CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761077Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 15, 2018
From	Heather Fitter, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 761077
Applicant	Amgen
Date of Submission	May 17, 2017
PDUFA Goal Date	May 17, 2018
Proprietary Name	Aimovig
Established or Proper Names	Erenumab-aooe (AMG 334)
Dosage Form(s)	Solution for subcutaneous (SC) injection 70 mg, 140 mg
Applicant Proposed Indication(s)/Population(s)	Prevention of migraine in adults
Applicant Proposed Dosing Regimen(s)	140 mg SC injection monthly
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Preventive treatment of migraine in adults
Recommended Dosing Regimen(s)	70 mg or 140 mg subcutaneous injection monthly

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Erenumab is a human monoclonal antibody that antagonizes the calcitonin gene-related peptide (CGRP) receptor. It is the first product of this class to be reviewed in an FDA marketing application. The applicant provided information supporting use in patients with both chronic migraine (i.e., at least 15 headache days/month, with features of migraine headache on at least 8 days/month) and episodic migraine (i.e., up to 14 migraine headache days/month).

There are several FDA-approved drugs for the prophylaxis of migraine. Topiramate, propranolol, valproate, and timolol are approved for the prophylaxis of migraine, and onabotulinumtoxinA is approved for the prophylaxis of chronic migraine in adults. Of note, the distinction between episodic and chronic migraine did not exist at the time of approval of topiramate, propranolol, valproate, and timolol (the diagnostic entity of chronic migraine was introduced in the international classification of headache in 2004), and their labels, therefore, do not include mention of episodic or chronic migraine (but the trial populations consisted mostly of patients who would now be described as having episodic migraine).

The efficacy of erenumab was demonstrated in three adequate and well controlled studies. The studies used a well validated and clinically interpretable primary endpoint, the number of monthly migraine days. Two studies were conducted in patients with episodic migraine, and one study in patients with chronic migraine. Both doses of erenumab tested (70 mg and 140 mg) were effective in both indications. In patients with episodic migraine, treatment with erenumab led to about 3 to 4 fewer migraine headache days/month, whereas placebo-treated patients had approximately 2 fewer migraine headache days/month, both groups improving, on average, from a baseline rate of about 8 days/month. The treatment effect size (the difference between erenumab and placebo; approximately 2 fewer migraine headache days/month) was similar to that observed with drugs already approved for episodic migraine. In patients with chronic migraine, treatment with erenumab led to about 7 fewer migraine headache days/month, while placebo-treated patients had about 4 fewer days/month, both groups improving from a mean baseline of about 18 days/month. Erenumab's treatment effect was similar to that of onabotulinumtoxinA, the only product currently approved for the treatment of chronic migraine. Approval of onabotulinumtoxinA was based on approximately 8 to 9 fewer headache days/month, compared with 6 to 7 fewer headache days/month in the placebo group.

It is noteworthy that a fraction of erenumab-treated patients experienced relatively large reductions in migraine headache days. There is, however, no way to identify these patients prospectively. The studies do not show superiority of the 140-mg dose of erenumab over the 70-mg dose, with a relatively flat dose-response. There were small numerical advantages favoring the 140-mg dose over the 70-mg dose for a few endpoints across clinical studies, suggesting that some patients may benefit from the higher dose. An initial recommended dose of 70 mg is appropriate, with an option to escalate the dose to 140 mg for patients who do not have an adequate response to the 70-mg dose.

No serious safety issues were identified in the erenumab safety database. It should be noted, however, that the trials enrolled generally young, healthy, female patients, excluding patients older than 65, and included few patients with major pre-existing cardiovascular disease. Notable adverse events in clinical trials included injection site reaction and constipation. As CGRP is a vasodilator, a theoretical concern has been raised in the literature that inhibition of CGRP could impair protective vasodilation in patients with tissue ischemia or infarction. Following a careful review of the nonclinical literature, however, we did not find that the animal data rasied substantial concern of the potential for adverse cardiovascular reactions in patients.

