but only one recommended in labeling in the United States: topiramate, which was approved in 2014 for the indication of the prophylaxis of migraine headache in adolescents 12 through 17 years of age. While topiramate is approved for preventive treatment of migraine in this pediatric population, the pivotal pediatric efficacy study only enrolled subjects with episodic migraine. This approval in pediatrics followed the approval of topiramate in adults with migraine. At the time of approval in the adult population (2004), the distinction between episodic and chronic migraine was not yet made in labeling, as the introduction of chronic migraine in the international classification of headache disorders was not introduced until the second edition, which was in 2004.

The American Academy of Neurology with the American Headache society published a guideline in 2019 summarizing the evidence for preventive treatments in pediatric migraine (7). In this guideline, amitriptyline with cognitive behavioral therapy was the only treatment listed as having high confidence of a benefit over placebo. This guideline was written after both the approval of topiramate for pediatric migraine in ages 12-17 years, and after the findings from the Childhood and Adolescent Migraine Prevention Study (detailed below) were published. Topiramate and cinnarizine were listed as being probably more likely than placebo to be effective. Propranolol was listed as possibly more effective than placebo. Treatments commonly used but noted to have insufficient evidence for efficacy included: divalproex, amitriptyline (alone), flunarizine, nimodipine and onabotulinum toxin A.

The Childhood and Adolescent Migraine Prevention Study (CHAMP) was designed to investigate the efficacy of what was considered standard of care for the preventive treatment of migraine (either amitriptyline or topiramate) in pediatric subjects aged 8-17 years compared to placebo (8). The study was stopped early due to futility, as there was no difference in the primary endpoint of a 50% reduction in migraine frequency between the active treatment arms and placebo. Further, adverse events were higher in the active treatment arms. A previous study by the same investigators found the addition of cognitive behavioral therapy to amitriptyline may be beneficial (9).

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

| Product (s) Name | Relevant Indication | Year of Approval | Route and Frequency of Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments (e.g., subpopulation not addressed |
|---|---|---|---|---|---|---|
| FDA Approved Treatments [Combine by Pharmacologic Class, if relevant] | | | | | | |
| topiramate | Preventive treatment of migraine in patients 12 | 2014 | oral | -1.3 mean monthly migraine days in randomized, | Weight loss, paresthesias, cognitive effects/somnolence, | Not approved for under 12 years of age |

| | | | | | | |
|---|---|---|---|---|---|---|
| | years of age and older | | | double-blind, placebo-controlled trials<br><br>Higher percentage of reduction in monthly attack rate for higher dose (100mg) | dizziness, metabolic acidosis | |

# 3. Regulatory Background

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

Fremanezumab was approved in September 2018 for the preventive treatment of migraine in adults at two doses: 225 mg subcutaneous monthly or 675 mg subcutaneous quarterly.

Per section 11 of the most recent Development Safety Update Report (DSUR, August 2023-August 2024), there have been no postmarketing experiences resulting in changes or new safety concerns. Since August 2024, however, there have been labeling changes under Warnings and Precautions to add hypertension and Raynaud's phenomenon (March 21, 2025).

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 106533 was opened on October 2009 for fremanezumab for the preventive treatment of migraine in adults. The "May Proceed" notification was issued on July 2012. The product was approved on September 2018, for the preventive treatment of migraine in adults at two doses: 225 mg SC monthly and 675 mg SC quarterly.

An initial pediatric study plan (iPSP) was submitted under IND 106533. An Agreed iPSP letter was issued on June 2017. The Agreed iPSP included a plan for a waiver for pediatric studies for those 0-5 years of age, and a plan to conduct studies to evaluate the safety and efficacy of fremanezumab for the preventive treatment of episodic migraine in pediatric subjects 6-17 years of age, and the preventive treatment of chronic migraine in subjects 6-17 years of age.

At the time of approval of BLA 761089, the Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) were issued, including PMR 3485-1 for a juvenile animal toxicology study, PMR 3485-2 for a pharmacokinetic (PK) study in ages 6-11 years of age, as well as PMR 3485-3 and PMR 3485-4 to study the preventive treatment in pediatrics for episodic and chronic

migraine, respectively.

Studies 30083 and 30084 were designed to fulfill PMR 3485-3. Study 30083 was conducted under a Special Protocol Assessment (SPA) Agreement. In addition, a Written Request was issued on September 2019, which included the studies listed in the Approval letter as PREA PMRs.

The Applicant indicated their plan to submit this sBLA for the efficacy in episodic migraine in pediatric patients in an emailed correspondence July 7, 2024, but did not request a pre-BLA meeting. This application was submitted for the indication of preventive treatment of episodic migraine in subjects weighing at least 45kg based on data from studies 30083 and 30084 which included dosing for subjects weighing less 45kg. CMC information was not submitted to support dosing for those weighing less than 45kg as, per the applicant, development (b) (4) for patients <45kg is ongoing. Further, this application did not include the CM efficacy study (study 30082), or unblinded safety data for CM subjects in studies 30082 and 30084.

### 3.3. Foreign Regulatory Actions and Marketing History

Fremenazumab was approved in the European Union March 2019 for the prophylaxis of migraine in adults who have at least 4 migraine days per month. As of the end of the last annual reporting period (September 2024), products with the active substance from fremanezumab are registered by the applicant in 55 countries world-wide.

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

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

Site inspection results were consistent with the study being conducted adequately with data generated by the inspected sites appearing acceptable in support of the respective indication. See review by Cara Alfaro for further details.

### 4.2. Product Quality

No additional product quality information was submitted with this application since the Applicant plans to use the marketed product in the pediatric population age 6 to 17 years and who weigh 45 kg and more.

### 4.3. Clinical Microbiology

Not applicable.

### 4.4. Nonclinical Pharmacology/Toxicology

See nonclinical review by Dr. Elizabeth Khoury.

### 4.5. Clinical Pharmacology

Support for weight-based dosing for pediatrics was deemed adequate. See Clinical Pharmacology review by Dr. Ping Du for further details.

### 4.6. Devices and Companion Diagnostic Issues

Both the prefilled syringe and autoinjector for the 225 mg dose are commercially available and will be used for the pediatric population 6-17 years of age weighing 45 kg or more.

### 4.7. Consumer Study Reviews

Not applicable.

## 5. Sources of Clinical Data and Review Strategy

### 5.1. Table of Clinical Studies

Table 2: Listing of Relevant Clinical Trials

| 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 |
|---|---|---|---|---|---|---|---|---|
| | | *Controlled Studies to Support Efficacy and Safety* | | | | | | |
| 30083 | NCT 04458857 | Double-blind, placebo-controlled trial | 120mg SC (<45kg)<br><br>225mg SC (≥45kg)<br><br>Vs.<br>placebo | Primary endpoint: Change from baseline in monthly migraine days over 12wk treatment period<br><br>Secondary endpoints: Mean change from baseline in monthly headache days over 12 wk period<br><br>Proportion reaching at least 50% reduction in monthly average number of migraine days over 12wk period<br><br>Mean change from baseline in monthly average number of days of acute medication use over | 28 day baseline period<br><br>12-week treatment period (including 4 week follow up after the last dose of IMP)<br><br>Optional enrollment into study 30084 | 235<br>(<45kg, n=36)<br>(≥45kg, n=87) | Subjects with episodic migraine 6-17 years of age<br><br>27% 6-11 years of age | 74 sites<br><br>Canada, Finland, Germany, Israel, Italy, Netherlands, Poland, Spain, USA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 12wk period<br><br>Mean change from baseline in migraine related disability score, measured by PedMIDAS, at 12 wks<br><br>Mean change from baseline in quality of life as measured by PedsQL measured at 12wks | | | | |
| | | *Studies to Support Safety* | | | | | | |
| 30084 | NCT 04530110 | Open label, long-term safety trial | 120mg SC (<45kg)<br><br>225mg SC ($\geq$45kg) | Primary endpoints include safety endpoints of:<br><br>Adverse events throughout trial<br><br>Changes from baseline in clinical laboratory results, height and weight<br><br>Abnormal electrocardiogram findings | 9 months of OL treatment<br><br>5-month follow-up after last dose of IMP | 427<br>(220- EM)<br>(207- CM) | Subjects with episodic migraine 6-17 years of age and subjects with chronic migraine 12-17 years of age | 65 sites Canada, Finland, Germany, Israel, Italy, Netherlands, Poland, Spain, USA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Changes from baseline in vital signs<br><br>Abnormal physical examination findings<br><br>Suicidal ideation and behaviour | | | | |
| | | *Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)* | | | | | | |
| 10141 | No NCT # available | Open-label, single-dose, PK trial | 75mg SC | PK endpoints | Single dose | 15 | Healthy subjects 6-11 years of age (6 weighing <30kg) | 5 sites USA |

### 5.2. Review Strategy

This application included one efficacy study in EM (study 30083) and one long term safety study (study 30084) including subjects with EM and CM. Because unblinded data from the CM studies were not submitted with this application, the unblinded safety analyses from the EM population is the focus of the safety review. Additional safety review was performed on the following: 1. pooled datasets from the long-term safety study with both blinded data from EM subjects and unblinded data from CM subjects, and 2. safety data from study 10141 (PK study). Study 30082, the pivotal efficacy study in chronic migraine, was not submitted with this application because it was still blinded at time of submission of this application.

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

### 6.1. Study 30083: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy, Safety, and Tolerability of Subcutaneous Administration of Fremanezumab Versus Placebo for the Preventive Treatment of Episodic Migraine in Pediatric Patients 6-17 Years of Age

#### 6.1.1. Study Design

Overview and Objective

This primary objective of study 30083 was to evaluate the efficacy of fremanezumab as compared to placebo for the preventive treatment of episodic migraine (EM) in pediatric subjects 6 through 17 years of age.

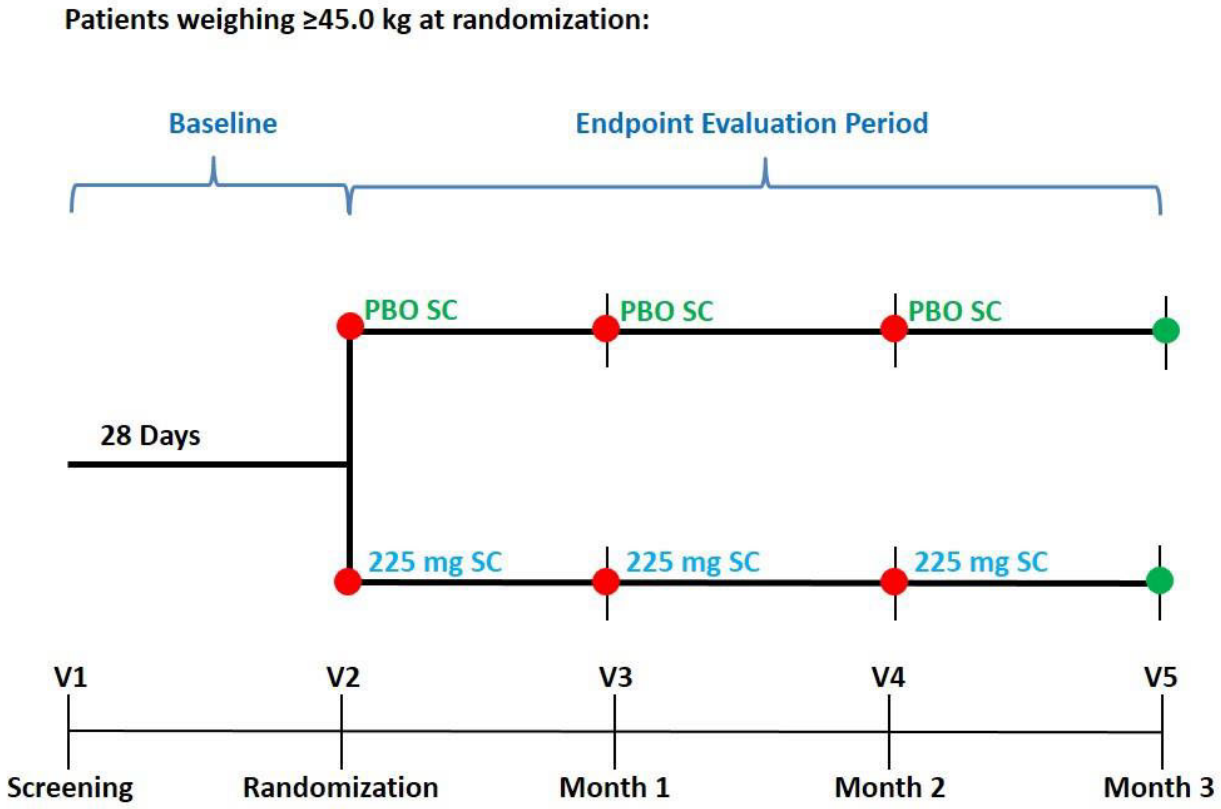
Trial Design

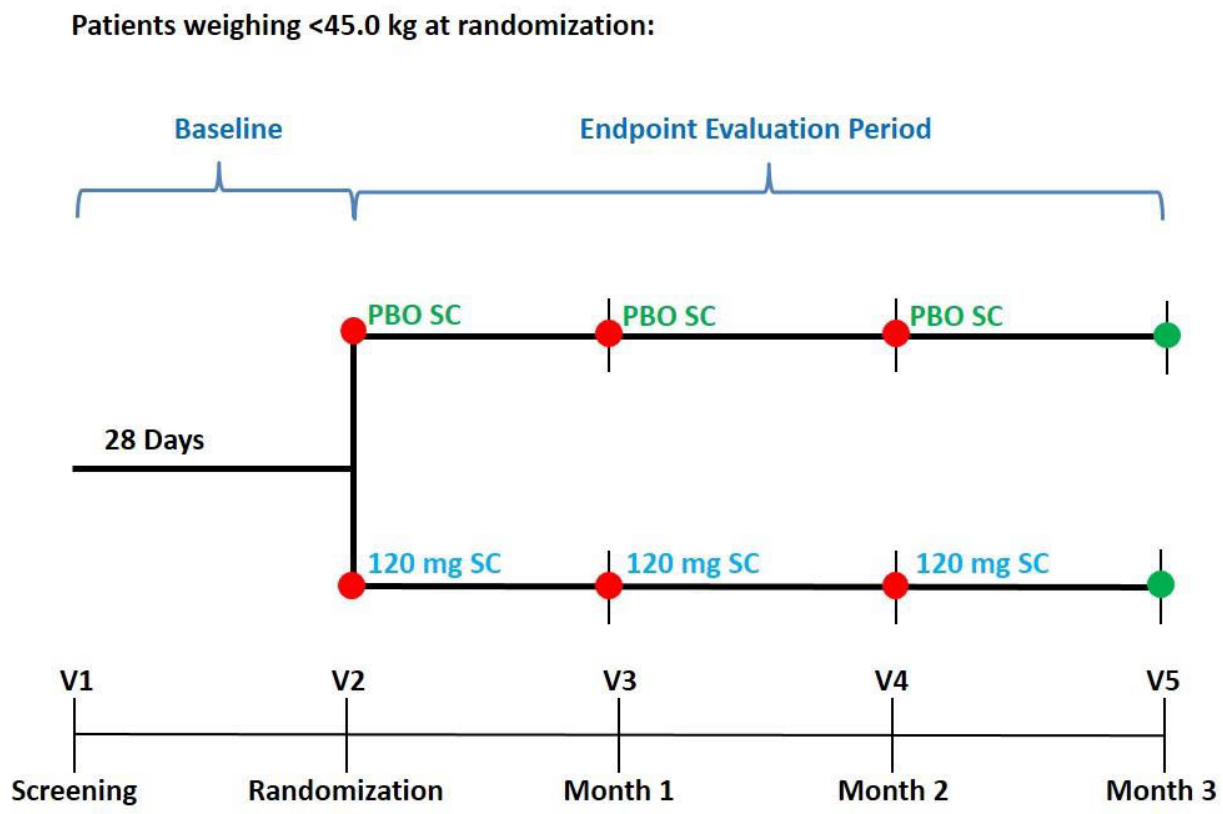
Study 30083 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of pediatric subjects 6-17 years of age with a history of episodic migraine with or without aura. The study was conducted in 74 centers across the United States, Europe, Canada, and Israel. Approximately 30% of enrolled subjects were from sites in the United States. Subjects were screened over a 4-week period and then randomized in a 1:1 fashion to receive either placebo or fremanezumab. Fremanezumab was dosed based on weight. Subjects weighing <45 kg were given 120 mg subcutaneously every month, whereas subjects weighing ≥45 kg were given 225 mg subcutaneously every month, over the 12-week treatment period. The Applicant

is requesting an indication only for the ≥45 kg cohort given the [redacted] (b) (4) lower dose of 120 mg is still in development. Efficacy findings for the full cohort will be presented, followed by efficacy findings for subgroups, including subgroups <45 kg and ≥45 kg by weight.

Basic Study Design:
Screening Period: 28 days
Treatment Period: 12 weeks
Follow-up: Subjects had an end of study visit at week 12, which was 4 weeks after the last dose of investigational medical product (IMP). Subjects then had the option to enroll in study 30084, the long-term safety trial for an additional 9 months of OL treatment, or, if they declined further treatment, a 5 month follow up visit from the last dose of IMP.

Figure 1: Study 30083: Study Flow Chart for Subjects by Weight






Source: Study 30083, Applicant's protocol, Figure 1

Key Inclusion Criteria:

- Age 6-17 years at time of randomization
- History of migraine by the International Classification of Headache Disorders -3 (ICHD-3) criteria for at least 6 months prior to screen, and a history of <15 headache days per month in each of the 3 months prior to screen
- Between 4-14 migraine days during the 28-day baseline period

  "migraine day" is defined for this purpose as a having at least 1 of the following characteristics:

  a. head pain of moderate to severe intensity lasting for 2 or more hours in duration and accompanied by either throbbing quality, predominantly unilateral location, or aggravation with normal activities

  b. headache accompanied by a migraine-associated symptoms such as photophobia,

phonophobia, nausea, or vomiting, headache preceded by aura

c. headache preceded by an aura, as described by ICHD-3 criteria

d. headache treated by nonsteroidal anti-inflammatory drug (NSAID), triptan, paracetamol, or ergot preparation.

*Reviewer comment: This definition of migraine day includes migraine and probable migraine by ICHD-3 criteria, with a shortened duration as appropriate for pediatric migraine definitions. It is a different definition than what was included in the statistical analysis plan as the operational definition for the primary efficacy analysis, which did not include probable migraine.*

- Females who are postmenarchal or at least 12 years of age and sexually active must use highly effective birth control methods for the duration of the study and for 6 months after the last dose of IMP. Males who are sexually active with female partners must use a condom for the duration of the study and for 6 months after the last administration of IMP.

- Not using migraine preventive medications prohibited during the study (see below), or using no more than 2 allowed migraine preventive medications for migraine or any medical condition (see below) if stable for at least 2 months prior to screening. Enrollment of subjects on any migraine preventive medication was limited to 30%.

<u>Key Exclusion Criteria:</u>

- Clinically significant cardiovascular, endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, or renal disease or complications of an infection, at the discretion of the investigator.

- Pregnant or breastfeeding

- Known hypersensitivity to injected proteins, including mAbs, or a history of Stevens-Johnson Syndrome or toxic epidermal necrolysis

- Use of opiates or barbituates for the treatment of migraine during the 3 months prior to screening visit

- Current or past history of hemiplegic migraine

- Use of an intervention/device for the treatment of migraine or in the head or neck for

any condition during the 2 months prior to the day of the screening visit

Dose Selection:

Aside from effects of weight, no anticipated differences in the pharmacokinetic profile of fremanezumab between adults and children were expected due to physiologic differences. The applicant chose a weight cutoff of 45 kg using a conservative approach by considering 40 kg the typical threshold for adult-dosing of mAbs. The approved adult dose of 225mg SC monthly was therefore chosen for pediatric subjects weighing ≥45 kg. The dose of 120mg SC monthly for subjects weighing <45 kg was based on modeling with additional data from Study 10141, a Phase 1 pharmacokinetic study in subjects 6-11 years of age.

Study Treatment/Blinding:

This was a double-blind, placebo-controlled trial. IMP was administered as 225 mg SC (≥45 kg), 120 mg SC (<45 kg), or matching placebo.

Assignment to Treatment:

Subjects were randomized 1:1 to active treatment: placebo with randomization stratified by sex, puberty status, preventive medication, and country. Active product and placebo kits for each dose were managed by interactive response technology (IRT) and kept refrigerated on site.

Dose Modification or Discontinuation:

The dose of IMP was fixed and could not be adjusted.

Administrative Structure:

There was no data monitoring committee.

Procedures and Schedule

Table 2: Study 30083 Summary of Schedule of Study Procedures and Assessments

| | Screening | Double-Blind Treatment Phase (12 weeks) | | |
|---|---|---|---|---|
| **Assessment** | | Day 1 | Weeks 4 &8 | Week 12 |
| Physical exam/Vital signs | x | x | x | x |

| | | | | |
|---|---|---|---|---|
| Labs/LFTs | x | | x (wk 4) | x |
| Pregnancy testing | x | x | x | x |
| ECG | x | x | x | x |
| Puberty status assessment | | x | | x |
| AE review | x | x | x | x |
| Columbia-Suicide Severity Rating Scale for suicidality tracking | x | x | x | x |
| Electronic headache diary instructions/training | x | | | |
| PedMIDAS, PedsQL Questionnaires | | x | | x |

Source: Study 30083 Clinical Study Report (CSR)

Dietary Restrictions:

N/A

Concomitant Medications:

Use of up to 2 of the following concomitant medications for the preventive treatment of migraine was allowed in up to 30% of subjects so long as dose and regimen remained stable beginning 2 months prior to study:

- Antidepressants: amitriptyline, nortriptyline, fluoxetine, desipramine, venlafaxine, duloxetine
- Antiepileptics: topiramate, valproic acid, levetiracetam, zonisamide, gabapentin, pregabalin
- Antihistamines: cyproheptadine, pizotifen
- Beta blockers: propranolol, metoprolol, nadolol, timolol
- Calcium-channel blockers: flunarizine, verapamil, nimodipine
- Onabotulinumtoxin A or B

Regular use of opiates, barbituates, and lamotrigine were prohibited during the study.

Live vaccines were disallowed within the 12-week period prior to screening.

Treatment Compliance:

The IMP was administered by qualified staff at trial centers with all injections recorded.

Rescue Medication:

Medications taken on an as needed basis, including rescue medications for the acute treatment of migraine, were allowed during the study.

Subject Completion, Discontinuation, or Withdrawal:

Subjects were free to voluntarily withdraw from the study or discontinue the IMP at any time. Subjects were withdrawn if any of the following occurred:

1. Consented to withdrawal for any reason;
2. Developed an illness that would interfere with his/her continued participation;
3. Was noncompliant with study procedures and assessments or administration of IMPs;
4. Took prohibited concomitant medications chronically;
5. Had a confirmed pregnancy;
6. Withdrawal requested by the applicant;
7. Experienced an adverse event or other medical condition that, in the opinion of the investigator, indicates that continued participation is not in the best interest of the subject;
8. Demonstrated suicidal ideation or behavior.