The risk/benefit profile of erenumab is clearly favorable for patients with episodic or chronic migraine. Absent head-to-head studies comparing erenumab to currently approved therapies, it is not possible to determine whether erenumab has a greater efficacy than those products, but it is clear that erenumab will be an important addition to the migraine prophylaxis armamentarium, as it is the first drug of a new therapeutic class, and will offer a treatment alternative to patients with episodic or chronic migraine.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 and 72 hours in adults. About one-third of people with migraine experience transient neurological symptoms before and/or during an attack, referred to as a migraine aura. • Migraine was found to be the sixth highest cause of disability in the Global Burden of Disease Study in 2013. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S, thus resulting in a major impact to public health.	Migraine is a serious and at times disabling condition that can impact the quality of patients' lives.
Current Treatment Options	• There are several FDA-approved therapies for migraine prophylaxis: topiramate, propranolol, timolol, valproate, approved for migraine prophylaxis, and onabotulinumtoxinA, approved for prophylaxis of chronic migraine only. All have a number of contraindications, warnings and precautions, as well as side effects limiting their use. Some patients do not currently have a tolerable migraine prophylaxis drug available to them. In addition, many other drugs and supplements are used off-label for migraine prophylaxis. • With the exception of onabotulinumtoxinA, all are taken orally and must be taken daily (1-3 times per day). OnabotulinumtoxinA is recommended to be administered intramuscularly every three months.	Approved treatments are moderately effective; generally, none render patients migraine-free. These drugs have a number of important side effects and harms, and some patients lack a tolerable drug for the preventive treatment of migraine.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Benefit</td><td>

The efficacy of erenumab was demonstrated in three adequate and well controlled clinical studies (Studies 296 and 297 in patients with episodic migraine; Study 295 in patients with chronic migraine). The studies used a well validated and clinically interpretable primary endpoint, the number of migraine days per month. Results are summarized in the table below; comparisons between the erenumab groups and placebo are highly statistically significant:

<table>
<tr><th></th><th>Baseline</th><th>On treatment</th><th>Change from baseline</th></tr>
<tr><td>Study 296</td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>8.25</td><td>6.33</td><td>-1.95</td></tr>
<tr><td>Erenumab 70 mg</td><td>8.31</td><td>4.95</td><td>-3.36</td></tr>
<tr><td>Erenumab 140 mg</td><td>8.33</td><td>4.48</td><td>-3.83</td></tr>
<tr><td>Study 297</td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>8.38</td><td>6.49</td><td>-1.96</td></tr>
<tr><td>Erenumab 70 mg</td><td>8.13</td><td>5.24</td><td>-2.98</td></tr>
<tr><td>Study 295</td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>18.24</td><td>14.03</td><td>-4.18</td></tr>
<tr><td>Erenumab 70 mg</td><td>17.94</td><td>11.34</td><td>-6.64</td></tr>
<tr><td>Erenumab 140 mg</td><td>17.78</td><td>11.28</td><td>-6.63</td></tr>
</table>

The 70-mg and 140-mg doses had similar efficacy; the 140-mg dose had numerical advantages over the 70-mg dose for a few endpoints across studies.
Of note, the majority of patients enrolled in the trials had received other migraine drugs in the past. Importantly, however, a history of previous use of a drug is not tantamount to therapeutic failure. In other words, the applicant has not shown erenumab’s value in treatment-resistant patients, i.e., the applicant has not shown that patients who did not respond to other drugs (non-responders) responded to erenumab. (To demonstrate this, they would have needed to perform studies that randomized patients to erenumab or the drug that had failed.)

</td><td>Erenumab 70 and 140 mg were both found to be effective in reducing the number of monthly migraine days in patients with episodic and chronic migraine. The magnitude of the treatment effect observed in these trials was similar to that of other products approved for migraine prophylaxis (an effect size over placebo of approximately 1 to 2 days per month).

Erenumab is administered monthly rather than daily, which could be a convenience factor for some patients. (Approved oral agents are given at least daily.) Monthly subcutaneous injections (single injection for erenumab 70 mg and two injections for erenumab 140 mg) may be more tolerable then 31 injections given every three months with onabotoxilinumA.

Erenumab offers a new alternative for patients who do not tolerate, or do not have an adequate response to, currently marketed drugs. Like other approved drugs for migraine, this drug is not likely to render patients migraine-free.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	*Risk* • No serious safety issues were identified with a clear causal relationship to erenumab. • The most common adverse reactions (occurring in ≥ 3% of treated patients and more often than in placebo) were injection site reactions and constipation, and these were generally self-limited. • CGRP is a vasodilator, and there is a theoretical concern from animal studies that CGRP inhibition could impair protective vasodilation in patients with tissue ischemia or infarction. A detailed review of the literature from the Division of Cardiovascular and Renal Products found no convincing evidence that CGRP antagonism would induce vasoconstriction or affect the severity of ischemia secondary to coronary artery stenosis or occlusion. It appears that if CGRP plays a role in the regulation of coronary vascular tone, there are redundant systems to override its inhibition. There are also reassuring data in healthy men that nitroglycerin-induced vasodilatation is not CGRP-dependent, and therefore, patients with CGRP blockade should remain responsive to sublingual nitrates. A review of cardiovascular events, ECGs, and vital signs in the erenumab database did not identify a cardiovascular risk to patients; however, the number of patients at risk was too small to be very reassuring. Two cardiac-related deaths were reported in the erenumab database, but neither death appears to be related to erenumab. Isolated ischemic events were also reported, but the rate of these events was no greater than the background rate in this patient population. • Liver toxicity was an area of special interest because liver toxicity has been observed with an oral CGRP antagonist in development, and there are concerns about a class effect. There was no evidence of liver toxicity attributable to erenumab in the safety database. *Risk Management:* routine pharmacovigilance is appropriate for erenumab. The following PMRs will be required: • A pregnancy registry study • Pediatric studies in patients age 6-17 years	Erenumab has an acceptable safety profile for the migraine population. No major safety issues related specifically to erenumab have been identified to date. Although there is a theoretical concern that CGRP receptor blockade with erenumab could precipitate ischemic events in patients with underlying cardiovascular disease, we found no compelling evidence that CGRP antagonism would induce vasoconstriction or affect the severity of ischemia secondary to coronary artery stenosis or occlusion. It appears that if CGRP plays a role in the regulation of coronary vascular tone, there are redundant systems that would override its inhibition. The applicant's plan to defer the study of pediatric patients age 6-17 years for episodic migraine, and age 12-17 years for chronic migraine, is acceptable. In addition, the applicant will be required to conduct a juvenile toxicology study. A pregnancy registry study must also be conducted.

2. Background

This memo discusses the data presented by Amgen in support of a new biologics license application (BLA) for erenumab solution for subcutaneous injection, a calcitonin gene-related peptide (CGRP) receptor inhibitor proposed for the preventive treatment of migraine.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 and 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura.

Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD). The second edition (2004) of that classification introduced the diagnostic entity of chronic migraine, defined as ≥15 headache days per month, with features of migraine headache on ≥8 days per month. Patients with ≤14 migraine headache days per month are defined as having episodic migraine. The distinction between episodic and chronic migraine did not exist prior to 2004, and all drugs approved for migraine prophylaxis prior to 2010 have an indication without reference to the episodic or chronic nature of migraine. The first drug to include an indication specific to the prophylaxis of chronic migraine was Botox, which was approved for that indication in 2010. Although there is clearly a continuum and overlap between episodic and chronic migraine, differences in epidemiology, biological mechanisms, and treatment response have been described, and it is noteworthy that multiple adequate and well controlled studies failed to show the efficacy of Botox for the treatment of episodic migraine, whereas Botox was shown to be effective for chronic migraine.

The Division had extensive interactions with the applicant during the development program with respect to the design of the clinical studies, and it was agreed that a single study in patients with episodic migraine and a single study in patients with chronic migraine would support an application for both populations. The applicant provides data from three efficacy studies, two in episodic migraine and one in chronic migraine. Two doses of erenumab were evaluated in pivotal efficacy studies: 70 and 140 mg.