Study Endpoints

Primary endpoint:

- mean change from baseline (28-day baseline period) in the monthly average number of migraine days during the 12-week period after the first dose of study drug

*Reviewer comment: This is a recommended primary endpoint for establishing efficacy in the preventive treatment of migraine in Guidance for Industry, Migraine: Developing Drugs for Preventive Treatment, June 2023 (10).*

Secondary endpoints (in hierarchical order):

- mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug
- mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug

  *Reviewer comment: These first three secondary endpoints were considered clinically meaningful.*

- mean change from baseline (day 1) in migraine-related disability score, as measured by the PedMIDAS questionnaire, at 12 weeks after administration of the first dose of study drug
- mean change from baseline (day 1) in quality of life, as measured by the PedsQL, at 12 weeks after administration of the first dose of study drug
  *Reviewer comment: The clinical meaningfulness of the secondary endpoints involving the PedMIDAS and PedsQL are unclear.*
- proportion of patients developing ADAs throughout the study. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive patients allows.

Statistical Analysis Plan

The statistical analysis plan (SAP) was amended 4 times (see statistical review). The most recent review of the SAP was May 22, 2024, after the fourth amendment was submitted April 2024.

Analysis Populations:
The intent-to-treat (ITT) analysis set included all randomized subjects.

The safety analysis set included all randomized subjects who received at least 1 dose of IMP.

The full analysis set (FAS) included all subjects in the ITT who received at least 1 dose of study drug and had at least 10 days of diary entries postbaseline for efficacy assessments on the primary endpoint.

The per-protocol analysis set included all subjects in the FAS who completed with study without any important deviations.

Sample Size Estimation:
The planned sample size was 220 subjects (110 evaluable subjects completing the study per treatment group) based on an assumption of a treatment difference of 1.8 days (reduction in monthly average number of migraine days) and a common SD of 4.31 to provide at least 87% with an alpha level of 0.05.

Hypothesis Testing:
The principal analysis of the primary endpoint used an analysis of covariance method. This model included treatment, sex, puberty status, region, baseline weight category, and preventive medication use at baseline as fixed effects with baseline number of migraine days as a covariate. 95% confidence intervals were constructed for the least squares mean differences between the fremanezumab group and placebo group.

Migraine Day Definition:
There were multiple definitions provided for "migraine day," as used to perform the efficacy analysis, with different definitions provided by study protocol, section 6.2 of the SAP and Appendix B in the SAP. In an IR sent by the Division on March 4, 2025, clarification of the definition used was requested. After correspondence, it was ultimately confirmed by the Applicant the efficacy analysis used the definition of migraine day as defined in Appendix B of the SAP, which excluded probable migraine.

Headache Day Definition:
A headache day of at least moderate severity was defined as a calendar day where the subject reported a day with headache pain lasting at least 2 hours of at least moderate severity or a day where the subject used acute medication to treat a headache of any severity or duration.

Missing Data:
Efficacy variables based on diary data were prorated to a monthly rate. Sensitivity analyses for the primary efficacy endpoint were conducted using a multiple imputation method for missing data.

Multiplicity:
A hierarchical testing procedure (fixed-sequence) was used to control the Type I error rate. If the resulting 2-sided p-value from the 1st comparison was less than or equal to 0.05, then the next comparison of interest was interpreted at the alpha level of 0.05. This processed continued until a resulting 2-sided p-value for a comparison (secondary endpoint) was >0.05.

Subgroup Analysis:
Planned subgroup analyses were conducted for the primary efficacy variable on subjects by region (United States vs other), sex, weight (<45 kg vs ≥45 kg) age cohort (6-11 vs 12-17),

puberty status (Tanner stage 1-5), race (Caucasian vs non-Caucasian), and use of concomitant medications (Y/N) for the preventive treatment of migraine.

Interim Analysis:
An interim analysis with blinded sample size re-estimation was conducted by evaluating the pooled variability (SD) of the primary endpoint using the total number of participants (regardless of the treatment assignment) once 50% (±10%) of participants had completed at least 3 months of treatment or had withdrawn from the trial early.

Protocol Amendments

There were 10 protocol amendments, including 9 with notable changes. They are listed below.

May 21, 2024: A goal of 25% of enrollees was listed for subjects in the 6-11 year cohort (from the proposed 20% in September 2023)
*Reviewer comment: The Division issued a SPA agreement letter with this change in June 2024.*

September 24, 2023: The sample size was reduced from 288 to 230 randomized subjects with a goal of 20% of subjects in the 6-11 year age cohort (from 30%).
*Reviewer comment: The Division did not agree with the reduction in the cohort 6-11 years of age, but did agree to the reduction in sample size to 230 randomized subjects based on power calculations.*

December 9, 2021: This amendment clarified potential sample size changes resulting from the interim analysis noting if the pooled variability of the primary endpoint (SD) was <4.8, then there would be no change in enrollment, if the pooled SD was >5.2, then the sample size would increase to approximately 400 subjects, and if the pooled SD was between 4.8 and 5.2, then the sample size would increase to approximately 340 subjects. This amendment also changed inclusion criteria from 6-14 migraine days a month during the baseline period to 4-14 migraine days a month during the baseline period. Eligibility criteria were also changed to specify subjects with hemiplegic migraine would be excluded. Concomitant therapies were changed to allow up to 30% of enrolled subjects (rather than 20%) to be a concomitant medication for the preventive treatment of migraine. Finally, subgroup analyses for sex, region, and use of preventive migraine medications were added.

August 20, 2020: Updates to provide guidance for remote assessments during the COVID-19 pandemic were provided in this amendment.
*Reviewer note: Enrollment began after this amendment.*

June 27, 2020: Eligibility criteria were updated to exclude subjects on lamotrigine (due to risk of

Stevens-Johnson Syndrome). Opiates and barbituates were also specified as prohibited medications. Withdrawal criteria were updated to include subjects who experience a severe hypersensitivity reaction or anaphylaxis. Removed sentence stating study personnel would be unblinded to the results of the interim analysis and clarified that any sample size re-estimation based on the interim analysis would be blinded. Added that a supplementary analysis using the ITT population for the primary efficacy endpoint would be conducted.

April 20, 2020: Eligibility criteria were updated to specify subjects with a history of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome, as well as those with Hepatitis B or C were excluded.

February 3, 2020: Onabotulinum toxin was added as a preventive migraine medication allowed during the study

December 5, 2019: Updated protocol with dosing information and findings from the Phase 1 PK study (10141)

June 21, 2019: Updated eligibility criteria to exclude subjects who used an intervention or device for the treatment of migraine during the 2 months prior to screen. Updated injection site assessments to be performed after administration as well as before subjects leave the investigational site.

#### 6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states the study was conducted in compliance with the ICH Guideline for Good Clinical Practice E6, as well as all applicable national and local laws and regulations, including the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70).

Financial Disclosure

There were no investigators with disclosable financial interests. See Appendix 13.2

Patient Disposition:

*Enrolled:* 411
*Randomized*: 237
*Randomized data set (ITT*): 235

*Received at least 1 dose of IMP (SAS):* 235
*Efficacy analysis set (FAS, evaluable):* 234
*Per-protocol analysis set (PP):* 184
*Completed the DBTP:* 225 (95% in placebo cohort, 92% in 120 mg fremanezumab cohort, 99% in 225 mg fremanezumab cohort, and 97% in all fremanezumab cohort)
*Rolled over into long-term study*: 220 (102 in placebo, 33 in 120 mg fremanazumab, 85 in 225 mg fremanezumab)

Of those who were randomized but did not complete the trial:

- -in the placebo cohort, 2 withdrew voluntarily, and 4 were lost to follow up
- -in the 120 mg fremanezumab cohort, 1 was withdrawn due to an adverse event, 1 was withdrawn due to noncompliance with trial procedures, and 1 was lost to follow up
- -in the 225 mg fremanezumab cohort, 1 was withdrawn voluntarily by a parent/guardian

Two subjects who were randomized and not included in the randomized ITT dataset included 1 subject assigned to 225 mg fremanezumab and 1 subject assigned to placebo at a site due to good clinical practice non-compliance of the site.

The only subject who was randomized and included in the ITT dataset but excluded from the full analysis set was excluded due to having less than 10 days of post-baseline efficacy data, which was a pre-specified reason for not being included in the efficacy analysis set.

Protocol Violations/Deviations

Important protocol deviations were comparable across treatment groups. The most common deviations were related to procedure compliance. Important protocol deviations were grouped by the Applicant as summarized in the table below.

Table 3: Study 30083: Protocol Deviations (ITT set)

| Deviation | Placebo (n=112) | Fremanezumab 120mg (n=36) | Fremanezumab 225mg (N=87) | All Fremanezumab (N=123) | Total (N=235) |
|---|---|---|---|---|---|
| Subjects with at least 1 deviation | 60 (54) | 18 (50) | 49 (56) | 67 (54) | 127 (54) |
| Informed consent | 12 (11) | 8 (22) | 11 (13) | 19 (15) | 31 (13) |
| Eligibility criteria | 11 (10) | 3 (8) | 9 (10) | 12 (10) | 23 (10) |
| Trial drug | 3 (3) | 2 (6) | 2 (2) | 4 (3) | 7 (3) |

| | | | | | |
|---|---|---|---|---|---|
| Lab/endpoint data | 8 (7) | 3 (8) | 5 (6) | 8 (7) | 16 (7) |
| Procedure compliance | 29 (26) | 11 (31) | 22 (25) | 33 (27) | 62 (26) |
| Visit/procedure window | 1 (<1) | 1 (3) | 0 | 1 (<1) | 2 (<1) |
| Prohibited co-medication | 3 (3) | 2 (6) | 2 (2) | 4 (3) | 7 (3) |
| Other* | 18 (16) | 4 (11) | 18 (21) | 22 (18) | 40 (17) |

Source: Study 30083 CSR, adapted from Table 8 by reviewer
*Other protocol deviations included failure to report SAE within required time window, incorrect stratification by preventive medication at baseline (including for supplements used for the treatment of migraine), and pregnancy test not performed or documented.

Within the above table are two subjects who were incorrectly dosed with fremanezumab 225 mg rather than 120 mg at one visit. For data analysis, both subjects were allocated to the dose they should have received throughout the trial (120 mg).

There were no important protocol deviations that led to withdrawal of a subject from the trial.

*Reviewer comment: Sensitivity analyses including using the PP set and stratification factors using the FAS are included below in this section.*

Table of Demographic Characteristics

The average age of subjects was 13.3 years. No baseline imbalances were noted between treatment groups by demographic characteristics (Error! Reference source not found.) or baseline historical migraine characteristics (Error! Reference source not found.).

Table 4: Study 30083: Demographic Characteristics of All Randomized Subjects (ITT set)

| Demographic Parameters | Control Group (N=112) n (%) | Treatment Group | | | |
|---|---|---|---|---|---|
| | | Fremanezumab 120mg (N= 36) n (%) | Fremanezumab 225mg (N= 87) n (%) | All Fremanezumab (N=123) | Total (N=235) n (%) |
| Sex | | | | | |
| Male | 48 (43) | 20 (56) | 37 (43) | 57 (46) | 105 (45) |
| Female | 64 (57) | 16 (44) | 50 (57) | 66 (54) | 130 (55) |
| Age (years) | | | | | |
| Mean | 13.4 | 11.0 | 14.2 | 13.3 | 13.4 |
| Median | 14.0 | 11.0 | 15.0 | 13.0 | 13.0 |
| Min, max | 6, 17 | 6, 17 | 6, 17 | 6, 17 | 6, 17 |
| Age Group | | | | | |
| 6-11 years | 32 (29) | 19 (53) | 13 (15) | 32 (26) | 64 (27) |
| 12-17 years | 80 (71) | 17 (47) | 74 (85) | 91 (74) | 171 (73) |
| Weight (kg) | | | | | |
| <45kg | 33 (29) | 36 (100) | 0 | 36 (29) | 69 (29) |
| >=45kg | 79 (71) | 0 | 87 (100) | 87 (71) | 166 (71) |
| Mean | 52.1 | 35.3 | 59.7 | 52.6 | 52.3 |
| Median | 50.9 | 36.4 | 56.0 | 51.3 | 51.0 |
| Min, max | 19.8, 88.0 | 20.5, 44.6 | 45.0, 102.6 | 20.5, 102.6 | 19.8, 102.6 |
| Puberty Status | | | | | |
| Stage 1 | 21 (19) | 18 (50) | 7 (8) | 25 (20) | 46 (20) |
| Stage 2 | 18 (16) | 8 (22) | 6 (7) | 14 (11) | 32 (14) |
| Stage 3 | 11 (10) | 6 (17) | 13 (15) | 19 (15) | 30 (13) |
| Stage 4 | 32 (29) | 3 (8) | 30 (34) | 33 (27) | 65 (28) |
| Stage 5 | 30 (27) | 1 (3) | 31 (36) | 32 (26) | 62 (26) |
| Race | | | | | |
| White | 84 (75) | 28 (78) | 68 (78) | 96 (78) | 180 (77) |
| Black or African American | 4 (4) | 1 (3) | 4 (5) | 5 (4) | 9 (4) |
| Asian | 0 | 0 | 2 (2) | 2 (2) | 2 (<1) |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| Other[1] | 3 (3) | 2 (6) | 0 | 2 (2) | 5 (2) |
| Missing* | 21 (19) | 5 (14) | 13 (15) | 18 (15 | 39 (17) |

| | | | | | |
|---|---|---|---|---|---|
| Ethnicity | | | | | |
| Hispanic or Latino | 9 (8) | 4 (11) | 8 (9) | 12 (10 | 21 (9) |
| Not Hispanic or Latino | 102 (92) | 31 (86) | 75 (86) | 106 (86) | 208 (89) |
| Missing* | 1 (<1) | 1 (3) | 4 (5) | 5 (4) | 6 (3) |
| Region | | | | | |
| United States | 36 (32) | 10 (28) | 24 (28) | 34 (28) | 70 (30) |
| Rest of the World** | 76 (68) | 26 (72) | 63 (72) | 89 (72) | 165 (71) |

Sources: Study 30083 CSR, Table 15.1.2.3 and confirmed with OCS created demographic table using Analysis Studio, demographics.
*Missing data for race and ethnicity exist for subjects enrolled in certain regional sites due to the Finnish Data Protection Act
**only ~9% of subjects in the ITT analysis set were from non-USA and non-Western European sites

Table 5: Study 30083: Other Baseline Characteristics (ITT set)

| Baseline Characteristic | Placebo (N=112)* | Fremanezumab 120mg (N=36) | Fremanezumab 225mg (N=87) | All Fremanezumab (N=123) |
|---|---|---|---|---|
| Mean time since migraine diagnosis (years) | 4.4 | 3.8 | 4.7 | 4.4 |
| History of migraine with aura | 30 (27%) | 9 (25%) | 32 (37%) | 71 (30%) |
| Mean Migraine days/mo * | 7.5 | 7.6 | 7.9 | 7.8 |
| Mean Headache days of at least moderate severity/mo * | 7.9 | 8.0 | 8.3 | 8.2 |
| Mean Acute medication use days/mo * | 5.6 | 6.1 | 5.7 | 5.8 |
| Mean days with nausea or vomiting/mo * | 3.7 | 3.8 | 4.1 | 4.0 |
| Mean days with photophobia or phonophobia/mo | 5.9 | 5.5 | 5.6 | 5.6 |
| Concomitant medications for preventive treatment of migraine | 25 (22%) | 8 (22%) | 17 (20%) | 25 (20%) |
| Triptan use | 49 (44%) | 12 (33%) | 40 (46%) | 52 (42%) |

Sources: Study 30083 CSR, Tables 3 & 4 with results confirmed with ADSL dataset by reviewer and OCS using Analysis Studio, custom table tool, demographics
*These variables were based on the 28-day (1 month) baseline period. The medians for each of these was also provided, with similar numbers for medians across the treatment arms, as well.
**The ITT analysis set contained one subject in the placebo group not included in the FAS used to evaluate efficacy. This one subject's data did not notably impact the numbers provided in the table above, with most of the percentages staying the same with this subject's inclusion or exclusion in the calculation for the above characteristics

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study intervention compliance was monitored by administering IMP at research facilities. As noted under protocol deviations above, there were 2 subjects who erroneously received 225 mg of fremanezumab during one of their 3 injections, and this was ultimately treated as if the subjects received their intended (randomized) dose of 120 mg.
*Reviewer comment: Removing these two subjects from the efficacy analysis did not change the*

*primary analysis results.*

Most subjects received concomitant medications with 98% receiving concomitant medications for migraine during the trial and use of concomitant medications being comparable across treatment groups. Anti-inflammatory products and analgesics were the most commonly used therapies.

Treatment with migraine preventive medication at the time of randomization was a stratification factor for this study. Subjects were allowed to take up to 2 preventive medications for migraine so long as the dose and regimen were stable for at least 2 months prior to study entry. There were approximately 21% of subjects in the ITT analysis set and FAS taking a preventive medication at the time of randomization.

Efficacy Results – Primary Endpoint

The primary endpoint for this study was the change from baseline in the mean number of migraine days per month over the 12-week double-blind treatment period.

There was a statistically significant mean reduction in the change from baseline in the fremanezumab cohort compared to placebo (Table 6: Study 30083: Results for the Primary Endpoint (Weeks 1-12) (Full Analysis Set). The placebo-corrected treatment effect was a 1-day reduction in monthly migraine days, with a separation between fremanezumab and placebo arms beginning at month 1 (Error! Reference source not found.).

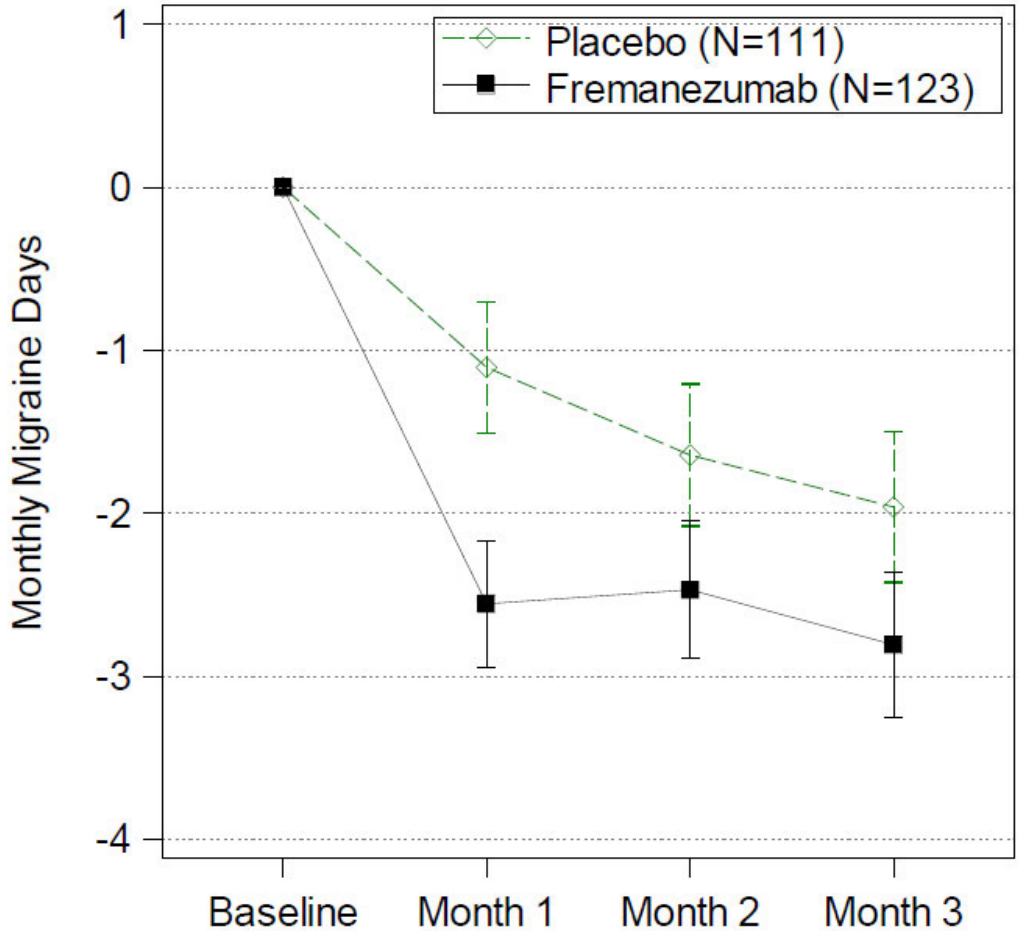
Table 6: Study 30083: Results for the Primary Endpoint (Weeks 1-12) (Full Analysis Set)

| | Placebo N=(111) | Fremanezumab 120mg (N=36) | Fremanezumab 225mg (N=87) | All Fremanezumab (N=123) |
|---|---|---|---|---|
| Baseline | | | | |
| Mean MMD (SD) | 7.5 (2.85) | 7.6 (2.92) | 7.9 (3.21) | 7.8 (3.12) |
| Change from baseline in MMD over 12 weeks (DBTP) | | | | |
| Mean | -1.7 (3.6) | -2.0 (4.70) | -3.3 (3.42) | -2.9 (3.86) |
| Median | -1.5 | -2.7 | -3.8 | -3.3 |
| Min, Max | -10.2, 11.2 | -8.6, 13.3 | -9.4, 8.5 | -9.4, 13.3 |
| Adjusted Analysis | | | | |

| | | | | |
|---|---|---|---|---|
| LS mean (SE) | -1.4 (0.39) | - | - | -2.5 (0.38) |
| 95% CI of LSM | -2.22, -0.67 | - | - | -3.22, -1.72 |
| LSMD from placebo | | - | - | -1.0 (0.44) |
| 95% CI of the difference | | - | - | -1.90, -.016 |
| Adjusted p-value | | - | - | 0.0210 |

Source: Study 30083 CSR, Tables 15.2.5 and 9, with results confirmed by statistics reviewer

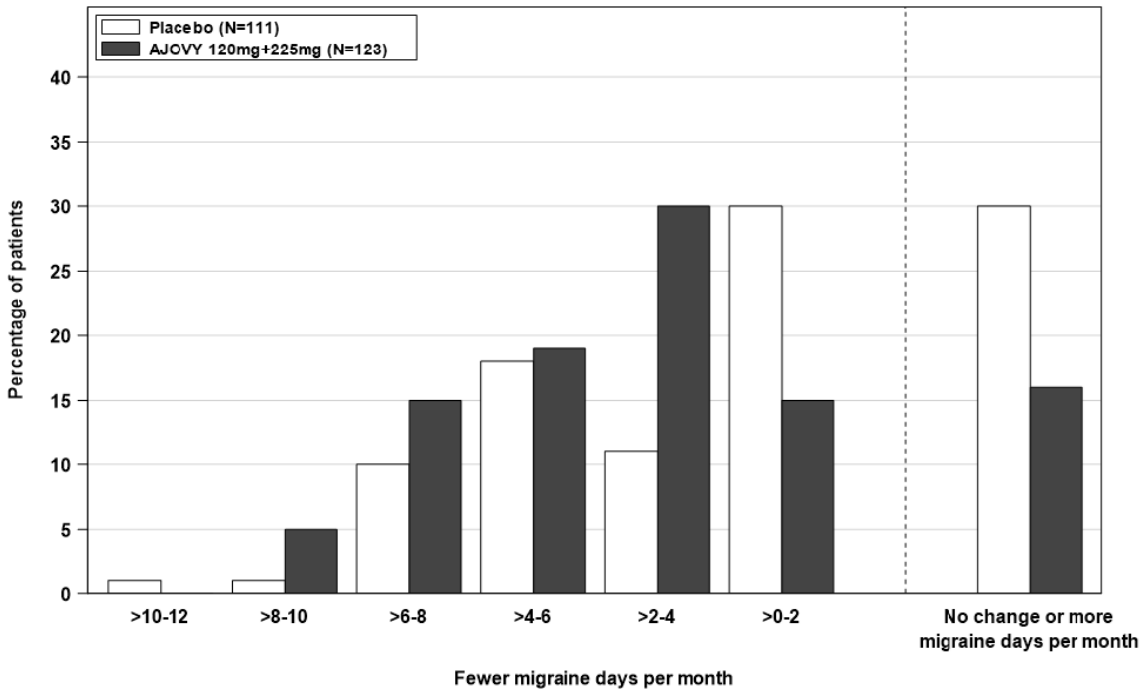
Figure 1: Study 30083: Line Plot of Primary Endpoint: Change from Baseline in Monthly Average Migraine Days During 12-Week DBTP (Full Analysis Set)

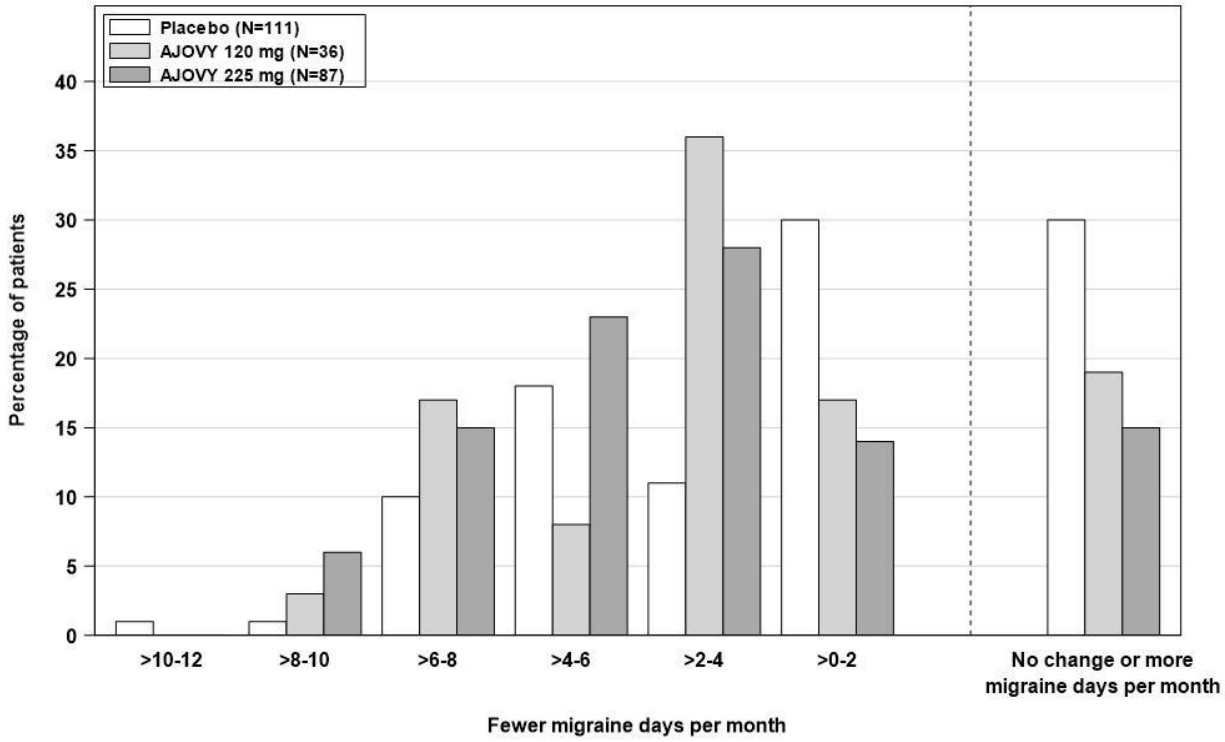



Source: Study 30083 CSR Figure 15.1.1

The distribution of effects for the primary efficacy variable are shown in Figure 3. Overall, there were larger proportions of subjects in the fremanezumab arms with >2-10 monthly migraine day reductions compared to placebo, and larger proportions of subjects with no change, worsening or small (>0-2) monthly migraine day reductions in the placebo arm compared to the fremanezumab arms.

Figure 2: Distribution of Change from Baseline in Mean Monthly Number of Migraine Days Over the 12-week Treatment Period by Treatment Groups (Full Analysis Set)






Source: Applicant provided figures in responses to IR (June 13, 2025 and July 3, 2025)

*Reviewer comment: Overall, results based on the primary efficacy variable are consistent with supporting efficacy of fremanezumab. The Applicant used a definition of migraine day for their efficacy analysis that was based on strict ICHD-3 criteria for migraine and did not include probable migraine. While this definition of migraine day was deemed acceptable, it was noted this could have resulted in less robust efficacy being observed by the primary endpoint. If probable migraine had been included in the efficacy analysis definition of a migraine day, then more events may have been reported resulting in more power to detect an effect.*

Data Quality and Integrity

Data quality were reviewed. As a whole, no issues were identified. Two sites were selected for site inspections based on high enrollment at the sites. The study was determined to have been conducted adequately at these sites based on the site inspection results. See Office of Scientific Investigations review by Cara Alfaro.

Efficacy Results – Secondary and other relevant endpoints

There were a total of 6 secondary endpoints included in the testing hierarchy:

- mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first

dose of study drug
- proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug
- mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug
- mean change from baseline (day 1) in migraine-related disability score, as measured by the PedMIDAS questionnaire, at 12 weeks after administration of the first dose of study drug
- mean change from baseline (day 1) in quality of life, as measured by the PedsQL, at 12 weeks after administration of the first dose of study drug
- proportion of patients developing ADAs throughout the study. The impact of ADAs on safety and efficacy will be analyzed if the number of ADA-positive patients allows.

The first 3 secondary endpoints were found to be statistically significant as shown in Table 7. Separation in treatment effects compared to placebo were observed for all secondary endpoints by month 1 as shown in Error! Reference source not found., Error! Reference source not found., and Error! Reference source not found..

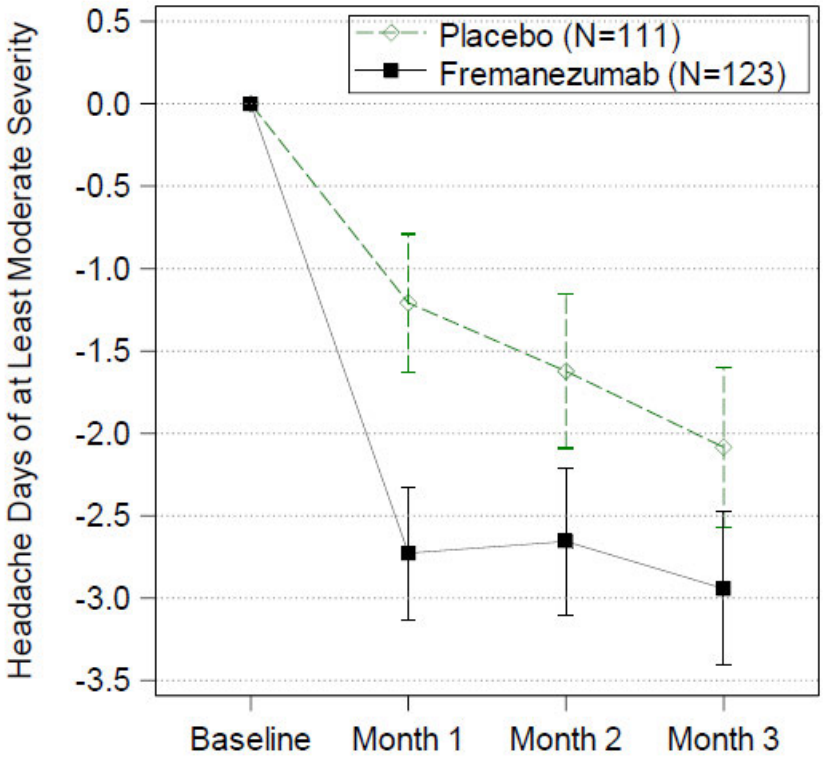
Table 7: Study 30083: Results for Secondary Endpoints (Weeks 1-12) (Full Analysis Set)

| | Placebo (N=111) | All Fremanezumab (N=123) |
|---|---|---|
| Mean change from baseline in monthly HA days | | |
| LS (SE) | -1.5(0.42) | -2.6 (0.40) |
| 95% CI | -2.32, -0.66 | -3.42, -1.83 |
| LSMD with placebo (SE) | - | -1.1(0.47) |
| 95% CI of difference | - | -2.06, -0.20 |
| p-value | - | 0.0172 |
| Proportion with at least 50% reduction in MMDs | | |
| Y | 30 (27%) | 58 (47.2%) |
| N | 81 (73%) | 65 (52.8%) |
| Odds ratio (95% CI) | - | 2.482 (1.409, 4.371) |
| Difference from placebo | - | 20.1% |
| p-value | - | 0.0016 |
| Change from baseline in monthly acute med days | | |
| LS (SE) | -1 (0.30) | -2.1 (0.29) |
| 95% CI | -1.56, -0.36 | -2.64, -1.48 |

| | | |
|---|---|---|
| LSMD with placebo(SE) | - | -1.1 (0.34) |
| 95% CI of difference | - | -1.77, -0.42 |
| p-value | - | 0.0016 |

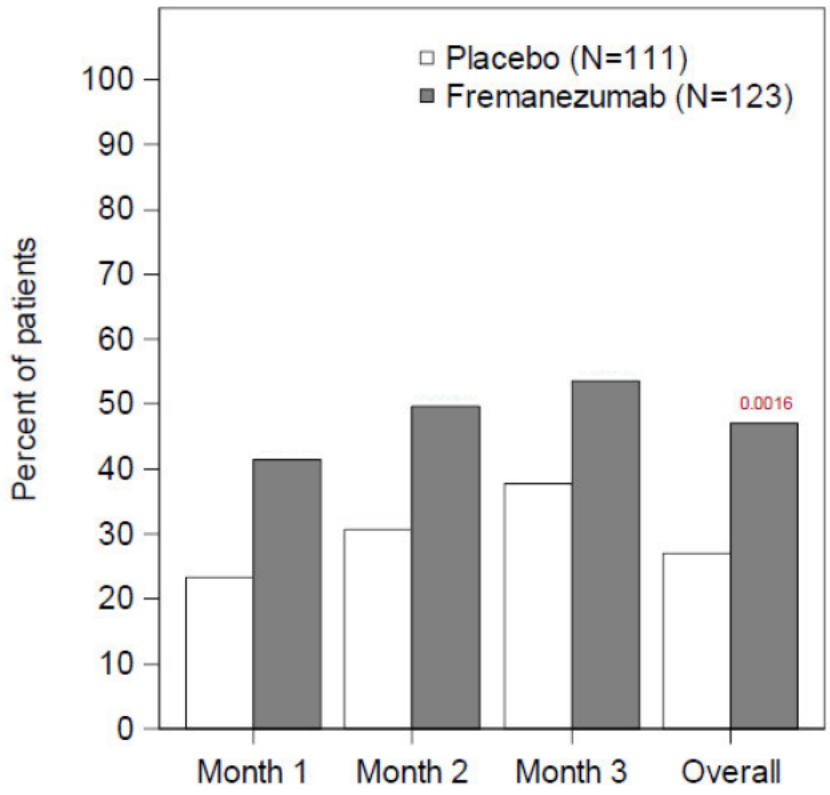
Source: Study 30083 CSR, Tables 15.3.2.1, 15.3.1.2, 15.3.3.1 with results confirmed by statistics reviewer

Figure 3: Study 30083, Line Plot of Secondary Endpoint: Mean Change from Baseline in Average Monthly Headache Days of at Least Moderate Severity During 12-week DBTP (Full Analysis Set)



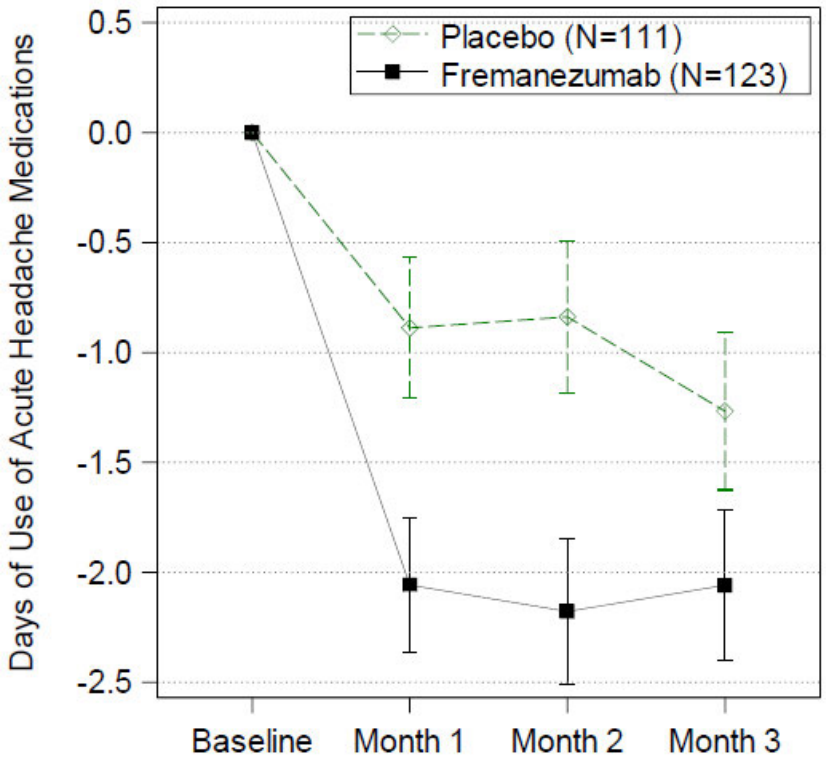

Source: Study 30083 CSR, Figure 15.2.1

Figure 4: Study 30083, Bar Graph of Secondary Endpoint: Proportion of Subjects with at least 50% Reduction from Baseline in Monthly Average Number of Migraine Days During 12-week DBTP (Full Analysis Set)




Source: Study 30083 CSR Figure 15.2.4

Figure 5: Study 30083, Line Plot of Secondary Endpoint: Mean Change from Baseline in Monthly Average Number of Days of Use of Acute Headache Medications During 12-Week DBTP (Full Analysis Set)




Source: Study 30083 CSR, Figure 15.2.6

*Reviewer comment: Data for the primary endpoint and first three secondary endpoints in the hierarchy are consistent in supporting efficacy, with sustained efficacy supported over the 12-week treatment period for each of these endpoints.*

Dose/Dose Response

No dose finding was conducted for the pediatric population, instead the Applicant used exposure matching based on the adult studies.

Additional Analyses Conducted on the Individual Trial

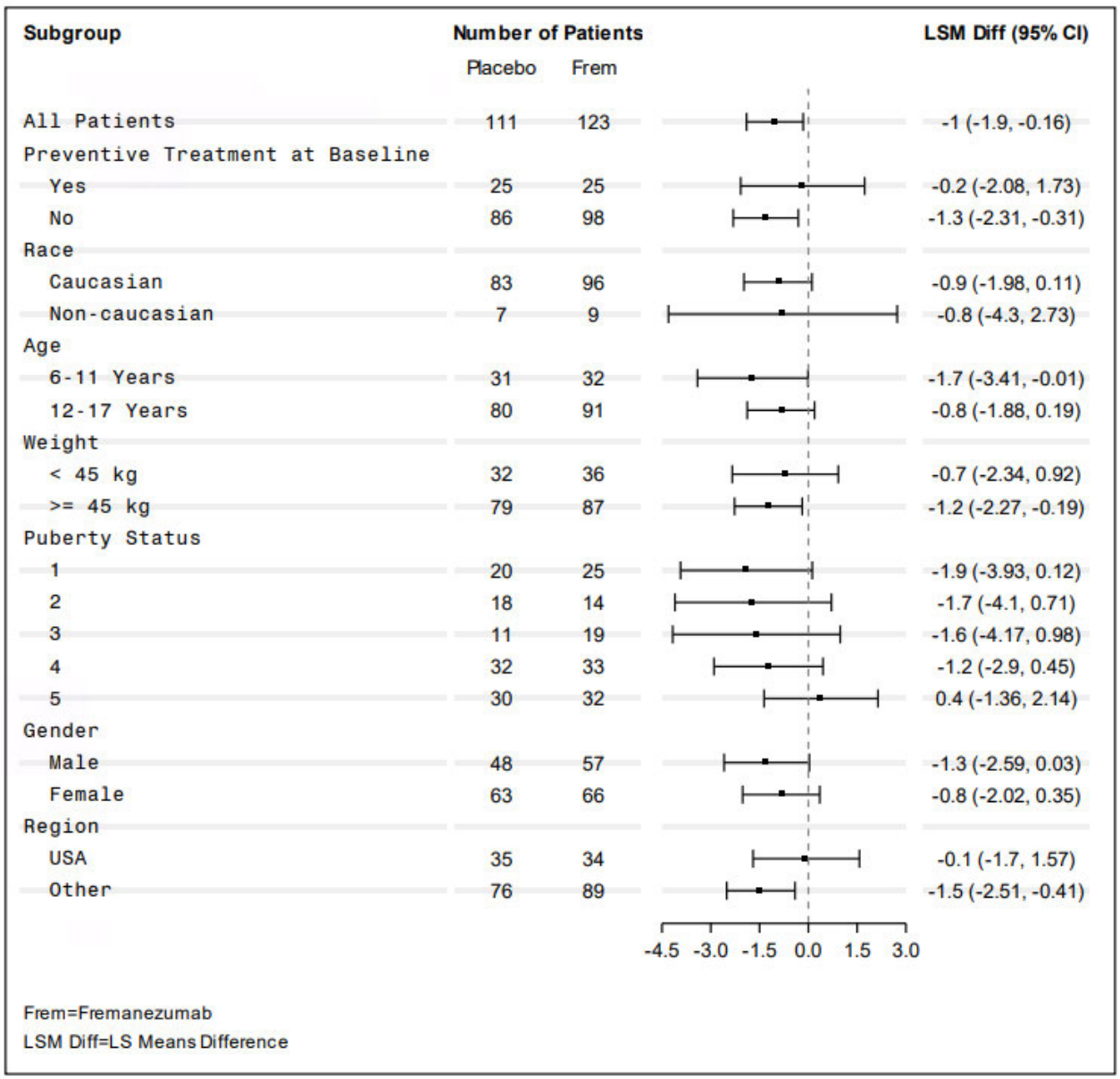
The primary efficacy variable showed significant differences when analyzed with the FAS, PP and ITT datasets ($p<0.05$) with subjects in the fremanezumab cohort having a larger reduction in mean monthly migraine days during the DBTP.

Additional Sensitivity Analyses:
Sensitivity analyses were performed for the primary efficacy variable using the mixed-effects model for repeated measures (MMRM) across the 12-week DBTP for the FAS, PP and ITT data sets. The MMRM model included baseline value, treatment, demographics, baseline medication, month and treatment-by-month interaction as fixed effects and patient as a random effect. Further, sensitivity analyses using analysis of co-variance (ANCOVA) with multiple imputation for missing data and using ANCOVA with actual stratification values for those mis-stratified at enrollment were completed for the primary efficacy variable.

These sensitivity analyses were consistent with the primary efficacy analysis (see statistical review by Anupam Kundu).

Subgroup Analyses:
Subgroup analyses for the primary efficacy variable were performed by sex, age cohort, weight group, puberty status, preventive treatment at baseline, race and region (Error! Reference source not found.). These analyses are limited by the smaller cohorts within them, with wider confidence intervals for many smaller cohorts. While most subgroups in the fremanezumab arm showed a trend numerically in reduction of mean monthly migraine days compared to the placebo arm, only 6 subgroups demonstrated nominal significance for the primary endpoint (Error! Reference source not found.): age group 6-11 years region “other” (outside of the USA), no preventive treatment for migraine at baseline and weight group of at least 45 kg. There were three subgroups where no trends nor nominal significance favoring the fremanezumab arm for the primary endpoint were observed. Two subgroups showed a point estimate that was close to 0 for the primary endpoint (subgroup of USA and preventive treatment for migraine at baseline), and one subgroup showed a numerical trend of an increase in mean monthly migraine days compared to placebo (Tanner stage 5).
The Applicant provided their rationale for regional applicability for data from subjects outside of the United States, noting the majority of subjects outside of the United States were European, with migraine being similar between European and North American populations, and that previous PK studies support applicability across races.

Figure 6: Study 30083, Forest Plot for Subgroup Analysis on Primary Endpoint (Full analysis set)




Source: Study 30083, CSR Figure 8, with results confirmed by statistics reviewer

Table 8: Subgroup Analysis by Age and Weight for the Primary Endpoint (Change in Mean Monthly Migraine Days)

| Statistic | Placebo | Fremanezumab |
|---|---|---|
| **Age = 6-11 Years** | | |
| n | 31 | 32 |
| LS mean (SE) | -1.7 (0.61) | -3.4 (0.60) |
| 95% confidence interval | -2.88, -0.46 | -4.57, -2.19 |
| Comparison with placebo | | |
| LS mean (SE) | - | -1.7 (0.86) |
| 95% confidence interval | - | -3.41, -0.01 |
| p-value | - | 0.0488 |
| **Age = 12-17 Years** | | |
| n | 80 | 91 |
| LS mean (SE) | -1.8 (0.38) | -2.7 (0.36) |
| 95% confidence interval | -2.58, -1.07 | -3.37, -1.96 |
| Comparison with placebo | | |
| LS mean (SE) | - | -0.8 (0.53) |
| 95% confidence interval | - | -1.88, 0.19 |
| p-value | - | 0.1096 |

| Statistic | Placebo | Fremanezumab |
|---|---|---|
| **Weight < 45 kg** | | |
| n | 32 | 36 |
| LS mean (SE) | -1.3 (0.60) | -2.0 (0.57) |
| 95% confidence interval | -2.52, -0.14 | -3.16, -0.92 |
| Comparison with placebo | | |
| LS mean (SE) | - | -0.7 (0.83) |
| 95% confidence interval | - | -2.34, 0.92 |
| p-value | - | 0.3923 |
| **Weight ≥ 45 kg** | | |
| n | 79 | 87 |
| LS mean (SE) | -2.0 (0.38) | -3.2 (0.37) |
| 95% confidence interval | -2.71, -1.20 | -3.91, -2.47 |
| Comparison with placebo | | |
| LS mean (SE) | - | -1.2 (0.53) |
| 95% confidence interval | - | -2.27, -0.19 |
| p-value | - | 0.0208 |

Source: Study 30083, Clinical Study Report Summaries 15.2.19 and 15.2.22 with results confirmed by statistics reviewer

As demonstrated in Error! Reference source not found., there was not a nominally statistical

effect for the primary endpoint with fremanezumab treatment for subjects aged 12-17 years or subjects weighing under 45 kg, but there was a nominally significant effect seen for the primary endpoint in subjects aged 6-11 years and subjects weighing at least 45 kg. To further investigate these nominal differences, the Applicant provided first the number of subjects for each age-weight combination subgroup (Table 9), and second, a supplementary analysis of fremanezumab and placebo cohorts by age-weight combination subgroup (Table 10).