3. Product Quality

The technical lead on the Office of Product Quality review was Dr. Joslyn Brunelle (refer to her review for the entire OPQ list of participants in the review of this application). Erenumab is a human monoclonal antibody of the immunoglobulin IgG2 subclass manufactured in mammalian cells with a theoretical mass of 148,761 Daltons. Erenumab is in the pharmacologic category of calcitonin gene-related peptide receptor (CGRP-R) antagonists.

The product binds to the extracellular domain of the CGRP-R and prevents interaction with the neuropeptide CGRP. Erenumab drug product is a single-use, sterile, preservative-free, colorless to light yellow solution, supplied as 70 mg/mL for monthly subcutaneous (SC) injection via prefilled syringe (PFS) or autoinjector (AI/pen). Administration of the 140-mg dose requires the use of two PFS/AI.

Consults were obtained from Drs. Robert Meyer and John McMichael from CDRH/ODE and Dr. Daniel Ramsey from CDRH/OC. There were no outstanding device issues, and both recommend approval.

Drs. James Weaver and Kristina Howard from the Division of Applied Regulatory Science/Office of Clinical Pharmacology performed the evaluation of assays for erenumab, anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (nADA) for this application. They conclude that the assay for measurement of erenumab in plasma is acceptable. The assays for measurement of ADA and nADAs were also found acceptable.

Dr. Kathleen Jones conducted the product quality microbiology review on the drug substance and recommends approval. Dr. Lakshmi Narasimhan conducted the drug product quality microbiology review and recommends approval.

There were no other outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Ed Nesti, with Dr. Lois Freed performing the secondary review. As discussed by Dr. Freed, Dr. Nesti has concluded that the nonclinical studies conducted by the applicant support approval of erenumab for the prophylaxis of migraine in adults.

Dr. Freed discusses in her memorandum the concerns that were raised regarding potential adverse effects of chronic CGRP antagonism in humans, specifically, the potential for erenumab to induce a direct vasoconstrictive effect on coronary arteries and/or to inhibit compensatory vasodilation in coronary vessels that occurs in response to an acute ischemic event.

Dr. Freed notes that the applicant assessed the potential for erenumab to induce vasoconstriction in an *in vitro* study, in which erenumab was incubated with segments of proximal and distal human coronary arteries with and without human CGRP. Sumatriptan was included as a positive control. Erenumab antagonized CGRP-induced vasodilation of distal segments, but had no intrinsic vasoconstrictive effects. In contrast, sumatriptan induced vasoconstriction. Erenumab had no effect on sumatriptan-induced vasoconstriction.

In her memorandum, Dr. Freed also discusses the applicant's review of the literature related to the theoretical risk of worsened ischemia with CGRP antagonism, and the Division of Cardiovascular and Renal Products (DCaRP) consultative review of this issue. Dr. Freed notes

the overall conclusion from the DCaRP consultative review that the published literature indicates that chronic antagonism of the CGRP system, resulting in blocking of CGRP-induced vasodilation, "does not result in tissue threatening vasoconstriction" because of the "multiple redundant mechanisms controlling regional and tissue specific blood flow." Dr. Freed also discusses in her memorandum the potential impact of CGRP antagonim on the phenomenon of ischemic preconditioning, under which pre-exposure of the heart to a preconditioning agent is thought to attenuate subsequent damage incurred by an ischemic episode. Dr. Freed notes that the studies cited by the sponsor and reviewed by DCaRP suggest that CGRP antagonism has the potential to adversely inhibit ischemic preconditioning. Dr. Freed comments that the applicant's position is that available data do not establish that ischemic preconditioning exists in humans, but observes that recent publications claim that ischemic preconditioning is well-established in animals and humans.