Table 9: Subjects by Age and Weight Subgroup

| | Age Group | | |
|---|---|---|---|
| **Weight Group** | **6-11 years** | **12-17 years** | **Total** |
| < 45 kg | 41 (60%) | 27 (40%) | 68 (100%) |
| ≥ 45 kg | 22 (13%) | 144 (87%) | 166 (100%) |

Source: Applicant provided table in response to IR (July 3, 2025)

Table 10: Subgroup Analysis of Primary Endpoint by Age (6-11 years and 12-17 years) and Weight (<45 kg vs. at least 45 kg)

| | Age Group | |
|---|---|---|
| **Weight Group**<br>**Statistic** | **6-11 years** | **12-17 years** |
| **< 45 kg** | | |
| LS Mean (SE) | -2.1 (1.06) | 1.3 (1.35) |
| p-value | 0.0493 | 0.3538 |
| **≥ 45 kg** | | |
| LS Mean (SE) | -0.4 (1.49) | -1.3 (0.56) |
| p-value | 0.7657 | 0.0220 |

Source: Applicant provided table in response to IR (July 3, 2025)

*Reviewer comment: A trend favoring placebo is only observed for subjects weighing <45 kg and aged 12-17 years among the age-weight combination subgroups. This subgroup is small, but this observation could suggest the lower weight-based dose of 120 mg is less effective in the adolescent population and/or subjects near the 45 kg cut-off.*

Subgroup analyses for age (6-11 years and 12-17 years) were also performed for the secondary

endpoints, including change in monthly average number of days of use of acute headache medications and change in monthly average number of headache days of at least moderate severity, which favored fremanezumab.

R*eviewer comment: Overall, subgroup analyses for the primary and secondary endpoints are consistent with favoring fremanezumab compared to placebo, but there were a few subgroups where there was nearly no numerical difference or the numerical difference favored placebo for the primary endpoint, as discussed above. The Applicant provided a rationale that is acceptable for one of these subgroups (region USA), in which there was nearly no numerical difference and the subgroup is small, limiting interpretation. The other subgroup for which there was nearly no numerical difference (use of concomitant preventive therapy for migraine) also had a small subgroup. Eligibility criteria allowed use of up to 2 concomitant preventive therapies, but it is not clear if this impacted results. The subgroup of Tanner stage 5, favored placebo and is closest to the adult population developmentally of the pubertal subgroups. This subgroup, among the puberty stage subgroups, would presumably have the largest proportion of subjects within it who have established their adult migraine phenotypical pattern and treatment response. Fremanezumab has proven efficacy in the adult population. Therefore, it is unclear why there was a numerical trend favoring placebo for this subgroup, and this observed trend may simply be reflective of a small sample size. Finally, there was an observed trend favoring placebo in the supplementary subgroup analysis of age-weight combination subgroups for subjects who were aged 12-17 years and weighing <45 kg. It is unclear what resulted in this observation. Dose efficacy at the upper limit of the lower weight-based cohort as well as other factors related to the adolescent population itself were considered, but no relationships were identified. Overarchingly, small numbers of subjects in subgroups limit the ability to draw statistical conclusions for each subgroup or between subgroups.*

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

The Applicant submitted a single efficacy study. However, there are previous efficacy trials relevant to this application, notably the pivotal adult efficacy trial in episodic migraine (study 30050) which used the same primary endpoint as the pediatric controlled trial (study 30083), which was the mean change from baseline in the monthly average number of migraine days during the 12-week DBTP. Study 30050 tested 2 dosing regimens of fremanezumab:225 mg SC monthly and 675 mg SC quarterly. In study 30050, the mean number of migraine days at baseline was approximately 9 days for both active treatment arms and the placebo arm, similar to, but slightly higher than the baseline in the pediatric controlled study, which included subjects with an average baseline of under 8 migraine days a month. The difference in the adult study (30050) in mean change from baseline in the monthly average migraine days between

fremanezumab 225 mg SC monthly and placebo was -1.5, favoring fremanezumab, and between fremanezumab 675 mg SC quarterly and placebo was -1.3, favoring fremanezumab (Table 11). There was a similar demonstration of sustained efficacy with fremanezumab treatment in study 30050 as was observed in study 30083 (Figure 7). Notably, the Applicant included probable migraine operationally into their definition of migraine day for the analysis of the primary endpoint in the adult study (30050) but not the pediatric study (30083), which, if impactful, could have made the findings for this efficacy endpoint in study 30050 more robust than if probable migraine had not been included in the primary efficacy analysis. The slightly higher baseline of MMDs in subjects treated in study 30050 compared to those treated in study 30083 could have also impacted the efficacy observed. Overall, the primary efficacy results of study 30050 appeared similar to the efficacy results for the primary endpoint in study 30083 with a mean effect of fremanezumab treatment being approximately 15-16% in adults and approximately a 12-13% in pediatrics.

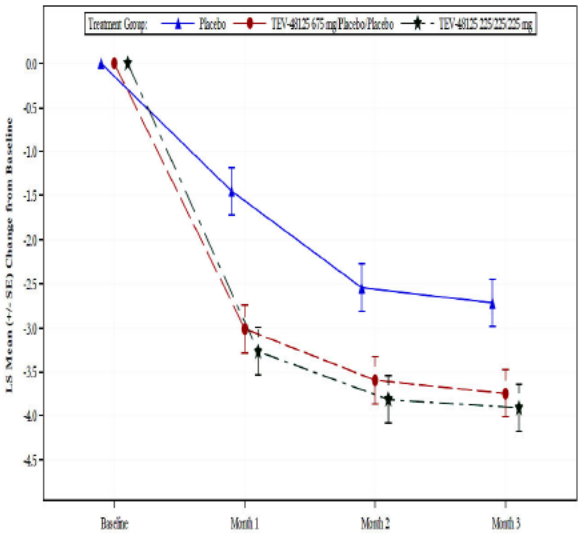
Table 11: Study 30050 (Adult EM Study and Study 30083 (Pediatric EM Study) Primary Efficacy Results for Change from Baseline in Monthly Migraine Days

| Dose | Placebo | Fremanezumab 225mg SC monthly (or weight-based dose equivalent – pediatrics) |
|---|---|---|
| Study 30050 (Adults) | | |
| Baseline Mean Monthly Migraine Days | 9.1 | 8.9 |
| LS Mean (SE) | -2.2 (0.24) | -3.4 (0.25) |
| LS Mean Difference v Placebo | - | -1.5 |
| Study 30083 (Pediatrics) | | |
| Baseline Mean Monthly Migraine Days | 7.5 | 7.8 |
| LS Mean (SE) | -1.4 | -2.5 (0.38) |
| LS Mean Difference v Placebo | - | -1.0 |

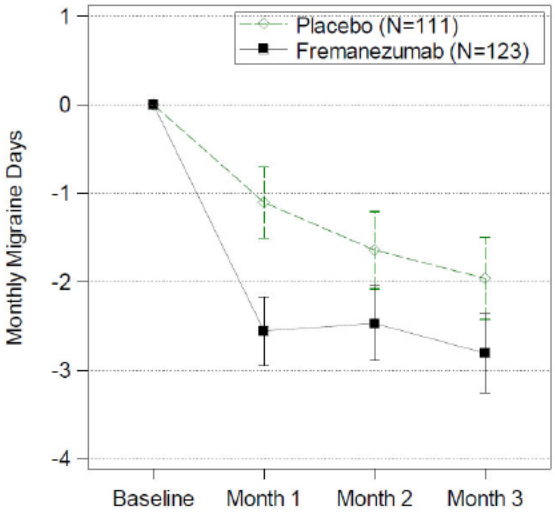
Sources: BLA 761089 original clinical review and Study 30083 CSR, Tables 15.2.5 and 8

Figure 7: Pivotal Adult Efficacy Trial (Study 30050) compared to Pivotal Pediatric Efficacy Trial (Study 30083) for Primary Endpoint: Change from Baseline in Monthly Average Number of Migraine Days

a. Study 30050




b. Study 30083




Sources: a. BLA 761089 (Figure 17.1.1, CSR for Study 30050), b. Study 30083 CSR Figure 15.1.1

Secondary endpoints in study 30050 included two secondary endpoints analyzed in study 30083: proportion of subjects with at least a 50% reduction in monthly migraine days, and mean change from baseline in the monthly average number of days of use of acute headache medications across the 12-week DBTP. These reached statistical significance for both active treatment groups in the adult study (30050) as they did in the pediatric study (30083).

Adult and pediatric migraine may differ, including by placebo response as well as patterns and phenotypical characteristics of the attacks. Despite this, the results between adult and pediatric subjects with episodic migraine appear similar for efficacy based on studies 30050 and 30083.

## 7.2. Additional Efficacy Considerations

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

Overall, the Applicant included a population similar to the one expected to utilize this product in the postmarket setting for the preventive treatment of episodic migraine, including by disease burden based on the baseline average number of migraine days per month for subjects in study 30083 of approximately 7-8. However, the population that ultimately uses this product in the postmarket setting may have more refractory disease.

### 7.2.2. Other Relevant Benefits

This is the first anti-CGRP product for the preventive treatment of episodic migraine in the

pediatric population 6-17 years of age and the first product for the preventive treatment of migraine in the pediatric population 6-11 years of age, although its use in the 6-11 year age group is particularly limited by the lack of availability of a dose for those patients weighing under 45 kg. It is also only the second product for the preventive treatment of episodic migraine in the pediatric population 12-17 years of age.

## 7.3. Integrated Assessment of Effectiveness

The Applicant submitted substantial evidence of effectiveness to support this application based on a single adequate and well-controlled trial in pediatrics with confirmatory evidence provided by the adequate and well-controlled trials demonstrating efficacy in the adult population in the original application.

In the pediatric study, the primary endpoint of mean change from baseline in monthly average migraine days, as well as the first three secondary endpoints in the hierarchy including mean change from baseline in monthly headache days of at least moderate severity, proportion of subjects reaching at least a 50% reduction in mean monthly migraine days, and mean change from baseline in monthly average days of acute headache medication use demonstrating consistency in findings of efficacy for fremanezumab. Sensitivity analyses including with the per protocol set demonstrating confirmed findings of the primary analysis. Analyses by subgroup, including age and weight, were limited by small numbers, but overall, efficacy results by pre-defined subgroups were consistent in favoring fremanezumab.

The Applicant chose to seek approval for only pediatric patients with episodic migraine 6-17 years of age weighing at least 45 kg given ongoing development of the (b) (4) 120 mg dose.

In terms of labeling, I recommend broadening the current indication to include the preventive treatment of episodic migraine in patients 6-17 years of age weighing 45 kg or more. In addition, I recommend including results from study 30083 in section 14 with results from the primary endpoint, as well as the following three secondary endpoints:

- Mean change from baseline (28-day baseline period) in monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of study drug
- Proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of study drug
- Mean change from baseline (28-day baseline period) in the monthly average number of days of use of any acute headache medications during the 12-week period after the first dose of study drug

# 8. Review of Safety

## 8.1 Safety Review Approach

The safety review includes pediatric subjects with episodic migraine from studies 30083 (double-blind, placebo-controlled trial) and 30084 (open label, long-term safety trial with subjects from study 30083 rolled over into this trial). The Applicant defined the safety population as any subject who received at least one dose of IMP from these studies. I also reviewed the CSR and summaries for study 10141, which was the PK study dosing a small number of healthy subjects with a lower dose (75 mg) of fremanezumab. The Division additionally requested reports of any SAEs, deaths, and severe AEs within study 30082 (double-blind, placebo-controlled pediatric chronic migraine trial) which were provided by the Applicant and included in this review. Datasets and the final CSR for study 30082 were not available at the time of this review.

In this review, I summarize information from the Applicant's materials, and supplement this with confirmatory and additional analyses I conducted using pooled and individual trial datasets. The main cohort for analysis used safety data from study 30083, with supplementary cohorts for analysis using safety data from study 30084 and pooled safety data from EM subjects in both studies 30083 and 30084 by the original submission data and then further supplemented with the 120-day safety update provided by the Applicant. Further groupings by age cohort (6-11 and 12-17) and weight (<45 kg and ≥45 kg) were done to analyze safety by these subgroups. Analyses I performed on datasets were carried out using the JMP software program (version 17).

Table 12: Clinical Studies Contributing to the Review of Safety

| Study | Dose | Subjects with Episodic Migraine |
|---|---|---|
| Controlled Trials | | |
| 30083 | 120mg<br>225mg<br>pbo | 36<br>87<br>112 |
| Uncontrolled Trials | | |

| | | |
|---|---|---|
| 30084* | 120mg<br>225mg | 58<br>161 |
| Other | | |
| 10141 | 75mg | NA (35 healthy subjects) |

*Study subject numbers for study 30084 are at time of original submission

Safety areas of interest prespecified by reviewer:

- Hypertension
- Raynaud's Phenomenon
- Severe hypersensitivity and anaphylaxis
- Injection site reactions

*Reviewer comment: Fremanezumab has hypertension, Raynaud's phenomenon, severe hypersensitivity and anaphylactic reactions, and injection site reactions labeled under warnings and precautions for use in adults.*

- Hepatic function (Liver enzymes)

*Reviewer comment: Elevation of hepatic enzymes has been labeled for another product targeting the CGRP pathway but there has been no clear signal seen with any of the mABs in this class.*

- Vision/Retinal effects

*Reviewer comment: There was one case of bilateral retinal detachment in the adult DBPC pivotal trial in addition to nonclinical findings in one animal study (cynomolgus monkey) of a potential signal of vasculitis of the ciliary body with fremanezumab although the finding was not confirmed in other nonclinical studies (see review for adult indication under BLA761089)*

Design of the Open-Label Study 30084

This was an open-label, parallel cohort study with 2 weight-based dosing cohorts (120 mg SC monthly for <45 kg and 225 mg SC monthly for ≥45 kg). Subjects with both episodic migraine and chronic migraine 6-17 years of age were enrolled in this study after completed studies 30083 (EM) and 30082 (CM). The duration of the study was up to 9 months of treatment, providing up to 1 year of exposure as noted below. Subjects were followed until approximately 5 months after last IMP administration in study 30084. Subjects who completed study 30083 and did not wish to receive further administration of IMP, as well as subjects who did not complete study 30083 were able to enroll in study 30084 for a follow-up visit for safety and anti-drug antibody (ADA) assessments approximately 5 months after receiving the last dose of IMP in study 30083.

While data for subjects from study 30082 were included in the datasets provided for study 30084, these subjects were not included in the safety analyses of study 30084, as data from study 30082, and thus, drug exposure, remained blinded at the time of the review of the datasets.

Design of PK study 10141:
This was a single dose, open-label, PK study of 75 mg fremanezumab in healthy subjects 6-11 years of age.

Design of CM Pediatric Study 30082:
This was a DBPC trial mirroring study 30083 in design. Subjects 6-17 years of age with CM were enrolled, with 1:1 randomization to placebo and fremanezumab. Subjects were dosed with fremanezumab by weight, receiving 225 mg SC monthly if weighing at least 45 kg and 120 mg SC monthly if weighing under 45 kg.

## 8.2 Review of the Safety Database

### 8.2.1 Overall Exposure

As shown in Table 13, at the time of filing, a total of 203 EM subjects were exposed to fremanezumab for at least 6 months and 87 subjects were exposed for at least 12 months. The average duration of treatment was 276 (+/-81) days with a median of 272 days. Study 30084 was ongoing at the time of submission.

The majority of subjects in the double-blind, placebo-controlled study (study 30083) received all 3 doses of IMP (96% in placebo cohort and 97% in fremanezumab cohort), with only 12 of the 235 subjects in the safety dataset not receiving all 3 doses. Subjects who completed study 30083 rolled over from study 30083 to study 30084.

Table 13: Duration of Exposure for EM subjects from Studies 30083 and 30084 Combined*

| | Number of patients exposed to the active treatment | | |
|---|---|---|---|
| Age | >= 1 dose | >=6 months[1] | >=12 months |
| *6-11 years* | N=61 | N=55 | N=18 |
| *12-17 years* | N=164 | N=148 | N=69 |
| *Dose* | | | |
| *120mg* | N=61 | N=55 | N=20 |
| *225mg* | N=164 | N=148 | N=67 |
| *Any Dose* | N=219 | N=203 | N=87 |

Source: Applicant response to IR May 5, 2025, sequence 1001
*at the time of original submission

At the time of the 120-day safety update, an overall of 225 pediatric patients with EM had been exposed to fremanezumab. Of these subjects with EM, 61 had been exposed to at least one dose of 120 mg, 164 had been exposed to at least one dose of 225 mg, 209 had been exposed to any dose for at least 6 months and 100 had been exposed to any dose for at least 12 months.

### 8.2.2 Relevant characteristics of the safety population:

Demographic characteristics in the safety population were very similar to that of the FAS, with only 1 subject in the placebo cohort included in the safety population being omitted from the FAS, and that 1 subject not having any significant outlying demographic information. Tables 3 and 4 are therefore representative of the safety population demographics.

Migraine occurs equally in male and female children until around menarche when it becomes more common in females, by about 2 to 3-fold by later adolescence. Safety population demographics from study 30083 seem relatively representative of this female:male prevalence of migraine in childhood and adolescence, with 45% of subjects being male and 55% of subjects being female in the safety population given about 27% of subjects were aged 6-11 years, about 32% were aged 12-14 years, and about 41% were aged 15-17 years and assuming a steady increase from a 1:1 ratio of migraine prevalence by sex at age 10 to a 2:1 ratio by sex by age 15.

The smaller proportion of subjects in the 6-11 year cohort is in line with the smaller proportion of subjects with a lower body weight (the <45 kg cohort), which was 30% of subjects. The Applicant met their enrollment goal for this younger age cohort (25%), which was agreed to by the Division in a SPA agreement letter June 2024.

Approximately 65% of subjects in the safety population had at least 1 finding in their medical history, largely due to minor, common disorders of childhood such as allergies, near-sightedness (myopia), nausea, constipation and gastroesophageal reflux. The most common categories were gastrointestinal and immune system disorders, with seasonal allergies accounting for the large majority of the immune system disorders. Subjects with any clinically significant cardiovascular, endocrine, gastrointestinal, genitourinary, hematologic, hepatic, immunologic, neurologic, ophthalmic, pulmonary, or renal disease was excluded from the study at the discretion of the investigator.

### 8.2.3 Adequacy of the safety database:

The safety database includes sufficient long-term safety data based on the recommendations in the *Guidance for Industry, Migraine: Developing Drugs for Preventive Treatment, June 2023 (10).*

## 8.3 Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1 Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was provided by the Office of Computational Sciences (OCS) and reviewed by me. Based on my review, there were no concerns regarding the data from Study 30083, in general. Additional datasets for pooled data from studies 30083 and 30084 were requested and received.

### 8.3.2 Categorization of Adverse Events

Applicant's Definitions of AEs, SAEs, and TEAEs

The Applicant defined an adverse event (AE) as any new untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

AEs were coded according to MedDRA 26.0. Review of the verbatim AE terms showed that MedDRA coding was adequate.

Of note, migraine exacerbations (including acute headache) were collected as part of the efficacy assessment in these studies, and were only recorded as an AE "if the presentation and/or outcome was more severe than would typically be expected from the normal course of the disease in a particular patient, or if they were severe enough to require hospitalization of the patient, in which case they were recorded as serious adverse events."

*Reviewer comment: This approach was also taken in the adult studies and allowed for acceptable separation of adverse events from expected disease process.*

Categorization of reasons for discontinuation were also accurate, in general.

All adverse events were followed until resolution, until the subject is referred for continued care to another health care professional, or until a determination of a cause unrelated to the study drug or procedure was made.

Serious adverse events (SAEs) were defined as an AE that results in any of the following outcomes or actions: death, a life-threatening event, hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, an important medical event that may jeopardize the patient and may require medical intervention to prevent one of the aforementioned outcomes in this definition, and drug-induced liver injury that meets Hy's law criteria.

Intensity of AEs:

The Applicant categorized AEs as mild, moderate or severe in intensity. The following definitions were provided in the protocol:
Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

Applicant defined AEs of Special Interest:
AEs of special interest (AESIs) included ophthalmic-related adverse events of at least moderate severity and severe hypersensitivity or anaphylactic reactions. Reporting of AESIs was the same as that for all other AEs.

### 8.3.4 Routine Clinical Tests

In study 30083, blood and urine samples were collected at screen, week 4 (dose 2), and week 12 (dose 3- end of treatment or early withdrawal), whereas ADA samples were collected at day 1 (dose 1), week 4 (dose 2) and month 3 (EOT or early withdrawal). In study 30084, blood and urine samples were collected at day 1 (dose 1), month 3 (dose 4), month 6 (dose 7), and month 9 (end of treatment or early withdrawal). ADA samples in study 30084 were collected at day 1 (dose 1), month 3 (dose 4), month 6 (dose 7), month 9 (end of treatment/early termination) and end of trial (month 14). Detailed safety laboratories are presented in Error! Reference source not found..

Table 14: Clinical Laboratory Tests from Studies 30083 and 30084

| | |
|---|---|
| Chemistry | Sodium, Potassium, Chloride, Creatinine, BUN, Glucose, Calcium, Phosphate, Magnesium, Bicarbonate, Protein, Albumin, |
| Hematology | Hemoglobin, Hematocrit, RBC count, RBC indices, Platelets, Leukocytes, |
| Urinalysis | Color and appearance, protein, glucose, ketones, blood, leukocyte esterase, nitrite, bilirubin, pH, specific gravity, microscopic tests (bacteria, erythrocytes, leukocytes, crystals, casts) |
| Coagulation | Prothrombin time, Partial thromboplastin time, INR |
| Liver Enzymes & function tests | Bilirubin, ALT, AST, GGT, LDH, Bilirubin (total and direct) |
| Urine drug screen | |

| | |
|---|---|
| Pregnancy test | Serum beta HCG for all female subjects at least 12 years of age or post-menarchal |

Sources: Studies 30083 and 30084 protocols, submitted by Applicant, with a correction regarding bicarbonate

Vital signs:
Vital sign measurements including pulse, systolic and diastolic blood pressure, temperature and respiratory rate were measured at screen, day 1 and months 1-3 in study 30083, and at day 1 and months 1-9 in study 30084. For any abnormal vital sign, the measurement was repeated.

## 8.4 Safety Results

### 8.4.1 Deaths

There were no reported deaths in studies 30083, 30084, 30082 or 10141.

### 8.4.2 Serious Adverse Events

Study 30083:
In the controlled trial, there were 2 SAEs in the fremanezumab treated cohorts and 3 SAEs in the placebo cohort. One SAE in the fremanezumab cohort was migraine resulting in hospitalization, occurring approximately 3 weeks after the last dose of fremanezumab with resolution within 1 day and no clear relationship to fremanezumab. The second SAE occurring in a second subject in the fremanezumab cohort was hepatitis and is detailed below.

Hepatitis:
Subject (b) (6) was a 17-year-old male who experienced hepatitis infectious mononucleosis on trial day 91, 16 days after the third dose of 225 mg fremanezumab. The subject was hospitalized for this event on trial day 91, and experienced symptoms of fever, fatigue, and muscle pain. His Ebstein Barr Virus (EBV) IgM antibody was positive on days 91 and 96. His liver transferases were elevated (alanine aminotransferase of 190U/L and aspartate aminotransferase of 83 U/L). He received intravenous fluids, ibuprofen, ornithine aspartate, choline bitartrate and ursodeoxycholic acid. He was discharged on day 96 and enrolled in the long-term safety study with 8 additional doses of 225 mg fremanezumab received with no reported episodes of hepatitis or liver enzyme elevation.

*Reviewer comment: Narrative details for subject (b) (6) are consistent with a viral hepatitis that is unrelated to the IMP of fremanezumab.*

Study 30084:
At the time of review, there were a total of 10 subjects with episodic migraine who experienced

12 serious adverse events. These included the following SAEs in the 225 mg cohort: seizure (or syncope) in setting of cannabinoid use, 2 subjects with COVID-19, tonsillitis, 2 subjects with gastritis (see below), vulvitis, EBV hepatitis (see below), rhabdomyolysis (see below) and status migrainosus. In the 120 mg cohort, there were 2 SAEs: migraine and influenza (see below). There was one additional SAE in a subject with EM reported in the 120-day safety update, which was migraine.

Gastritis:

Subject (b) (6) is a 17-year- old female who experienced gastritis on trial day 167, 26 days after the 6th open label dose of 225 mg fremanezumab, which was also the 5th consecutive trial dose of fremanezumab (including study 30083). This subject had a history of recurrent abdominal pain, and had ongoing abdominal pain reported as an AE beginning 12 days before enrollment in the open label study (30084). The subject was hospitalized on trial day 168 for gastritis, assessed as moderate intensity, and underwent gastroscopy showing erythema of antral mucosa. Ileocolonoscopy and abdominal sonography were normal. There was no recent use of non-steroidal anti-inflammatory drugs. The gastritis resolved on trial day 178 and the AE of abdominal pain persisted through the end of the trial. The subject received 3 further doses of fremanezumab with no further AEs of gastritis. This subject also experienced an unrelated SAE of vulvitis on trial day 322.

Subject (b) (6) is a 13-year-old male who experienced gastritis on trial day 137, 22 days after 5th dose of 225 mg fremanezumab in the open label study (30084), which was the 8th consecutive trial dose of fremanezumab including the controlled study (30083). The subjected experienced gastritis, assessed as moderate severity and initially thought to be either gastritis or pleurisy, on trial day 137 along with pharyngeal inflammation, resulting in hospitalization. The subject was given paracetamol and omeprazole, and was discharged from the hospital on trial day 140. The events of gastritis and pharyngeal inflammation resolved by trial day 148. The subject was notably on non-steroidal anti-inflammatory drugs (ibuprofen) prior to the onset of this SAE. The subject received 4 further doses of fremanezumab 225 mg in study 30084 without further events of gastritis or related AEs. This subject also experienced an unrelated SAE of COVID-19 infection on trial day 264.

*Reviewer comment: While there were two cases of gastritis, there were other possible alternative causes in both cases, negative rechallenges in both cases, and no clear relationship to the IMP. The first case fits a historic pattern of recurrent upper abdominal pain (subject (b) (6) whereas the second case includes associated symptoms suggestive of a concomitant viral infection (pharyngeal inflammation) and concurrent non-steroidal anti-inflammatory use (subject (b) (6)), which provide alternative explanations for the AEs of gastritis.*

Three other cases worth mentioning include the cases of EBV with transaminitis, influenza with

transaminitis, and rhabdomyolysis, given these cases affect liver enzyme analyses:

EBV Hepatitis:
Subject (b) (6) was a 16-year-old female who, at day 222 (1 day after the 9th dose of 225 mg of fremanezumab in study 30084, which was the 12th consecutive trial dose of fremanezumab including the controlled study (30083), developed symptoms of an upper respiratory tract infection (URI). Her symptoms worsened, and by day 225, she presented to the emergency room due to tachycardia (heart rate of 110 beats per minute) and continuing to have URI symptoms including cough. An electrocardiogram (ECG) and blood test was normal. She was thought to have a viral URI and was sent home with advice to hydrate and take antipyretics as needed. The following day (trial day 226), a worsening cough was noted and by trial day 229, she experienced a viral xanthem as well as "moderate, non-serious" elevations in her serum liver transaminases (AST and ALT) without values reported. She also had reported evidence of a bacterial URI (details not available), and was given amoxicillin and codeine. On trial day 231, follow up laboratories were performed and revealed thrombocytopenia (reported as 0.84mL), liver transaminase elevations (reported as AST 0.184mL, ALT 0.163mL) and elevation of acute inflammatory markers (C-reactive protein reported as 28.6 mg). She was hospitalized that day due to new onset eyelid edema and rash (torso and extremities) and noted to have persistently elevated liver transaminases, a low platelet count and elevated C-reactive protein and leukocytes (values not reported). A diagnosis of EBV infection was established. She was discharged from the hospital trial day 239. Her liver transaminase values returned to baseline by trial day 253 (ALT 31U/L, AST 36U/L). Her platelets had normalized to 209 10^9/L. Her rash resolved by day 280. She had no reported thrombocytopenia or increases in liver enzymes prior to this event reported in either study 30083 or study 30084.

Rhabdomyolysis/Elevated Liver Transaminases:
Subject (b) (6) was a 14-year-old male who experienced rhabdomyolysis on trial day 85, 25 days after his 3rd dose of 225 mg fremanezumab in study 30084 and 3rd dose overall including both studies 30083 and 30084. During the subject's 5th scheduled visit in the trial, his laboratories revealed elevated levels of creatine kinase at 44093 U/L, ALT at 177 U/L , AST at 714 U/L and LDH at 1720 U/L. Urinalysis results were normal, as was renal function by serum laboratories. The subject reported completing a strenuous gym workout the day prior after which he had muscle soreness and fatigue. He was diagnosed with rhabdomyolysis. On trial day 87 he was admitted to the hospital and his scheduled 4th dose of 225 mg fremanezumab in study 30084 was given. A repeat laboratory workup revealed a decrease in the aforementioned values with his creatine kinase being 6919, LDH 166, ALT 146, AST 286 (units not provided in report). It was reported that the subject was in good condition and he was advised to avoid gym visits. The event of rhabdomyolysis resolved on trial day 91. He subsequently completed the trial, receiving a total of 9 doses in study 30084 with no further elevations in CK or liver enzymes.

Influenza/Elevated Liver Transaminases:
Subject (b) (6) a 9-year-old female subject was diagnosed with influenza B on trial day 56. The event occurred 27 days after her 1st dose of fremanezumab 120 mg in study 3008, which was the 4th consecutive trial dose including the controlled study (30083). She was hospitalized with a high fever and vomiting that had been ongoing for 2 days on trial day 56 (onset trial day 54). Her laboratories on trial day 56 revealed elevated liver transaminases (AST of 156 U/L Land ALT of 199 U/L). The exact means of diagnosis of her influenza B infection was not provided. She was given oseltamivir, ondansetron, and electrolyte repletion. She was discharged on trial day 59 (3 days after hospitalization and 5 days after onset of the symptoms resulting in hospitalization based on report). On trial day 66, her laboratories revealed downtrending liver transaminases (AST 29 U/L and ALT 60 U/L). Her event of influenza was reported as resolved on trial day 70. She completed a further 8 doses of fremanezumab with no elevations in liver transaminases.

*Reviewer comment: These three cases of elevated liver enzymes are each associated with probable alternative causes, but an association with IMP (fremanezumab) was not ruled out. Further analysis of fremanezumab effects on liver enzymes is provided under section 8.4.6: Laboratory Findings.*

Study 10141:
There were no reported SAEs in this PK study.

Study 30082:
In the placebo-controlled pediatric chronic migraine trial, per the Applicant, there were 9 SAEs, including 4 in the fremanezumab treated cohort, all of which were migraine.

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

Study 30083:
In the controlled trial, there was one subject who discontinued IMP due to an AE, which was a non-serious adverse event of elevated ALT. This subject ( (b) (6) ) experienced an elevation of ALT on trial days 28 and 56, which were 0 and 28 days after receiving dose 2 of IMP (fremanezumab 120 mg), respectively. ALT elevation at baseline was mild at 23U/L (ref range <19U/L), increased to 60U/L on trial day 28 (day of dose 2 of fremanezumab), decreased back to 29 U/L the day after dose 2 (trial day 29), and then increased to 68U/L confirmed by a second draw on trial day 56, which was the early termination visit. Her AST, while staying within the specified normal range, also increased from 29U/L at screen to 49 on trial day 28, 30 on trial day 29, and 61 on trial day 56. Alkaline phosphatase mildly increased from 196U/L at screen to 226U/L on trial day 56, and also stayed within the specified normal range. Bilirubin values did not increase. This subject was on multiple concomitant medications, including a recent change with initiation of escitalopram.

*Reviewer comment: The mild elevations in liver enzymes is possibly related to IMP (fremanezumab) given onset after initiation of fremanezumab, but there are confounding factors including concomitant medications with a recent initiation of escitalopram.*

Study 30084:
At time of original submission, in the open-label trial, there was a total of 5 subjects with EM who discontinued the trial or IMP due to an adverse event, including 3 associated with injection site reactions and 2 associated with suicidal ideation. These are listed in Error! Reference source not found. below.

Table 15: Study 30084, Discontinuations Due to Adverse Events

| System Organ Class MedDRA 26.0 PT | Fremanezumab 120mg (N=58) | Fremanezumab 225mg (N=161) | Total (N=219) |
|---|---|---|---|
| General disorders and administration site conditions | 0 | 3 (2) | 3(1) |
| Injection site erythema | 0 | 2(1) | 2(<1) |
| Injection site pruritus | 0 | 2(1) | 2(<1) |
| Injection site rash EM x1 | 0 | 1(<1) | 1(<1) |
| Injection site swelling EMx1 | 0 | 1(<1) | 1(<1) |
| Psychiatric disorders | 1(2) | 1(<1) | 2(<1) |
| Suicidal ideation | 1(2) | 1(<1) | 2(<1) |

Source: Study 30084, Clinical Study Report Summary 15.7.1 and Listing 16.2.7.01 and 16.2.7.07 with results confirmed by OCS using Analysis Studio, Safety Explorer

Suicidal Ideation:
Subject (b) (6) is a 13-year-old male who experienced suicidal ideation 4 days after the 4th dose of fremanezumab 225 mg in study 30084, which was the 7th consecutive trial dose of fremanezumab including the controlled study (30083). The AE was graded as moderate and resolved within 2 months. There was no medical history reported of suicidal ideation or mood disorders and no confounding medications, but there was a referenced traumatic experience. The IMP of fremanezumab was discontinued.

Subject (b) (6) is a 15-year-old female who experienced suicidal ideation one week after the first dose of fremanezumab 225 mg in study 30084 (1st trial dose of fremanezumab overall, including study 30083). The AE was graded as moderate and resolved within a few days. There was no medical history provided, but it was noted that among concomitant medications was

topiramate, which was reported as started in 2010. The IMP (fremanezumab) was discontinued.

*Reviewer comment: Both cases are confounded by alternative causes, but a causal association with fremanezumab cannot be ruled out.*

Injection site reactions with recurrence:
Subject (b) (6) is a 17-year-old female who experienced an injection site rash on trial day 114, 1 day after the 5th dose of fremanezumab 225 mg in study 30084, which was the 5th trial dose of fremanezumab overall including study 30083, which resulted in withdrawal from the study. She initially had a mild injection site rash trial day 59 after her second dose of fremanezumab 225 mg, which was treated with diphenhydramine, and, after her 5th dose on trial day 114, had another mild injection site rash which resolved on trial day 137. She withdrew from the trial on day 146 due to the injection site rash.

Subject (b) (6) was a 17-year-old female who experienced injection site erythema and pruritis twice, and ultimately resulting in withdrawal from the study. The first event was on trial day 57, the day of her second dose of fremazumab 225 mg in study 30084, which was the 2nd trial dose of fremanezumab overall including study 30083. She reportedly had a flat, dime-sized erythematous lesion at the site of injection which resolved by the next day (trial day 58). Then, on trial day 87, the subject had a larger erythematous area resulting after her 4th dose of IMP in study 30084. It was described as tennis ball sized and associated with pruritis. These events were classified as mild by the investigator and resolved by trial day 92. The subject withdrew on trial day 124.

*Reviewer comment: These cases are consistent with a hypersensitivity reaction with both resulting in recurrence with rechallenges and increased severity of the injection site reactions with increased frequency of exposure. The safety finding of hypersensitivity is currently described in labeling.*

There were another 3 subjects in the CM cohort from study 30084 who withdrew from the trial or IMP due to an adverse event, including 1 subject with the recurrent event of injection site pain (3 occurrences), 1 subject with recurrent injection site erythema and pruritis (3 events, all resolved within 1 day) and 1 subject with rhabdomyolysis. The case of rhabdomyolysis is detailed below given the other reported case of rhabdomyolysis reported as an SAE in study 30083.

Subject (b) (6) was a 15 year old male with CM who rolled over from study 30082 and experienced rhabdomyolysis resulting in hospitalization on trial day 88. His exposure prior to study 30084 is not known. He had 4 doses of fremanezumab 225 mg in study 30084, with report of elevated liver transaminases on the day of his 4th dose during a scheduled trial visit

(AST 150U/L, ALT 51U/L), as well as elevated CK (10788 U/L). On trial day 86, his exam was reportedly normal, but his liver transaminases and CK increased on laboratory follow up (AST 490 U/L, ALT 211 U/L, and CK 14527 U/L). The subject was hospitalized on trial day 88 for elevation of liver transaminases and CK. On repeat testing trial day 88, his laboratories revealed downtrending, but still elevated, transaminases (AST 162U/L, ALT 149 U/L). His serum CK level was not provided for this time point, but the Applicant stated it was reported his laboratories improved. He was afebrile, normotensive and had a normal heart rate. His urine toxicology screen was negative. No alternative cause for his elevated transaminases or CK was provided. On trial day 89, he was discharged from the hospital. He received no further doses of fremanezumab and he withdrew from the trial on trial day 144.

*Reviewer comment: This case is concerning for rhabdomyolysis associated with the IMP of fremanezumab, but the association is not clear. The subject had mildly elevated transaminases in a muscle (rather than liver) pattern the day of his scheduled 4th dose of IMP, but then had a notable worsening within 5 days of that dose. It is possible the rhabdomyolysis was associated with fremanezumab, and the 4th dose of fremanezumab escalated the process, but it's also possible there was another cause not revealed in the case report text. This case was of interest in the context of the other case of rhabdomyolysis. A further discussion of rhabdomyolysis is provided in section 8.5.*

At the time of the 120-day safety report, there was one additional EM subject who withdrew due to an AE:
Subject (b) (6) is a 10year old female with EM who experienced an event of idiopathic intracranial hypertension (IIH) on day 121, 2 days after the 5th dose in the OL study (8th consecutive dose overall) of fremanezumab 120 mg. This subject had a history of "optic disc drusen" diagnosed in 2023 and removed at the time of this reported AE of IIH. She was started on acetazolamide in response to the AE of IIH during the trial. She withdrew from the trial on day 147 due to the event of IIH.

*Reviewer comment: The AE of IIH does not appear related to the IMP of fremanezumab. The patient had a medical history of optic disc drusen, which suggests the patient's pre-existing diagnosis was changed from optic disc drusen to papilledema/IIH at the time of AE, and that this was not a new diagnosis/event.*

Study 10141:
There were no reported dropouts or discontinuations due to AEs.

Study 30082:
There were no reported dropouts or discontinuations due to AEs in the fremanezumab-treated subjects. There was one subject who withdrew from the study due to suicidal ideation in the

placebo cohort.

### 8.4.4 Significant Adverse Events

T

AEs by Intensity:

Adverse events by intensity in EM subjects at the time of original submission are shown in Table 16 and Error! Reference source not found.. In both Studies 30083 and 30084, the majority of AEs in EM subjects were of mild intensity. The percentage of subjects with severe AEs in study 30083 was similar in the placebo and all fremanezumab groups (4% and 3%, respectively). The severe AEs in the fremanezumab-treated subjects in study 30083 included migraine or headache (3) and one case of EBV hepatitis. The case of EBV hepatitis was previously detailed under section 8.4.2: Serious Adverse Events.

Table 16: Study 30083, Adverse Events by Intensity

| | Placebo N=112 (%) | Fremanezumab 120mg N=36 (%) | Fremanezumab 225mg N=87 (%) | All Fremanezumab N=123 (%) |
|---|---|---|---|---|
| mild | 36 (32) | 12 (33) | 33 (38) | 45 (37) |
| moderate | 15 (13) | 6 (17) | 13 (15) | 19 (15) |
| severe | 4 (4) | 2 (6) | 2 (2) | 4 (3) |

Source: Derived from Applicant provided ADAE dataset from Study 30083 by Reviewer, confirmed by OCS using Analysis Studio, Safety Explorer

The severe AEs in EM subjects in the open label trial (study 30084) included 1 event of severe injection site pain and 1 event of severe infection. There were no trends or unexpected severe adverse events in the EM subjects in the open label trial. There were no new severe adverse events reported in the EM subjects at the time of the 120-day safety update.

Table 17: Study 30084 Adverse Events by Intensity in EM Subjects

| | Fremanezumab 120mg N=58 (%) | Fremanezumab 225mg N=161 (%) | All Fremanezumab N=219 (%) |
|---|---|---|---|
| mild | 20(35) | 68(42) | 88 |
| moderate | 17(30) | 49(30) | 66 |
| severe | 1(2) | 1(1) | 2 |

Source: Derived from Applicant-provided ADAE dataset from Study 30084 by Reviewer, confirmed by OCS using

Study 10141: There were no reported significant adverse events in this PK study.

### 8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

Study 30083:
In the controlled trial (study 30083), approximately half of subjects in each treatment group experienced at least 1 AE. The most frequent AEs by system organ class (SOC) in all treatment arms were "infections and infestations" and "general disorders and administration site conditions."

Table 18: Study 30083, TEAEs by SOC Detailed by Preferred Terms where TEAE by Preferred Term occurred in least 2% of Subjects in Any Treatment Arm

| MedDRA SOC<br>MedDRA PT | Placebo<br>N=112<br>(%) | Fremanezumab<br>120mg<br>N=36<br>(%) | Fremanezumab<br>225mg<br>N=87<br>(%) | All Fremanezumab<br>N=123<br>(%) |
|---|---|---|---|---|
| Number of subjects with at least 1 AE | 55(49.1) | 20(55.6) | 48(55.2) | 68(55.3) |
| Infections & Infestations | 31(27.7) | 9(25) | 24(27.6) | 33(26.8) |
| Nasopharyngitis | 8(7.1) | 3(8.3) | 8(9.2) | 11(8.9) |
| COVID-19 | 6(5.4) | 2(5.6) | 5(5.7) | 7(5.7) |
| Upper respiratory tract infection | 5(4.5) | 2(5.6) | 4(4.6) | 6(4.9) |
| Pharyngitis streptococcal | 3(2.7) | 0 | 1 (1.1) | 1(<1) |
| General disorders and administration site conditions | 21(18.8) | 5(13.9) | 21(24.1) | 26(21.1) |
| Injection site erythema | 6(5.4) | 1(2.8) | 11(12.6) | 12(9.8) |
| Injection site pain | 6(5.4) | 0 | 6(6.9) | 6(4.9) |
| Injection site swelling | 1(<1) | 1(2.8) | 5(5.7) | 6(4.9) |
| Injection site urticaria | 2(1.8) | 1(2.8) | 0 | 1(<1) |
| Injection site irritation | 0 | 1(2.8) | 0 | 1(<1) |

| | | | | |
|---|---|---|---|---|
| Pyrexia | 1(<1) | 0 | 4(4.6) | 4(3.3) |
| Vaccination site pain | 1(<1) | 2(5.6) | 0 | 2(1.6) |
| Gastrointestinal disorders | 6(5.4) | 2(5.6) | 7(8) | 9(7.3) |
| Abdominal pain | 2(1.8) | 0 | 2(2.3) | 2(1.6) |
| Nausea | 2(1.8) | 1(2.8) | 2(2.3) | 3(1.6) |
| Constipation | 1(<1) | 1(2.8) | 1(1.1) | 2(1.6) |
| Diarrhea | 0 | 0 | 2(2.3) | 2(1.6) |
| Nervous system disorders | 6(5.4) | 3(8.3) | 6(6.9) | 9(7.3) |
| Headache | 2(1.8) | 2(5.6) | 0 | 2(1.6) |
| Migraine | 3(3) | 1(2.8) | 1(1.1) | 2(1.6) |
| Dizziness | 0 | 0 | 5(5.7) | 5(4.1) |
| Investigations | 5(4.5) | 2(5.6) | 4(4.6) | 6(4.9) |
| Alanine aminotransferase increased | 1(<1) | 1(2.8) | 2(2.3) | 3(2.4) |
| Aspartate aminotransferase increased | 1(<1) | 1(2.8) | 1(1.1) | 2(1.6) |
| Activated partial thromboplastin time prolonged | 0 | 1(2.8) | 0 | 1(<1) |
| Skin and subcutaneous disorders | 5(4.5) | 1(2.8) | 9(10.3) | 10(8.1) |
| Eczema | 0 | 0 | 2(2.3) | 2(1.6) |
| Rash | 0 | 1(2.8) | 2(2.3) | 3(2.4) |
| Musculoskeletal & connective tissue disorders | 4(3.6) | 1(2.8) | 4(4.6) | 5(4.1) |
| Pain in extremity | 0 | 1(2.8) | 0 | 1(<1) |
| Injury, poisoning, procedural complications | 3(2.7) | 0 | 3(3.4) | 3(2.4) |
| Ear & labyrinth disorders | 3(2.7) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | 3(2.7) | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 3(2.7) | 4(11.1) | 3(3.4) | 7(5.7) |
| Catarrh | 0 | 1(2.8) | 0 | 1(<1) |
| Cough | 0 | 1(2.8) | 1(1.1) | 2(1.6) |
| Epistaxis | 0 | 1(2.8) | 0 | 1(<1) |
| Oropharyngeal pain | 0 | 1(2.8) | 2(2.3) | 3(2.4) |
| Rhinorrhea | 0 | 1 (2.8) | 2(2.3) | 2(1.6) |
| Reproductive system and breast disorders | 2(1.8) | 1(3.8) | 1(1.1) | 2(1.6) |
| Genital rash | 0 | 1(2.8) | 0 | 1(<1) |
| Neoplasms | 0 | 0 | 1(1.1) | 1(<1) |
| Eye disorders | 1(<1) | 0 | 2(2.3) | 2(1.6) |
| Psychiatric disorders | 0 | 1(2.8) | 3(3.4) | 4(2.4) |
| Affective disorder | 0 | 1(2.8) | 0 | 1(<1) |
| Anxiety | 0 | 0 | 2(2.3) | 2(1.6) |
| Depression | 0 | 0 | 3(3.4) | 3(2.4) |

Sources: Study 30083 CSR, Table 18 confirmed by OCS using Analysis Studio, Safety Explorer, and by Reviewer using Applicant-provided ADAE dataset

The SOCs with greater numbers of events in both the fremanezumab and placebo-treated cohorts included infections and infestations and general disorders and administration site conditions. The SOCs with the greatest difference in percentage of subjects in any fremanezumab cohort compared to placebo included (in descending order): respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, skin and subcutaneous disorders, gastrointestinal disorders, nervous system disorders and psychiatric disorders. Each of these was assessed further:

The SOC of infections and infestations was largely driving by upper respiratory infections and COVID-19 infection. There was overall no difference seen between placebo and fremanezumab treated cohorts under this SOC.