Dr. Freed's conclusion is that while concerns regarding the potential for erenumab to have adverse effects in patients with cardiovascular risks may be mitigated, they cannot be dismissed based on the available information. She notes, however, that the issues are complex, and that there are likely multiple endogenous factors involved in acute ischemic events and ischemic preconditioning, as well as in normal hemodynamic processes, and that the role(s) of CGRP in these is unclear. Dr. Freed observes that there do not appear to be sufficient data, from a nonclinical standpoint, to understand the contribution of CGRP to potentially protective endogenous cardiovascular processes, and that the available data, although limited, suggest that the contribution of CGRP to compensatory vasodilation may be relatively small (based on the review by DCaRP). Dr. Freed does not recommend further nonclinical work to explore the issue, as such studies would be unlikely to provide useful information, considering the current state of knowledge.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Girish Bende (the primary reviewer), Dr. Sabarinath Sreedharan (the clinical pharmacology team leader), Dr. Gopichand Gottipati, and Dr. Kevin Krudys.

Pharmacokinetics
OCP notes that following a single SC dose of 140 mg of erenumab in healthy adults, peak serum concentration is reached in 4-6 days and absolute bioavailability is 54%. Based on population pharmacokinetics, the estimated absolute bioavailability is 82% following repeated dosing. The median T_{max} ranges from 4 to 11 days within the dose range of 1 to 210 mg. Following a single 140-mg IV dose, the mean steady state volume of distribution was estimated to be 3.9 L. Although erenumab exhibits nonlinear pharmacokinetics, exposure is approximately dose-proportional between 70 and 140 mg. Erenumab has two elimination phases, one at low concentration, through saturable binding to CGRP receptors, and one at high concentration, largely through a non-specific, non-saturable proteolytic pathway.

Food Effect
Erenumab has no relevant food-drug interactions.

Intrinsic Factors

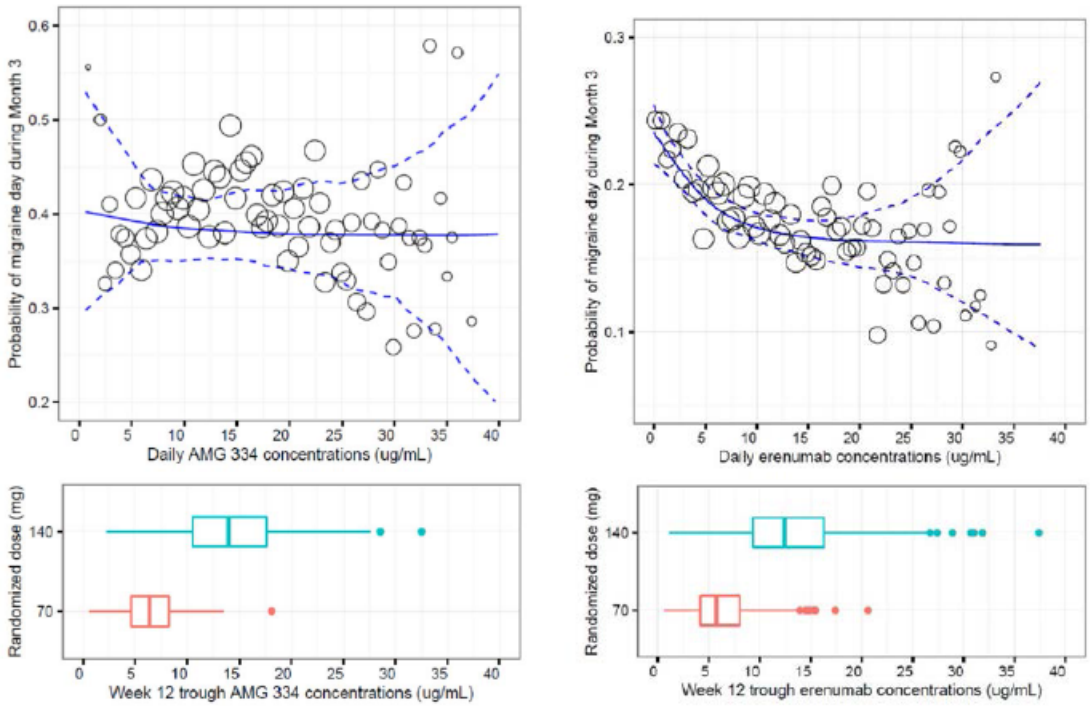
No clinically significant pharmacokinetic differences were noted by age or sex. Although there were pharmacokinetic (PK) differences noted by body weight, with a trend towards reduction in PK by increasing quartiles of body mass index (BMI), no differences in efficacy were found by quartiles of BMI in either episodic or chronic migraine. Therefore, no dose adjustment is recommended for body weight, sex, or age.