The SOC of general disorders and administration site conditions was largely driven by injection site reactions. Injection site reactions occurred in approximately 16% of subjects receiving fremanezumab(20% of subjects receiving 225 mg fremanezumab and 8% of subjects receiving 120 mg fremanezumab) and 13% of subjects receiving placebo (Table 19). One percent of all study subjects including 2% of subjects in the fremanezumab 225 mg cohort, 0% of subjects in the fremanezumab 120 mg cohort, and <1% in the placebo cohort had an injection site reaction that required treatment, including medication. The majority of injection site reactions were mild, with 15 subjects treated with fremanezumab (2 in 120 mg cohort and 13 in 225 mg

cohort) experiencing a mild injection site reaction and 5 subjects treated with fremanezumab (1 in 120 mg cohort and 4 in 225 mg cohort) experiencing a moderate injection site reaction. There were no SAEs or severe AEs associated with injection site reactions in fremanezumab-treated subjects in study 30083.

Table 19: Study 30083 Injection Site Reactions

| | Placebo N=112 (%) | Fremanezumab 120mg N=36 (%) | Fremanezumab 225mg N=87 (%) | All Fremanezumab N=123 (%) |
|---|---|---|---|---|
| Injection site reaction | 15(13.4) | 3(8.3) | 17(19.5) | 20(16.3) |
| Injection site erythema | 6(5.4) | 1(2.8) | 11(12.6) | 12(9.8) |
| Injection site pain | 6(5.4) | 0 | 6(6.9) | 6(4.9) |
| Injection site swelling | 1(<1) | 1(2.8) | 5(5.7) | 6(4.9) |
| Injection site urticaria | 2(1.8) | 1(2.8) | 0 | 1(<1) |
| Injection site haemorrhage | 1(<1) | 0 | 1(1.1) | 1(<1) |
| Injection site rash | 2(1.8) | 0 | 0 | 0 |
| Injection site bruising | 0 | 0 | 1(1.1) | 1(<1) |
| Injection site discoloration | 0 | 0 | 1(1.1) | 1(<1) |
| Injection site hypertrophy | 0 | 0 | 1(1.1) | 1(<1) |
| Injection site hypoaesthesia | 1(<1) | 0 | 0 | 0 |
| Injection site induration | 1(<1) | 0 | 0 | 0 |
| Injection site irritation | 0 | 1(2.8) | 0 | 1(<1) |
| Injection site pruritis | 0 | 0 | 1(1.1) | 1(<1) |
| Injection site warmth | 0 | 0 | 1(1.1) | 1(<1) |

Source: Derived from Applicant provided ADAE dataset from Study 30083 by Reviewer

The SOC of respiratory, thoracic, and mediastinal disorders included 4 subjects in the aged 6-11 year group treated with 120 mg fremanezumab who experienced at least 1 of the following events with total event counts listed for each: cough (n=1), epistaxis (n=1), catarrh (n=1), oropharyngeal pain (n=1), rhinorrhea (n=1). All these events were recorded as mild.

*Reviewer comment: The incidence of these TEAEs fall within expected background rates in this population.*

The SOC of skin disorders was driven by events in the aged 12-17 year cohort, where 8 subjects receiving 225 mg fremanezumab versus 3 subjects receiving placebo experienced an event. These events consisted of mostly potential allergic skin reactions by different PTs and were all mild severity. A grouping of possible hypersensitivity reactions including skin reactions was done subsequently to investigate this further (see section 8.5.1)

The SOC of gastrointestinal (GI) disorders included more subjects experiencing constipation (2% vs 1%), nausea (2.4% vs 1%) and diarrhea (2% vs 0) in those treated with fremanezumab compared to placebo, respectively, with no clear difference in these events between the fremanezumab 120 mg and 225 mg cohorts. All but one TEAE in the fremanezumab-treated subjects under this SOC was recorded as mild. There was one moderate event of nausea both the placebo and in the fremanezumab-treated (225 mg) groups. Liver enzyme elevation as a GI-related TEAE was also investigated despite being under the "investigations" SOC. Three subjects (2.4%) in the all-fremanezumab cohort (2.8% in the 120 mg fremanezumab cohort and 2.3% in the 225 mg fremanezumab cohort) and 1 (0.9%) subject in the placebo cohort had a TEAE of elevated liver enzymes. Numbers of liver enzyme elevation events in the fremanezumab cohort were as follows: ALT elevation (n=3), AST elevation (n=2). All liver enzyme elevation TEAEs were recorded as mild in the fremanezumab cohort. There was 1 subject with ALT and AST elevation in the placebo cohort with these AEs recorded as moderate. Liver enzyme trends are further discussed under section 8.4.6 with no safety signal for liver injury observed.
*Reviewer comment: There may be an association with fremanezumab and gastrointestinal disorders of constipation, nausea and/or diarrhea, which is biologically plausible given the mechanism of action, but the numbers of these AEs are very small and there is no clear trend.*

The SOC of nervous system disorders was largely driven by headache, migraine, and dizziness, with dizziness only occurring in the fremanezumab 225 mg cohort.

*Reviewer comment: Dizziness events were mild (n=3) to moderate (n=2) and may be associated with the IMP of fremanezumab, but the events themselves were mixed in characterization, representing a pooling of unrelated AEs, and had confounders. These events are further*

*discussed under adverse reactions below.*

The SOC of psychiatric disorders was driven by events of anxiety or depression in 3 adolescent subjects in the fremanezumab 225 mg cohort. Two of these three subjects (subjects (b) (6) and (b) (6)) appeared to have a related psychiatric history with both on potentially confounding medications at baseline, including antidepressants and topiramate. Both of these subjects had a TEAE of depression in addition to other psychiatric TEAEs (Subject (b) (6) had both worsening anxiety and worsening depression reported during the study and Subject (b) (6) had TEAEs of depression, obsessive compulsive disorder, autism and attention deficit disorder all reported on the same study day). Anxiety and depression related AEs for these two subjects were reported as unrelated to IMP. Both subjects had changes in medications for the mood disorder and/or anxiety disorder after the onset of the reported AE across the trials, beginning days or months later, including changing baseline concomitant medications with increases and decreases in dosage, and initiating a new medication. The third adolescent subject (Subject (b) (6)) had no reported history of any mood disorder and was not on any anti-depressants or confounding medications, however, this third subject had partial dates listed at the start of study 30083 for both reported adverse events of anxiety and depression so it remained unclear if these AEs started before or after the first dose of IMP. Given uncertainty of the dates, these AEs were both treated as TEAEs. There was no treatment change reported for Subject's (b) (6) AEs of anxiety and depression in study 30083, but this subject did initiate a medication for mood disorders in study 30084. There was also one subject ((b) (6)) aged 8 years and receiving fremanezumab 120 mg who experienced an AE of affective disorder without any history of mood disorders or confounding medications, who had no treatment changes resulting from this TEAE in either study. All TEAEs of anxiety, depression and affective disorder were mild-moderate and all except one (AE of depression in subject (b) (6)) were reported as resolving/recovering, or recovered (Subject (b) (6) despite receiving several further doses of IMP after rolling over into study 30084. A potential association with psychiatric disorders was further considered as discussed in section 8.5.5.

*Reviewer comment: These events are small in number, and may be the result of subjects' medical history and/or other confounders (including medication) or just the expected background rate, however, relation to fremanezumab cannot be ruled out. The clinical team sent an IR on 4/3/2025 to confirm that 2 events (1 each of anxiety and depression in one subject in the 225 mg cohort) had an unclear start date relative to the treatment start date.*

<u>Adverse reactions >2% placebo:</u>
To identify adverse drug reactions (ADRs), the Applicant looked at TEAEs with an incidence >3% in the fremanezumab cohort. The only TEAEs by PT with >3% occurrence in the fremanezumab cohort that were at least >2% the occurrence in the placebo cohort were injection site erythema, injection site swelling, pyrexia and dizziness. Of these TEAEs, injection site reactions were the most common, with injection site erythema being the only TEAE occurring in at least

5% of fremanezumab-treated subjects with at least >2% the occurrence in the placebo cohort. The Applicant considered injection site reaction AE that was at least >3% occurrence in the fremanezumab cohort ADRs in the pediatric population in study 30083 since injection site reactions are known ADRs in the adult population. These ADRs included injection site swelling and erythema, as well as injection site pain. Notably, injection site pain was not observed more frequently in the fremanezumab cohort than the placebo cohort in the pediatric controlled study, but the Applicant deemed its addition as an ADR justified since injection site pain was expected given the route of administration, temporal relationship, and adult experience. The applicant did not include the several other injection site reactions listed above in Table 19Table 19 in their list of ADRs since these other injection site reactions occurred in <3% of subjects in the fremanezumab cohort.

*Reviewer comment: Given the close association of these PTs, and the impact of splitting injection site reactions, this reviewer considered all PTs that were injection site reactions in the list of TEAEs supporting the ADR of injection site reactions. In doing this, injection site reactions remained in line with the known safety profile based on adult data, as discussed in section 8.5.2.*

Dizziness occurred in 4% of the fremanezumab cohort, with 5 subjects treated with 225 mg fremanezumab and no subjects treated with 120 mg fremanezumab or placebo experiencing this AE. The Applicant did not deem dizziness an ADR due to a lack of mechanistic or biological plausibility, presence of negative re-challenges, confounders, and the frequency of dizziness within the migraine population, including as part of migraine. Two of the subjects reporting dizziness experienced transient dizziness shortly after the injection. One subject had chronic dizziness with a reported ongoing episode about a month after dosing and another subject experienced dizziness while taking a triptan two weeks after dosing of fremanezumab. The last subject experienced dizziness the day after the injection with nausea in the setting of taking ibuprofen.

*Reviewer comment: The TEAEs of dizziness are diverse in description, likely representing unrelated events pooled into one PT, and, outside of the expected dizziness due to a vasovagal response presenting as lightheadedness from an injection, there is no clear relationship with fremanezumab. I agree with not including dizziness as an ADR.*

Pyrexia occurred in 4 subjects in the combined fremanezumab cohort. In two to three of these 4 cases, pyrexia was accompanied by other events suggestive of a concomitant infection. All cases had a negative re-challenge. The Applicant did not consider pyrexia an ADR.

*Reviewer comment: Given the confounders in at least 2 to 3 of the cases of pyrexia in fremanezumab-treated subjects, I agree with not including pyrexia as an ADR. However, pyrexia was included in an analysis of possible hypersensitivity reactions presented in section 8.5.1.*

TEAEs of special interest to review:
Regarding TEAEs of special interest in this review not already discussed above, there were 2 TEAEs under eye disorders for each of placebo and fremanezumab-treated cohorts. In the fremanezumab cohort, there was 1 TEAE of "blurred vision" and 1 TEAE of "periorbital swelling." Both were recorded as mild intensity.

*Reviewer comment: These eye disorder TEAEs do not seem related to IMP aside from the periorbital swelling event being a possible hypersensitivity reaction as analyzed in section 8.5.1.*

There were no TEAEs of anaphylaxis or severe hypersensitivity. Hypersensitivity reactions are further analyzed in section 8.5.1.

There were no TEAEs of hypertension or Raynaud's phenomenon.

*Reviewer comment: Overall, the TEAE data from study 30083 suggest the strongest association of fremanezumab with injection site reactions, which may be more common with the 225 mg dose. This is fitting with what was seen when reviewing the serious AEs in section 8.4.2. TEAE data also suggest a possible increased risk of hypersensitivity based on the skin disorders SOC and review of injection site reactions, which was reviewed further in section 8.5.2.*

Study 30084:

TEAEs in EM subjects from this trial were analyzed. At the time of the original submission, injection site erythema was the most common TEAE in EM subjects, occurring in 19% of subjects in the 120 mg cohort and 21% of subjects in the 225 mg cohort, followed by nasopharyngitis (12% in the 120 mg cohort and 17% in the 225 mg cohort) and COVID-19 (14% in each cohort). Subjects with at least 1 injection site AE included 24% of those in the 120 mg cohort and 31% of those in the 225 mg cohort (approximately 30% of EM subjects overall in study 30084). The TEAE profile remained similar at the time of the 120-day safety update, with no new safety signal observed.

Table 20: Study 30084 TEAEs by PTs Occurring in at Least 2% of all EM Subjects Grouped by SOC

| MedDRA SOC<br>MedDRA PT | Fremanezumab 120mg<br>N=58<br>(%) | Fremanezumab 225mg<br>N=161<br>(%) | All Fremanezumab<br>N=219<br>(%) |
|---|---|---|---|
| Subjects with at least 1 AE | 38 (66.5) | 118(73.3) | 156(71.2) |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | 5(5.2) | 23(14.3) | 26(11.9) |
| Abdominal pain | 2(3.4) | 6(3.7) | 8(3.7) |
| Nausea | 0 | 6(3.7) | 6(2.7) |
| General disorders and administration site conditions | 13(22.4) | 62(38.5) | 75(34.2) |
| Injection site erythema | 11(19) | 34(21.1) | 45(20.5) |
| Injection site swelling | 4(6.9) | 16(9.9) | 20(9.1) |
| Injection site pain | 3(5.2) | 11(6.8) | 14(6.4) |
| Injection site induration | 1(1.7) | 12(7.5) | 13(5.9) |
| Injection site pruritis | 1(1.7) | 4(2.5) | 5(2.3) |
| Pyrexia | 0 | 5(3.1) | 5(2.3) |
| Infections and infestations | 34(58.6) | 79(49.1) | 113(51.6) |
| COVID-19 | 8(13.8) | 22(13.7) | 30(13.7) |
| Nasopharyngitis | 7(12.1) | 28(17.4) | 35(16) |
| Gastroenteritis | 3(5.2) | 7(4.3) | 10(4.6) |
| Pharyngitis | 1(1.7) | 6(3.7) | 7(3.2) |
| Upper respiratory infection | 8(13.8) | 9(6.8) | 17(7.8) |
| Sinusitis | 2(3.4) | 6(3.7) | 8(3.7) |
| Musculoskeletal and connect tissue disorders | 7(12.1) | 12(7.5) | 19(8.7) |
| Pain in extremity | 3(5.2) | 4(2.5) | 7(3.2) |
| Nervous system disorders | 4(7) | 13(8) | 17(8) |
| Migraine | 3(5.2) | 5(3.1) | 8(3.7) |
| Respiratory, thoracic and mediastinal disorders | 9(15.5) | 20(12.4) | 29(13.2) |
| Oropharyngeal pain | 2(3.4) | 9(5.6) | 11(5) |
| Upper respiratory inflammation | 3(5.2) | 2(1.2) | 5(2.3) |

| | | | |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | 3(5.2) | 12(7.5) | 15(6.8) |
| Rash | 2(3.4) | 3(1.9) | 5(2.3) |
| Acne | 0 | 5(3.1) | 5(2.2) |
| Immune system disorders | 4(6.9) | 2(1.2) | 6(2.7) |
| Seasonal allergy | 4(6.9) | 1 (<1) | 5(2.3) |

Source: Study 30084 CSR, Table 27 and confirmed by OCS adverse event analysis using Analysis Studio, Safety Explorer and by reviewer using Applicant provided ADAE dataset

*Reviewer comment: The TEAE data from study 30084 do not show any new safety signals.*

Study 10141:
There were no reported TEAEs in this PK study.

### 8.4.6 Laboratory Findings

Study 30083:
There were no clinically meaningful differences or consistent trends between fremanezumab and placebo in chemistries, hematology, coagulation and urinalysis laboratory parameter changes (mean or median) from baseline in study 30083.

Shift analyses for study 30083 suggested a slightly higher risk of ALT, AST or alkaline phosphatase increase, but the shifts, if present, were small:

ALT: Approximately 10% of subjects in the fremanezumab cohort (14% of subjects receiving 120 mg fremanezumab and 8% of subjects receiving 225 mg fremanezumab) and 7% of subjects in the placebo cohort had a normal ALT baseline (defined as ALT<=1xULN) and an abnormal maximum post-baseline ALT (defined as ALT>1xULN).

No subjects receiving 120 mg fremanezumab, 2% of subjects receiving 225 mg fremanezumab and 3% of subjects in the placebo cohort with an elevated baseline ALT had a normal maximum post-baseline ALT.

AST:
Approximately 4% in the fremanezumab cohort (6% of subjects receiving 120 mg fremanezumab cohort and 4% of subjects receiving 225 mg fremanezumab cohort), and 0 in the placebo cohort had a normal baseline AST (defined as AST less than or equal to 1x ULN) and elevated post-baseline maximum AST (defined as AST at least 1x ULN.

No subjects in the fremanezumab cohort and 3% in the placebo cohort with an elevated baseline AST had a normal maximum post-baseline AST.

ALP:
Approximately 14% of subjects in the 120 mg fremanezumab cohort, 7% of subjects in the 225 mg fremanezumab cohort, 9% of subjects in the all-treated fremanezumab cohort and 4% of subjects in the placebo cohort had a normal baseline ALP (defined as ALP<=1xULN) and an elevated maximum post-baseline ALP (defined as ALP>1xULN).

Approximately 4% of subjects in the fremanezumab cohort (3% of subjects receiving 120 mg fremanezumab and 5% of subjects receiving 225 mg fremanezumab), and 2% of subjects in the placebo cohort with an elevated baseline ALP and normal maximum post-baseline ALP.

Bilirubin:
There were no differences in either active treatment arm compared to placebo in bilirubin shifts from normal to >1x ULN.

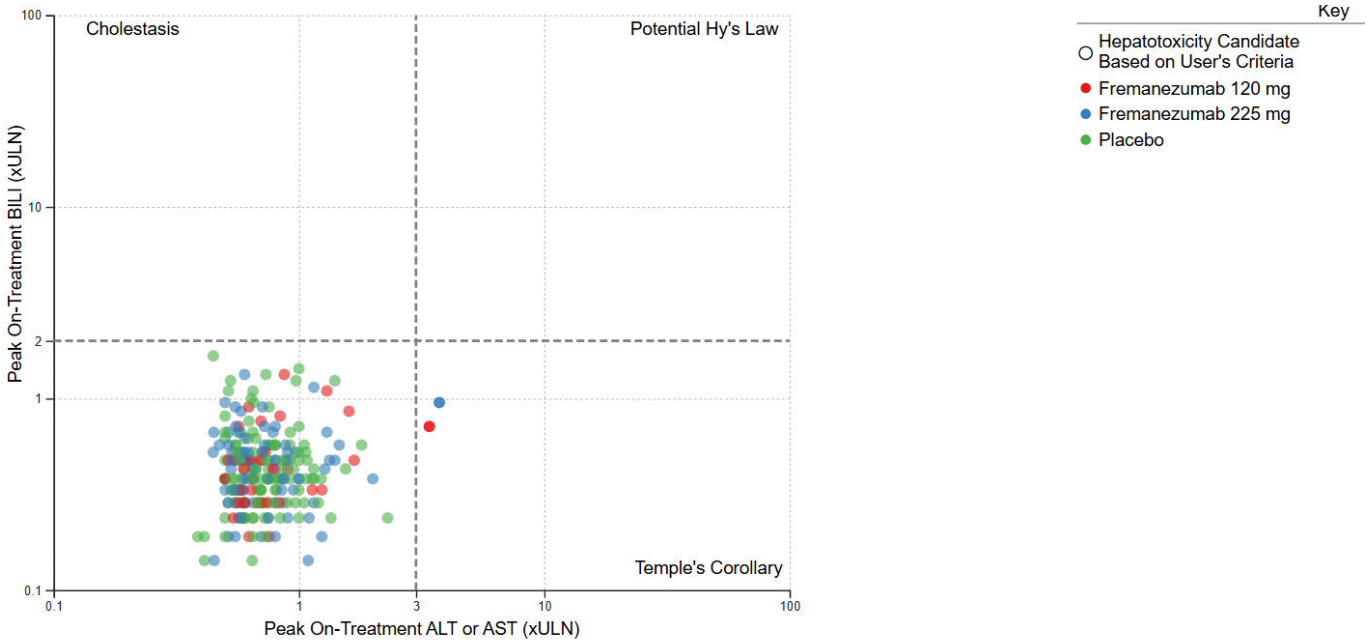
There were no Hy's law or potential Hy's law cases.

There were 4 cases with ALT >2x ULN in the fremanezumab cohort and 1 in the placebo cohort. Only two subjects in the fremanezumab cohort (both receiving 225 mg fremanezumab) had an ALT >3x ULN. One subject (subject (b) (6) with an ALT >3x ULN had an alternative cause which was a SAE of EBV hepatitis as previously discussed in section 8.4.2, and had return to baseline. The other subject with an ALT >3x ULN (subject (b) (6)) had laboratories fitting a myopathic pattern, and is discussed in section 8.5.6. The other 2 subjects with an ALT>2x ULN but maximum elevation of <3x ULN in the fremanezumab cohort included 1 subject ((b) (6)) with a maximum ALT reported at 60U/L and return to baseline of ALT despite continued dosing of fremanezumab, and 1 subject ((b) (6)) who dropped out of the study after mild elevation in ALT on a confounding medication, as discussed in section 8.4.3.

There were 3 cases of AST>2x ULN in the fremanezumab cohort (2 subjects receiving 225 mg fremanezumab and 1 subject receiving 120 mg fremanezumab), and 1 case of AST>2x ULN in the placebo cohort. The 3 fremanezumab-treated subjects with AST elevations >2xULN were subjects (b) (6) as discussed in the above paragraph. Subjects (b) (6) had return to baseline of AST with ongoing dosing of fremanezumab across studies 30083 and 30084, and alternative causes of liver enzyme elevation (rhabdomyolysis and EBV hepatitis) unrelated to drug-induced liver injury. Subject (b) (6) had a mild elevation in AST on a confounding medication, as discussed in section 8.4.3.

An eDish plot created by the Drug Induced Liver Injury Team for study 30083 is shown below, visually demonstrating the possible, but if present small, shift in liver enzymes with fremanezumab:

Figure 8: eDish Plot Study 30083




Source: OCS Analysis Studio, Hepatic Explorer.
Filters: None.
*Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
*Missing ULN values are imputed as the weighted mean of the present ULN values per lab test code per subject.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal.

*Reviewer comment: The numbers of subjects who experienced a shift above 1xULN for any of these liver-related laboratories are small, and when investigated by degree of elevation, were mostly mild. The only cases with notable liver enzyme elevation had alternative causes. Most cases of mild elevation had return to baseline of liver enzymes despite ongoing dosing. In evaluation of liver enzymes, there was 1 additional case identified of possible myopathy/rhabdomyolysis which was further investigated in section 8.5.6.*

Study 30084:
At the time of the original application, shift analyses using baseline values from screen for EM subjects suggested a possible mild shift in aminotransaminases as follows:

ALT:
Approximately 8% in the fremanezumab treated EM subjects (7% of subjects receiving 120 mg cohort and 8% of subjects receiving 225 mg fremanezumab) had a normal baseline ALT and an elevated maximum post-baseline ALT.

Approximately 3% of the fremanezumab treated EM subjects (2% of subjects receiving 120 mg and 4% of subjects receiving 225 mg) had an elevated baseline ALT and a normal maximum post-baseline ALT.

AST:
Approximately 3% of fremanezumab treated EM subjects (3% of subjects receiving 120 mg fremanezumab and 3% receiving 225 mg fremanezumab) had a normal baseline AST and an elevated maximum post-baseline AST.

Less than 2% of fremanezumab treated EM subjects (2% of subjects receiving 120 mg and <1% receiving 225 mg fremanezumab) had an elevated baseline AST and a normal maximum post-baseline AST.

ALP:
Approximately 7% of fremanezumab treated EM subjects (9% of subjects receiving 120 mg and, 6% of subjects receiving 225 mg), and had a normal baseline ALP and an elevated maximum post-baseline ALP.

Approximately 3% of fremanezumab treated subjects (2% of subjects receiving 120 mg and 3% of subjects receiving 225 mg) and had an elevated baseline ALP with a normal maximum post-baseline ALP.

In EM subjects, there were no Hy's Law or potential Hy's Law cases. Elevations in transaminases were again mild, with only 4 cases with ALT>2x ULN with no unexplained cases of ALT or AST at least 5x the ULN. When including available data from CM subjects in study 30084, there were also no Hy's Law or potential Hy's Law cases, nor unexplained cases of ALT or AST at least 5x the ULN. The Drug Induced Liver Injury team did not identify any cases of possible drug-induced liver injury in EM or CM subjects in study 30084.

At the time of the 120-day safety update, there was no new safety signal or trend observed for chemistries, including liver enzymes, and no Hy's law or potential Hy's Law cases reported at the time of the 120-day safety update.

Study 30082:
In the controlled CM pediatric study, there were no clinically meaningful laboratory trends observed by the applicant.

*Reviewer comment: In consultation with the drug induced liver injury(DILI) team, it was determined there was no hepatotoxicity signal in the pediatric studies.The DILI team reviewed data from studies 30083 and 30084 and found no cases of liver enzyme or bilirubin elevations*

*attributable to fremanezumab. In addition, the DILI team noted postmarket reports of DILI or hepatotoxicity associated with adult fremanezumab use in FDA Adverse Event Reporting System (FAERS), LiverTox, and the published literature are scant suggesting a low risk for adults with no reason to believe that children carry a higher risk for fremanezumab hepatotoxicity.*

### 8.4.7 Vital Signs

There were no clinically meaningful or consistent trends from baseline based on means or medians by visit in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), height or weight for placebo or fremanezumab groups in either study 30083 or EM subjects in study 30084. Height and weight as well as blood pressure were further analyzed under special analyses for growth and development and hypertension, respectfully. These are presented in section 8.5.

Study 30082:
In the controlled CM pediatric study, the Applicant reported no clinically meaningful trends in vital signs.

### 8.4.8 Electrocardiograms (ECGs)

Study 30083:
In the controlled trial, there were approximately 7% of fremanezumab and 15% of placebo-treated subjects with abnormal ECGs. No abnormalities were deemed clinically significant. Heart rates by ECG, PR intervals and QRS durations were similar at each month of the trial, beginning at screen and ending with the last (3rd) dose of IMP. There was one mild AE of palpitations. There were no ECG abnormalities reported as an AE for fremanezumab-treated subjects.

Study 30084:
In the open label trial, at the time of original submission, there were ~10% of EM subjects (5 receiving 120 mg fremanezumab and 18 receiving 225 mg fremanezumab) who had abnormal ECGs. None were considered clinically significant. There were no obvious changes by heart rate, PR interval or QRS duration in EM subjects. There was 1 ECG abnormality reported as an AE (mild) for an EM subject (b) (6). This subject was an 11-year-old female receiving 120 mg fremanezumab who had mild reported QTc prolongation up to 457ms. This subject's baseline QTc was 427ms and this subject had a prolonged QTc of 446ms reported as a TEAE during study 30083 while treated with placebo. There were no new trends or safety signals related to ECGs observed with the 120-day safety update.

*Reviewer comment: There were no trends or associations observed with the IMP of fremanezumab and ECG changes across studies 30083 and 30084.*

Study 30082:
In the controlled CM pediatric study, there were no clinically meaningful trends in ECGs observed by the Applicant.

#### 8.4.9 QTc

Not applicable.

*Reviewer note: Analyses of QT and QTc intervals in ECGs were conducted in Phase2/3 adult studies with no clinically significant findings. No dedicated QT studies were conducted in adults, in agreement with the Division.*

#### 8.4.10 Immunogenicity

Study 30083:
In the controlled trial, a total of 6 (2.4%) subjects who received fremanezumab had at least 1 positive anti-drug antibody test. Four of these 6 subjects with a positive anti-drug antibody test had positive pre-dose timepoint that did not increase at least 4-fold at any post-dose time-point, and so, were not classified as having a treatment-emergent ADA response. 1.6% (n=2) of subjects who received fremanezumab (1 in each dose group and 1 in each age category) tested positive for anti-drug antibodies (ADA) post-dose who had a negative antibody titre pre-dose. These two subjects were classified as having treatment-emergent ADA responses. Titres of ADAs for all 6 subjects ranged from 0.854 to 1.95 on a Log10 scale. Two subjects with ADA-positive samples were identified as having neutralizing antibody (NAb), with one of these subjects also having a treatment-emergent ADA response.

Study 30084:
See Clinical Pharmacology review. This study was ongoing at time of review and immunogenicity data are not conclusive.

### 8.5 Analysis of Submission-Specific Safety Issues

#### 8.5.1 Hypersensitivity

Given the higher reports of injection site reactions, cases of increased severity of injection site reactions after subsequent doses, and known hypersensitivity reactions associated with

fremanezumab in the adult population, further assessment of hypersensitivity in the pediatric population was conducted by regrouping preferred terms of TEAEs first in the controlled study (study 30083) to establish a grouping to define probable hypersensitivity reactions followed by an analysis of the chosen grouping for the open label safety study (study 30084) and then pooled data analyses to look an exposure duration effects. Three different groupings were conducted on review of data as presented in Error! Reference source not found. below. Injection site reactions are separately reviewed in 8.5.2, but were included in this analysis in case there was a relationship to hypersensitivity reactions.

Table 21: Study 30083 Possible Hypersensitivity Reactions

| Grouping #<br>Grouping Term<br>PTs | Placebo<br><br>(n=112)<br>N (%) | Fremanezumab 120mg<br>(n=36)<br>N (%) | Fremanezumab 225mg<br>(n=87)<br>N (%) | All Fremanezumab<br>(n=123)<br>N (%) |
|---|---|---|---|---|
| Group 1:<br>Possible allergic skin reactions: Urticaria, allergic dermatitis, rash, pruritis<br><br>Facial swelling: periorbital swelling | 1 (<1) | 1 (2.8) | 5 (5.7) | 6 (4.9) |
| Group 2:<br>Possible allergic skin reactions: Urticaria, allergic dermatitis, rash, pruritis<br><br>Facial swelling: periorbital swelling<br><br>Pyrexia | 2(1.8) | 1 (2.8) | 7 (8.0) | 8 (6.5) |
| Group 3:<br>Possible allergic skin reactions: Urticaria, allergic dermatitis, rash, pruritis<br><br>Facial swelling: periorbital swelling | 17 (15.2) | 4 (11.1) | 26 (29.9) | 30 (24.4) |

| | | | | |
|---|---|---|---|---|
| Pyrexia<br><br>Injection site reactions: Injection site erythema, pain, swelling, urticaria, rash, hypertrophy, discoloration, hypoaesthesia, induration, irritation, pruritis, warmth | | | | |

Source: Reviewer created using Applicant-provided ADAE dataset, study 30083

All these potential hypersensitivity TEAEs were mild-moderate in intensity with the majority being mild. No potential serious hypersensitivity or anaphylaxis TEAEs were identified.

The open-label safety study (study 30084) did not reveal an increased risk of hypersensitivity reactions with approximately 3% of EM subjects receiving fremanezumab at the time of original submission experiencing possible hypersensitivity reactions based on PTs grouped as defined by Group 1 in Error! Reference source not found.Error! Reference source not found.. There were no cases of severe hypersensitivity or anaphylaxis reported in study 30084.

Table 22: Study 30084, Possible Hypersensitivity Reactions

| Preferred Terms | Fremanezumab 120 mg (N = 58) | Fremanezumab 225 mg (N = 161) | All Fremanezumab (N = 219) |
|---|---|---|---|
| Total subjects with hypersensitivity | 2 ( 3.4%) | 5 ( 3.1%) | 7 ( 3.2%) |
| Rash | 2 ( 3.4%) | 3 ( 1.9%) | 5 ( 2.3%) |
| Rash papular | 0 ( 0.0%) | 1 ( 0.6%) | 1 ( 0.5%) |
| Urticaria | 0 ( 0.0%) | 1 ( 0.6%) | 1 ( 0.5%) |

Source: Created by reviewer Rui Lee in additional safety analysis, confirmed by clinical reviewer with ADAE dataset, study 30083
Safety population of episodic migraine subjects and TRTEMFL = Y
Hypersensitivity includes Pruritis, Pyrexia, Rash, Urticaria, Periorbital swelling, Eczema, Rash papular and Dermatitis allergic

Pooled data for EM subjects from studies 30083 and 30084 at the time of original submission showed no increased rate of possible hypersensitivity reactions or injection site reactions by

exposure duration to fremanezumab as shown in Error! Reference source not found. below.

| | Fremanezumab 120 mg | | | Fremanezumab 225 mg | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | **AEs Occurring at Less than 6mo Exposure (N=61)** | **AEs Occurring at 6mo to Less Than 12mo Exposure (N=55)** | **AEs Occurring at 12mo or More Exposure (N=20)** | **AEs Occurring at Less than 6mo Exposure (N=164)** | **AEs Occurring at 6mo to Less Than 12mo Exposure (N=148)** | **AEs Occurring at 12mo or More Exposure (N=67)** | **AEs Occurring at Less than 6mo Exposure (N=225)** | **AEs Occurring at 6mo to Less Than 12mo Exposure (N=203)** |
| **AESI Group** | | | | | | | | |
| **Preferred Term** | | | | | | | | |
| **Hypersensitivity Reaction** | **2 ( 3.3)** | **0** | **1 ( 5.0)** | **15 ( 9.1)** | **3 ( 2.0)** | **0** | **17 ( 7.6)** | **3 ( 1.5)** |
| Pyrexia | 0 | 0 | 0 | 8 ( 4.9) | 1 ( 0.7) | 0 | 8 ( 3.6) | 1 ( 0.5) |
| Rash | 2 ( 3.3) | 0 | 0 | 5 ( 3.0) | 1 ( 0.7) | 0 | 7 ( 3.1) | 1 ( 0.5) |
| Pruritus | 0 | 0 | 1 ( 5.0) | 1 ( 0.6) | 0 | 0 | 1 ( 0.4) | 0 |
| Rash papular | 0 | 0 | 0 | 2 ( 1.2) | 0 | 0 | 2 ( 0.9) | 0 |
| Urticaria | 0 | 0 | 0 | 1 ( 0.6) | 1 ( 0.7) | 0 | 1 ( 0.4) | 1 ( 0.5) |
| Dermatitis allergic | 0 | 0 | 0 | 1 ( 0.6) | 0 | 0 | 1 ( 0.4) | 0 |
| Periorbital swelling | 0 | 0 | 0 | 1 ( 0.6) | 0 | 0 | 1 ( 0.4) | 0 |

Source: OCS created using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', MIGCLASS = 'Episodic Migraine'; Column Variable 1: TRT01A (Actual Treatment for Period 01), Column Variable 2: EXPGRP ().
AESI Group Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESI = 'Hypersensitivity Reaction' or 'Injection Site Reaction'; Row Variable 1: AESI (), Row Variable 2: AEDECOD (Dictionary-Derived Term).

Table 23: ISS, Summary of EM Subjects with Possible Hypersensitivity Reactions by Exposure Duration

Hypersensitivity reactions, including severe reactions and anaphylaxis are labeled Warnings and Precautions in the current fremanezumab labeling for the adult indication. In the pivotal adult trials, there were cases of hypersensitivity AEs by preferred terms including PTs of rashes, dermatitis, urticaria, pruritis, and facial swelling/angioedema. Approximately 1-3% of fremanezumab-treated subjects compared to approximately 1% of placebo-treated subjects in the placebo-controlled adult trials experienced hypersensitivity reactions (excluding local injection site reactions), with approximately 2-4% of all fremanezumab-treated subjects across the pivotal adult trials experiencing hypersensitivity reactions. There have been cases of anaphylaxis with fremanezumab in the postmarket setting.

*Reviewer comment: Overall, the rates of hypersensitivity reactions in the pediatric population by this review seem comparable to what has been observed in adults and with no clear increase with drug exposure. While no cases of severe hypersensitivity reactions or anaphylaxis were observed in these pediatric trials, this may be due to smaller enrollment numbers in these pediatric studies compared to the adult studies, rather than a difference in risk.*

### 8.5.2 Injection site reactions

Injection site reactions occurred in 16% of fremanezumab-treated and 13% of placebo treated subjects in the controlled trial (study 30083), driven by reactions in the fremanezumab 225 mg cohort (those weighing at least 45 kg). There were no subjects experiencing injection site reactions resulting in discontinuation or withdrawal in the controlled study (study 30083), and 3 episodic migraine subjects experiencing injection site reactions resulting in discontinuation or withdrawal in the open label study (study 30084). Most injection site reactions were mild with only one episodic migraine subject experiencing an injection site reaction graded as severe (study 30084). None were serious adverse events in episodic migraine subjects across studies 30083 and 30084. There was no observed increased risk of injection site reactions with duration of fremanezumab exposure based on pooled data from episodic migraine subjects as shown in Error! Reference source not found..

Table 24: ISS, Summary of Episodic Migraine Subjects with Injection Site Reactions by Exposure Duration

| | Fremanezumab 120 mg | | | Fremanezumab 225 mg | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | AEs Occurring at Less than 6mo Exposure (N=61) | AEs Occurring at 6mo to Less Than 12mo Exposure (N=55) | AEs Occurring at 12mo or More Exposure (N=20) | AEs Occurring at Less than 6mo Exposure (N=164) | AEs Occurring at 6mo to Less Than 12mo Exposure (N=148) | AEs Occurring at 12mo or More Exposure (N=67) | AEs Occurring at Less than 6mo Exposure (N=225) | AEs Occurring at 6mo to Less Than 12mo Exposure (N=203) |
| AESI Group | | | | | | | | |
| Preferred Term | | | | | | | | |
| Injection Site Reaction | **13 (21.3)** | **7 (12.7)** | **0** | **55 (33.5)** | **19 (12.8)** | **0** | **68 (30.2)** | **26 (12.8)** |
| Injection site erythema | 11 (18.0) | 6 (10.9) | 0 | 34 (20.7) | 13 ( 8.8) | 0 | 45 (20.0) | 19 ( 9.4) |
| Injection site swelling | 3 ( 4.9) | 4 ( 7.3) | 0 | 19 (11.6) | 5 ( 3.4) | 0 | 22 ( 9.8) | 9 ( 4.4) |
| Injection site pain | 2 ( 3.3) | 1 ( 1.8) | 0 | 16 ( 9.8) | 4 ( 2.7) | 0 | 18 ( 8.0) | 5 ( 2.5) |
| Injection site induration | 1 ( 1.6) | 0 | 0 | 11 ( 6.7) | 4 ( 2.7) | 0 | 12 ( 5.3) | 4 ( 2.0) |
| Injection site pruritus | 1 ( 1.6) | 0 | 0 | 5 ( 3.0) | 1 ( 0.7) | 0 | 6 ( 2.7) | 1 ( 0.5) |
| Injection site discolouration | 1 ( 1.6) | 1 ( 1.8) | 0 | 3 ( 1.8) | 0 | 0 | 4 ( 1.8) | 1 ( 0.5) |
| Injection site rash | 0 | 0 | 0 | 4 ( 2.4) | 1 ( 0.7) | 0 | 4 ( 1.8) | 1 ( 0.5) |
| Injection site bruising | 1 ( 1.6) | 0 | 0 | 3 ( 1.8) | 0 | 0 | 4 ( 1.8) | 0 |
| Injection site inflammation | 0 | 0 | 0 | 2 ( 1.2) | 1 ( 0.7) | 0 | 2 ( 0.9) | 1 ( 0.5) |
| Injection site haemorrhage | 0 | 0 | 0 | 2 ( 1.2) | 0 | 0 | 2 ( 0.9) | 0 |
| Injection site urticaria | 1 ( 1.6) | 0 | 0 | 1 ( 0.6) | 0 | 0 | 2 ( 0.9) | 0 |
| Injection site warmth | 1 ( 1.6) | 0 | 0 | 1 ( 0.6) | 0 | 0 | 2 ( 0.9) | 0 |
| Injection site hypertrophy | 0 | 0 | 0 | 1 ( 0.6) | 0 | 0 | 1 ( 0.4) | 0 |
| Injection site irritation | 1 ( 1.6) | 0 | 0 | 0 | 0 | 0 | 1 ( 0.4) | 0 |

Source: OCS created using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', MIGCLASS = 'Episodic Migraine'; Column Variable 1: TRT01A (Actual Treatment for Period 01), Column Variable 2: EXPGRP ().
AESI Group Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESI = Site Reaction'; Row Variable 1: AESI (), Row Variable 2: AEDECOD (Dictionary-Derived Term).

Injection site reactions are labeled as an adverse reaction for fremanezumab in adults with migraine based on the pivotal trials in adults. Approximately 43-45% of subjects treated with fremanezumab compared to approximately 38% of subjects treated with placebo experienced injection site reactions in the pivotal controlled adult trials for the preventive treatment of migraine in adults.

*Reviewer comment: Injection site reactions in the pediatric trials are in line with the known safety profile for fremanezumab based on clinical trials in adults. There is not an observed difference in injection site reactions in the pediatric trials compared to the adult trials when reviewing the proportional differences between fremanezumab and placebo treated arms, which is near 20% for both adults and pediatrics in clinical trials.*

### 8.5.3 Hypertension

The Applicant provided an additional analysis of safety related to blood pressure from EM subjects in studies 30083 and 30084 using pooled data from these studies as well as data from only study 30083. This analysis included the following: proportion of subjects in each category of blood pressure (as defined by using the 2017 American Academy of Pediatrics hypertension clinical practice guidelines) by visit, shift tables showing proportion of subjects in each category of blood pressure shifting to a different category of blood pressure by visit, and number of new onset hypertension cases for both study 30083 and pooled studies 30083 with 30084.

Study 30083:
In the controlled study (study 30083), there were similar proportions of subjects in placebo and fremanezumab cohorts with normal blood pressure, elevated blood pressure, stage 1 hypertension (HTN) and stage 2 hypertension at each visit and at baseline. The majority of subjects had normal blood pressure at baseline and at each visit. There were similar numbers of subjects with new onset hypertension (stage 1 and 2) identified in fremanezumab (n=7) and placebo (n=9) cohorts during the study. Postbaseline shifts from normotensive to elevated and stage 1 HTN occurred in similar frequences in the fremanezumab and placebo treated cohorts. There was only 1 subject who had a shift from normotensive to stage II HTN that is unlikely due to study drug (details below).

Shift from normotensive to Stage II HTN:
Subject (b) (6) is a 12-year-old female with normal baseline blood pressure who experienced stage II hypertension on day 81 of the trial, 25 days after the 3rd dose of fremanezumab 225 mg. The stage 2 hypertension classification for this subject resulted from one read of a diastolic blood pressure of 93, which was 10mmHg above baseline. On the day of this event, the subject began study 30084 as a rollover subject and received a 4th dose of fremanezumab. This subject also received a further 8 subsequent doses of fremanezumab, with 1 further report of elevated blood pressure (month 6, day of dose 7) and normotensive readings the other 8 visits of study 30084. There was no overall trend observed in this subject for blood pressure elevation. No treatments for hypertension were initiated during the study.

In an outlier analysis investigating increases in systolic or diastolic blood pressure by over 20mmHg as well as decreases in systolic or diastolic blood pressure by over 20mmHg in the

controlled trial (Table 25) there was a suggestion of increased blood pressure risk with fremanezumab.

Table 25: Study 30083, Outlier Analysis of Blood Pressure Parameters*

| Parameters | Placebo (N = 112) | Fremanezumab 120 mg (N = 36) | Fremanezumab 250 mg (N = 87) | All Fremanezumab (N = 123) |
|---|---|---|---|---|
| Systolic Blood Pressure > 140 mmHg | 1 (0.9% ) | 1 (2.8% ) | 0 (0.0% ) | 1 (0.8% ) |
| Systolic Blood Pressure > 160 mmHg | 0 (0.0% ) | 0 (0.0% ) | 0 (0.0% ) | 0 (0.0% ) |
| Diastolic Blood Pressure > 90 mmHg | 0 (0.0% ) | 2 (5.6% ) | 1 (1.1% ) | 3 (2.4% ) |
| Diastolic Blood Pressure > 100 mmHg | 0 (0.0% ) | 1 (2.8% ) | 0 (0.0% ) | 1 (0.8% ) |
| Systolic Blood Pressure < 90 mmHg | 5 (4.5% ) | 1 (2.8% ) | 4 (4.6% ) | 5 (4.1% ) |
| Diastolic Blood Pressure < 50 mmHg | 1 (0.9% ) | 1 (2.8% ) | 0 (0.0% ) | 1 (0.8% ) |
| Systolic Blood Pressure increase > 20 mmHg | 3 (2.7% ) | 5 (14% ) | 6 (6.9% ) | 11 (8.9% ) |
| Diastolic Blood Pressure increase > 20 mmHg | 0 (0.0% ) | 2 (5.6% ) | 3 (3.4% ) | 5 (4.1% ) |
| Systolic Blood Pressure decrease > 20 mmHg | 7 (6.3% ) | 2 (5.6% ) | 5 (5.7% ) | 7 (5.7% ) |
| Diastolic Blood Pressure decrease > 20 mmHg | 1 (0.9% ) | 0 (0.0% ) | 3 (3.4% ) | 3 (2.4% ) |

Source: Table created by reviewer Rui Lee in an additional safety analysis
*Subjects had baseline normal and abnormal BP values

Pooled (Studies 30083 and 30084):
By visit, there were 4-13% of EM subjects across studies 30083 and 30084 who had a postbaseline shift from normotensive to elevated BP. A similar proportion (4-11%) of EM subjects across these studies had a postbaseline shift from normotensive to Stage 1 hypertension. Shifts from normotensive to Stage II hypertension were <1% at each study visit. While there were no TEAEs of hypertension in study 30083, there were 2 TEAEs of hypertension in study 30084.

HTN TEAEs:
Subject (b) (6) is a 17-year-old female who experienced hypertension 1 day after the fourth dose of fremanezumab 225 mg in study 30084, which was the 4th consecutive study dose of fremanezumab. The AE was graded as mild and resolved within 2 days. There were no further AEs of hypertension through the trial, with 5 subsequent doses of fremanezumab. The blood pressure read resulting in the AE of hypertension is not provided. However, this subject had a baseline blood pressure of 149/78 with the highest recorded post-baseline systolic blood

pressure in the datasets listed as 143mmHg while receiving fremanezumab and 166mmHg while receiving placebo, and the highest post-baseline diastolic blood pressure listed as 85mmHg while receiving fremanezumab and 80 while receiving placebo. This subject was taking a hormonal contraceptive concomitantly. There was no reported treatment initiated for the AE of HTN.
*Reviewer comment: A causal relationship with fremanezumab is not clear given confounding medication (contraceptive), baseline hypertension, and negative re-challenges.*

Subject (b) (6) is a 12-year-old male who experienced hypertension 26 days after the 3rd dose of fremanezumab 120 mg in study 30084, which was the 6th consecutive study dose including the controlled study (study 30083). This subject had baseline hypertension, with a blood pressure of 166/99 at screening. The highest systolic blood pressure available in the datasets is the screening blood pressure value. The highest diastolic blood pressure in the datasets is 112mmHg on day 1 of study 30084 (the day of the 1st dose of fremanezumab in the open label study, which was the 4th consecutive study dose). The AE of hypertension was graded mild and listed as unresolved. The subject initiated a medication for HTN 2 months after the reported AE.
*Reviewer comment: A causal relationship with fremanezumab is not clear given a lack of trend in blood pressure during the study and the subject's baseline hypertension.*

*Reviewer comment: Taken together, analyses of blood pressure in study 30083 and across studies 30083 and 3004 suggest a possible relationship between fremanezumab and an increase in blood pressure, which is in line with the known risk of hypertension in the adult population.*

### 8.5.4 Growth and development

There were no decreases in minimum weight or height in any cohort, and in all cohorts, there was a general trend for increase, as expected to occur with time in the pediatric population. The Applicant provided an assessment of safety related to growth and development using pooled data from EM subjects in studies 30083 and 30084, which was reviewed with the Department of Pediatrics and Maternal Health. No signals of precocious or delayed puberty were found in this assessment by the Applicant. Specifically, no subjects were identified who were female and progressed from Tanner stage 1 to 2/3 before age 8 years, or who were male and progressed from Tanner stage 1 to 2/3 before age 9 years. There were also no subjects identified who were female and did not progress from Tanner sage 1 to 2/3 by age 13 years or who were male and did not progress from Tanner stage 1 to 2/3 by age 14 years.

*Reviewer comment: No association between fremanezumab and growth and development was observed.*

### 8.5.5 Depression, anxiety, and suicidality

There were 4 subjects with mood disorders as a TEAE in the fremanezumab cohort in the controlled trial (study 30083) compared to zero in the placebo cohort (see section 8.4.5), as well as an additional 1 EM subject with a mood disorder reported as a TEAE in study 30084. About half of these subjects appeared to have a medical history of the mood disorder for which a TEAE was reported. In the controlled trial (study 30083), one subject lacked information on if the AE start date preceded the first dose of fremanezumab, so it remained unclear half or three quarters of subjects with a mood disorder TEAE in this trial had a history of the mood disorder that predated fremanezumab treatment in the study. 75% of EM subjects with mood disorder TEAEs in the controlled trial and 60% of EM subjects with mood disorder TEAEs across both studies were in the adolescent age group (12 to 17 years). All three adolescent subjects with a mood disorder TEAE across studies had other psychiatric AEs reported, with two having anxiety or worsening anxiety reported at the same time or shortly before the mood disorder was reported, and one having obsessive compulsive disorder, attention deficit disorder and autism reported simultaneously with depression. Three of the 5 EM subjects with a mood disorder TEAE had changes in medications potentially related to the reported mood disorder after the onset of the AE across studies 30083 and 30084. These medication changes occurred days (1 subject) to months (2 subjects) after the reported AE, and included changes to baseline medications by increases or decreases (1 subject) as well as initiation of a new medication (2 subjects). Concomitant medications at the time of AE report that could confound results were present in nearly half (40%) of the cases across studies 30083 and 30084, and were more common in the adolescent subjects (67%). All mood disorder TEAEs reported in EM subjects in studies 30083 and 30084 were listed as mild-moderate in intensity and subjects continued on fremanezumab after the onset of the TEAE, with several doses received on average after TEAE onset and no reported worsening.

There were two subjects with anxiety reported as a TEAE in the fremanezumab cohort in the controlled trial (study 30083) and an additional 2 EM subjects with anxiety reported as a TEAE in the open label safety trial (study 30084). The 2 subjects with anxiety reported as a TEAE in the controlled trial also had depression reported as a TEAE in this trial, either simultaneously, or shortly thereafter. While only 2 of the 4 EM subjects across studies 30083 and 30084 had a related psychiatric history by review of baseline data, the other two subjects may have had a related psychiatric history, as one had an unclear onset of anxiety that may have began before the first dose of fremanezumab, and the other subject had their AE reported as “aggravated anxiety” with a notation of “pre-existing medical condition” suggesting a predating history of anxiety that was not reported, and so, is of unclear onset. Three of the four subjects with a TEAE of anxiety had changes to medications after the reported AE that may have been related to the AE, with changes made days (2 subjects) to months (1 subject) after the AE was reported. Half of the subjects were on baseline concomitant medications related to and potentially

confounding the AE. All AEs of anxiety were reported as mild-moderate. Three of the four subjects received several doses of fremanezumab after the reported AE without reported worsening of the AE. One subject had no further doses of fremanezumab after the AE, but was reported as having resolution of the AE approximately 2 weeks after reported onset, which was 3 weeks after the last dose of fremanezumab.

There were also two AEs of suicidal ideation in study 30084, both of which resulted in drug discontinuation, and one AE of intentional self-injury (graded as mild) which did not result in drug discontinuation (subject (b) (6)) or recorded treatment intervention by medication, with this subject receiving 4 subsequent doses of 120 mg fremanezumab without reported recurrence or related AEs.

*Reviewer comment: While a relationship with fremanezumab cannot be ruled out for the cases of depression, anxiety and suicidality described above, there are small numbers of cases in these pediatric studies, confounders for at least half of these cases, and ongoing dosing of fremanezumab without reported worsening of the AE for most cases, although worsening or improvement of the AE is potentially confounded by concomitant medications in many cases. The reported number of cases also falls within expected background rates, particularly in the adolescent population, and some cases may be the result of unrelated diagnostic clarification given multiple diagnoses simultaneously reported. Fremanezumab is a monoclonal antibody, and as such, does not readily penetrate the blood-brain barrier. However, the complex relationship between central disorders and peripheral inputs is recognized, and, this reviewer does not consider psychiatric effects of fremanezumab impossible, particularly given the affective associations with migraine and fremanezumab's effects on migraine. It is unclear if fremanezumab overall may worsen, improve or have no effect on mood disorders or other psychiatric conditions. Improvement in these areas was not studied. There has not been an observed signal for any of these effects to date in the adult population with fremanezumab. I recommend ongoing routine surveillance for safety issues related to mood disorders, anxiety, and suicidality.*

### 8.5.6 Rhabdomyolysis

There were 3 cases identified with a myopathic pattern of laboratories. Two of these cases were previously discussed: Subject (b) (6) and Subject (b) (6), with both of these subjects having a pattern of laboratories consistent with rhabdomyolysis. Subject (b) (6) had an alternative cause for rhabdomyolysis and negative rechallenges for several doses with fremanezumab, making an association with fremanezumab seem less likely, while Subject (b) (6) did not have a clear alternative cause and did not undergo a rechallenge with fremanezumab, making an association with fremanezumab possible. A third subject was identified while conducting an analysis of liver-related laboratories (section 8.4.6).

Subject (b) (6) is a 16-year-old male with EM who experienced elevated creatine kinase trial day 31 of study 30083, which was the day of his second dose of fremanezumab 225 mg. The AE occurred before the dose was given based on laboratory draw times. His CK was 140U/L at baseline, increased to 679U/L on Day 31, then increased further to 3394U/L on Day 58 by labs drawn prior to the third fremanezumab dose, with a downtrend thereafter to 433U/L on Day 86. The AE was graded as moderate and unrelated. He had concomitant elevations in liver transaminases with his AST elevated to 40U/L Day 31 (ALT remained at baseline), AST peaking at 121U/L Day 58 and ALT peaking later at 112 U/L Day 63. Both liver transaminase levels downtrended to baseline by Day 73. This subject went on to receive 9 further doses of fremanezumab 225 mg in study 30084 (12 consecutive doses total). His creatine kinase returned to baseline by month 1 of study 30084 (month 4 consecutively in the studies), then increased again, peaking at 731U/L month 3 of study 30084 (month 6 overall), and then downtrending again. He had AEs reported in study 30084 of creatine kinase elevation and, later, joint ligament rupture and torn muscle.

*Reviewer comment: A causal relationship to fremanezumab cannot be ruled out for this case, but an alternative cause of recurrent musculoskeletal injury is possible.*

No other cases concerning for rhabdomyolysis or myopathy were identified. There were also no imbalances between fremanezumab and placebo cohorts observed in the controlled trial for potential related symptomatic terms, including myalgia, musculoskeletal discomfort, pain in extremity (not due to described injury), back pain, sacral pain, and arthralgia individually or by grouped PTs, with 3.6% placebo compared to 3.8% fremanezumab experiencing at least one of these PTs. There were also no overall trends in creatine kinase by laboratories.

*Reviewer comment: Overall, there was no clear association for rhabdomyolysis with fremanezumab in these pediatric trials. There were only 3 cases identified of rhabdomyolysis, with 2 of these cases having probable or possible alternative causes, and no related safety signals noted by laboratory or AE review.*

## 8.6 Safety Analyses by Demographic Subgroups

Data were further reviewed by age cohort (age 6-11 vs 12-17), and weight cohort (weight <45 kg, weight ≥45 kg).

Study 30083:
Weight:
In the controlled trial (study 30083), there was a similar proportion of subjects who experienced as least 1 TEAE in each weight cohort (~50-55%) across all treatment arms, as well as similar proportion of subjects who experienced an SAE across treatment arms as shown in Table 26.

Table 26: Study 30083, TEAEs and SAEs by Weight Group

| | Placebo <45kg N=33 (%) | Placebo ≥45kg N=79 (%) | Fremanezumab <45kg N=36 (%) | Fremanezumab ≥45kg N=87 (%) |
|---|---|---|---|---|
| Subjects with at least 1 TEAE | 18(55) | 37(47) | 20(56) | 48(55) |
| Subjects with an SAE | 1(3) | 2(3) | 1(3) | 1(1) |

Source: Reviewer derived from study 30083 Applicant provided ADAE dataset, confirmed in OCS adverse event analysis using Analysis Studio, Safety Explorer

The differences in percentages of subjects experiencing each TEAE between weight-matched cohorts (fremanezumab-treated subjects <45 kg compared with placebo-treated subjects <45 kg and fremanezumab-treated subjects >45 kg compared with placebo-treated subjects >45 kg) were also similar, outside of injection site reactions, and hypersensitivity reactions, as shown in Tables 28-31.

Table 27: Study 30083, Injection Site Reactions for Subjects Weighing <45 kg

| Preferred Terms | Placebo (N = 33) | Fremanezumab 120 mg (N = 36) |
|---|---|---|
| Total subjects with site reactions | 4 ( 12.1%) | 3 ( 8.3%) |
| Injection site erythema | 3 ( 9.1%) | 1 ( 2.8%) |
| Injection site swelling | 1 ( 3.0%) | 1 ( 2.8%) |
| Injection site haemorrhage | 1 ( 3.0%) | 0 ( 0.0%) |
| Injection site irritation | 0 ( 0.0%) | 1 ( 2.8%) |
| Injection site urticaria | 0 ( 0.0%) | 1 ( 2.8%) |

Reviewer created using OCS Analysis studio
Safety population and TRTEMFL = Y
Site reactions include all terms in the CSR Summary Table 15.7.9.1

Table 28: Study 30038, Injection Site Reactions for Subjects Weighing ≥45 kg

| Preferred Terms | Placebo (N = 79) | Fremanezumab 225 mg (N = 87) |
|---|---|---|
| Total subjects with site reactions | 11 ( 13.9%) | 17 ( 19.5%) |
| Injection site erythema | 3 ( 3.8%) | 11 ( 12.6%) |
| Injection site pain | 6 ( 7.6%) | 6 ( 6.9%) |
| Injection site swelling | 0 ( 0.0%) | 5 ( 5.7%) |
| Injection site rash | 2 ( 2.5%) | 0 ( 0.0%) |
| Injection site urticaria | 2 ( 2.5%) | 0 ( 0.0%) |
| Injection site bruising | 0 ( 0.0%) | 1 ( 1.1%) |
| Injection site discolouration | 0 ( 0.0%) | 1 ( 1.1%) |
| Injection site haemorrhage | 0 ( 0.0%) | 1 ( 1.1%) |
| Injection site hypertrophy | 0 ( 0.0%) | 1 ( 1.1%) |
| Injection site hypoaesthesia | 1 ( 1.3%) | 0 ( 0.0%) |
| Injection site induration | 1 ( 1.3%) | 0 ( 0.0%) |
| Injection site pruritus | 0 ( 0.0%) | 1 ( 1.1%) |
| Injection site warmth | 0 ( 0.0%) | 1 ( 1.1%) |

Source: Reviewer Created using Analysis studio, further confirmed using Applicant-provided ADAE dataset
Safety population and TRTEMFL = Y
Site reactions include all terms in the CSR Summary Table 15.7.9.1

Table 29: Study 30083 Possible Hypersensitivity Reactions in Subjects Weighing at least 45 kg

| Preferred Terms | Placebo (N = 79) | Fremanezumab 225 mg (N = 87) |
|---|---|---|
| Total subjects with hypersensitivity | 0 ( 0.0%) | 5 ( 5.7%) |
| Rash | 0 ( 0.0%) | 2 ( 2.3%) |
| Dermatitis allergic | 0 ( 0.0%) | 1 ( 1.1%) |

| Preferred Terms | Placebo (N = 79) | Fremanezumab 225 mg (N = 87) |
|---|---|---|
| Periorbital swelling | 0 ( 0.0%) | 1 ( 1.1%) |
| Rash papular | 0 ( 0.0%) | 1 ( 1.1%) |
| Urticaria | 0 ( 0.0%) | 1 ( 1.1%) |
| Pruritis | 0 ( 0.0%) | 1 ( 1.1%) |

Source: Reviewer created using Analysis studio, further confirmed using Applicant-provided ADAE dataset
Safety population and TRTEMFL = Y
Hypersensitivity includes Pruritis, Rash, Urticaria, Periorbital swelling, Rash papular and Dermatitis allergic

Table 30: Study 30083 Possible Hypersensitivity Reactions in Subjects Weighing Less than 45 kg

| Preferred Terms | Placebo (N = 33) | Fremanezumab 120 mg (N = 36) |
|---|---|---|
| Total subjects with hypersensitivity | 1 ( 3.0%) | 1 ( 2.8%) |
| Rash | 0 ( 0.0%) | 1 ( 2.8%) |
| Pruritis | 1 ( 3.0%) | 0 ( 0.0%) |

Source: Reviewer created using Analysis studio, further confirmed using Applicant-provided ADAE dataset
Safety population and TRTEMFL = Y
Hypersensitivity includes Pruritis, Rash, Urticaria, Periorbital swelling, Rash papular and Dermatitis allergic

*Reviewer comment: Given small sample sizes, particularly in the <45 kg cohorts, it is difficult to draw conclusions, but the increased occurrence of injection site reactions and hypersensitivity reactions in those subjects weighing at least 4 5kg who were treated with fremanezumab 225 mg is consistent with the initial analysis of these TEAEs in section 8.4.5, but is not outside of the expected safety profile based on the aforementioned adult clinical trial results for these reactions when looking at proportionality between treatment and placebo arms (see sections 8.5.1 and 8.5.2).*

Age:
In the controlled trial (study 30083), TEAEs by age cohorts of 6 to 11 years and 12 to 17 years

showed similar AE occurrences in the fremanezumab-treated subjects compared to placebo-treated subjects by age cohort.

Table 31: Study 30083, TEAEs by Age Cohort

| | Placebo 6-11 years N=32 (%) | Placebo 12-17 years N=80 (%) | Fremanezumab 6-11 years N=32 (%) | Fremanezumab 12-17years N=91 (%) |
|---|---|---|---|---|
| Subjects with at least 1 TEAE | 20(63) | 35(44) | 21(66) | 47(52) |
| Subjects with an SAE | 1(3) | 2(3) | 0 | 2(2) |

Source: Reviewer derived from study 30083, ADAE dataset, further confirmed with OCS adverse event analysis using Analysis Studio

*Reviewer comment: There were 13 fremanezumab-treated subjects in the 6-11 year cohort treated with 225 mg fremanezumab (ie weighing over 45 kg), so it was difficult to draw conclusions about this subpopulation. However, it was noted that 31% (n=4) of this subpopulation had an injection site reaction. All these injection site reactions were mild in severity. Overall, data by the age and weight subgroups were similar, fitting with the younger population being predominantly the lower weight population.*

Pooled analyses of EM subjects from studies 30083 and 30084: showed comparable findings by age and weight as in the individual studies discussed above.

## 8.7 Specific Safety Studies/Clinical Trials

Not applicable.

## 8.8 Additional Safety Explorations

### 8.8.1 Human Carcinogenicity or Tumor Development

Not applicable.

### 8.8.2 Human Reproduction and Pregnancy

There were no reported pregnancies in studies 30083 or 30084.

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

This entire review regards the pediatric population. See section 8.5.4 for an assessment on growth and development.

### 8.9 Safety in the Postmarket Setting

#### 8.9.1 Safety Concerns Identified Through Postmarket Experience

No additional safety issues not already addressed in this review have been identified in the postmarket setting. There is ongoing monitoring for safety, including specific monitoring in safety reports by the Applicant for cardiovascular effects and hypersensitivity reactions.

#### 8.9.2 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose, drug abuse, or withdrawal in the safety database.

#### 8.9.3 Expectations on Safety in the Postmarket Setting

The studies included to support this application for pediatric use (studies 30083 and 30084) excluded subjects with clinically significant cardiovascular, psychiatric, or other diseases, as well as subjects on more than 2 concomitant preventive migraine therapies, which could result in the trial populations being healthier and having less risk of drug interactions than the general pediatric migraine population. Small sample sizes, particularly of the youngest cohort (age 6-11 years) restricts this safety analysis in observing rare adverse events. This may be why no cases of anaphylaxis, as have been observed in the adult population, for instance, were observed. However, fremanezumab also has substantial postmarket use in the adult migraine population, providing additional information regarding its potential safety profile in pediatrics.

#### 8.9.4 Additional Safety Issues From Other Disciplines

Not applicable

### 8.10 Integrated Assessment of Safety

Fremanezumab is an anti-CGRP monoclonal antibody that binds to the CGRP ligand. It was approved in 2018 for the preventive treatment of migraine in adults.

Fremanezumab's safety profile from adult studies and postmarket data include risks of hypertension, Raynaud's phenomenon, injection site reactions and hypersensitivity reactions. There were concerns expressed during the review of the pivotal adult trials about long-term cardiovascular risks which continue to be monitored in the postmarket setting. There were also concerns about ocular effects, notably retinal detachment, which were monitored by enhanced

pharmacovigilance with no clear safety signal.

The safety analyses of this review suggest a similar safety profile in pediatrics as observed in adults, with no unexpected safety findings. There were no deaths, and there were few SAEs, severe AEs and AEs leading to drug discontinuation or study withdrawal. Findings in this review included injection site reactions, probable hypersensitivity reactions and probable blood pressure effects within the expectation of the known safety profile in adults. There were no clear differences by weight or age in the safety profile, aside from the risks of injection site reactions and probable hypersensitivity reactions seemingly driven by those receiving 225 mg fremanezumab (who were also those weighing at least 45 kg and largely those in the 12-17 year age cohort), but small numbers of subjects, particularly in the youngest cohort (6-11 years of age) and lower weight cohort (<45 kg), limit conclusions.

I recommend approval with routine postmarket safety surveillance.

# 9. Advisory Committee Meeting and Other External Consultations

Not applicable.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

Section 1:

- I recommended revising the indication statement to include the preventive treatment of episodic migraine in patients 6 to 17 years of age who weigh 45 kg or more from patients 6 to 17 years of age weighing at least 45 kg for the 225 mg SC dose for clarity.

Section 5:

- The descriptions of hypersensitivity and hypertension are acceptable with the observed safety findings in the pediatric trials.

Section 6:

- The exposure data should be changed to describe the exposure for pediatric patients

with episodic migraine, rather than the exposure for all pediatric patients (including those with blinded data/chronic migraine)

- I recommended changing "the only adverse reactions were injection site reactions" to "the most common adverse reactions were injection site reactions," to more accurately describe the safety findings of the pediatric controlled trial.

- Given my analyses in section 8.5.1 and 8.5.3, I recommended adding that hypersensitivity reactions were observed in the pediatric controlled trial.

- I suggested adding a statement noting the overall similarity in safety profile between adults and pediatrics, given safety analyses detailed above.

Section 8:

- Pediatric migraine should be separated into episodic and chronic to note the safety and efficacy has only been established for pediatric episodic migraine.

Section 14:

- I recommended adding a histogram showing the distribution of monthly migraine days.

### 10.2. Nonprescription Drug Labeling

Not applicable.

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

Not applicable.

## 12. Postmarketing Requirements and Commitments

Fulfilled

PMR 3485-1 A juvenile animal toxicology study in one species to evaluate effects of fremanezumab-vfrm on growth, reproductive development, and neurological and neurobehavioral development.

PMR 3485-2 An open-label pharmacokinetic, safety, and tolerability study in pediatric migraine patients ages 6 through 11 years with an optional open-label safety extension phase (40 weeks).

Not fulfilled

PMR 3485-3 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of episodic migraine in children and adolescents ages 6 through 17 years. This study includes a double-blind treatment phase (12 weeks) and an open-label safety extension phase (40 weeks). This study is to be submitted as a special protocol assessment (SPA).

This PMR is considered partially fulfilled because the study was conducted and was considered adequate and well-controlled, but dosing will not be marketed for pediatric subjects 6 to 17 years of age who weigh less than 45 kg because the dose strength preparation of 120 mg is not ready for marketing.

PMR 3485-4 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of chronic migraine in adolescents ages 12 through 17 years. This study includes a double-blind treatment phase (12 weeks) and an open-label safety extension phase (40 weeks). This study is to be submitted as a special protocol assessment (SPA).

PMR 3485-5 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Ajovy during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Ajovy before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR 3485-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3485-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-

gestational-age births in women exposed to Ajovy during pregnancy compared to an unexposed control population.

# 13. Appendices

## 13.1. References

1. Turner SB, Szperka CL, Hershey AD, Law EF, Palermo TM, Groenewald CB. Association of Headache With School Functioning Among Children and Adolescents in the United States. JAMA Pediatr. 2021;175(5):522–524.
2. Steinmetz, Jaimie D et al. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet Neurology. 2024; 23(4): 344 – 381.
3. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ and Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology 2002; 58: 885–894
4. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001 Jul-Aug;41(7):646-57.
5. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9.
6. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: A life-span study. *Cephalalgia*. 2010;30(9):1065-1072.
7. Oskoui M, Pringsheim T, Billinghurst L, Potrebic S, Gersz EM, Gloss D, Holler-Managan Y, Leininger E, Licking N, Mack K, Powers SW, Sowell M, Victorio MC, Yonker M, Zanitsch H, Hershey AD. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019 Sep 10;93(11):500-509.
8. Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, Korbee LL, Porter LL, and Hershey AD, for the CHAMP Investigators. N Engl J Med. 2017;376:115-124.
9. Powers SW, Kashikar-Zuck SM, Allen JR, LeCates SL, Slater SK, Zafar M, Kabbouche MA, O'Brien HL, Shenk CE, Rausch JR, Hershey AD. JAMA.2013 Dec 25;310(24):2622-2630.
10. Guidance for Industry: Developing Drugs for the Preventive Treatment of Migraine, June 2023 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/migraine-developing-drugs-preventive-treatment)

## 13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 30083

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes x | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 453 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | NA | No ☐ (Request explanation from Applicant) |

---

**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

---

/s/

---

PATRICIA D SCRIPKO
08/05/2025 11:05:27 AM

HEATHER D FITTER
08/05/2025 11:18:03 AM