No dedicated clinical studies were conducted to evaluate the effect of erenumab on PK in patients with hepatic or renal impairment.

Drug-drug Interactions

Erenumab administered with concomitant medications is not expected to result in clinically relevant interactions. In addition, erenumab is unlikely to have an effect on drug metabolizing enzymes or transporters because it is expected to be catabolized by general proteolytic degradation pathways. The applicant did not conduct specific *in vitro* permeability, *in vitro* metabolism, *in vitro* metabolic drug interaction studies, or nonclinical pharmacokinetic drug interaction studies. There was no effect of erenumab on oral contraceptive PK or on sumatriptan PK in drug-drug interaction studies. In addition, the applicant demonstrated that mean arterial pressure and resting blood pressure (BP) were not increased when erenumab was administered intravenously with sumatriptan SC, compared to sumatriptan administered alone.

Figure 1: Probability of migraine day vs. average daily erenumab concentrations during Month 3 in subjects with chronic migraine (left panel: Study 295)) or episodic migraine (right panel: Studies 178, 296 and 297)



Legend: symbol= observed data with symbol size is proportional to square root of observations per bin of daily concentrations (500 ng/mL bins). Blue lines = mean prediction and 95% CI based on exposure-response model estimates; boxplots represent distributions of Month 3 trough concentrations for the corresponding dose group. Figures taken from OCP review Figure 3-3 and 3-4.

Thorough QT Study
A thorough QT study was not required for this monoclonal antibody.

Pharmacometrics
OCP conducted a pharmacometric analysis to assess erenumab's dose-exposure response. There was a clear difference in exposure from the two dose levels tested, 70 and 140 mg, but the exposure response analysis showed no apparent relationship between efficacy and erenumab concentration, consistent with the lack of a dose-response observed in the efficacy studies (Figure 1).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Laura Jawidzik was the clinical reviewer for this application. Dr. Joanne Liu was the biometrics reviewer and Dr. Kun Jin was the biometrics team leader. Dr. Sarrit Kovacs from the Clinical Outcomes Assessment Team was the primary reviewer for the patient reported outcome (PRO) review for the Migraine Physical Function Impact Diary (MPFID).

The applicant conducted three pivotal placebo-controlled efficacy trials (Table 1): two trials in episodic migraine (EM) [Study 20120296 (referred to as 296 in this memo) and Study 20120297 (referred to as 297 in this memo)] and one trial in chronic migraine (CM) [Study 20120295 (referred to as 295 in this memo)].

Table 1: Clinical efficacy studies

	Population	Double-blind treatment period	Dose(s)
Study 296	Episodic migraine	6 months	70 and 140 mg
Study 297	Episodic migraine	3 months	70 mg
Study 295	Chronic migraine	3 months	70 and 140 mg

The primary endpoint for all trials was the change from baseline in the mean number of monthly migraine days (MMD). For Study 296, the baseline was compared to the last 3 months of the 24-week double-blind treatment period, and for Studies 297 and 295, the baseline was compared to the last month of the 3-month double-blind treatment period. The key secondary endpoints differed between studies.

Study 296 (Episodic Migraine)
Study 296 was a 24-week randomized, double-blind, placebo-controlled trial in patients with episodic migraine. After a four-week baseline period, patients were randomized in a 1:1:1 ratio to receive placebo, erenumab 70 mg, or erenumab 140 mg SC monthly. After participation in the double-blind portion of the trial, patients were offered enrollment into either a 28-week open-label (dose-blind) treatment period, or a 12-week safety follow-up

period (off study medication). Patients entering the 28-week open-label treatment period were re-randomized to either 70 or 140 mg.

Subjects eligible for enrollment into this study were adults 18 to 65 years of age with a history of migraine with or without aura for ≥ 12 months who experienced ≥ 4 to < 15 migraine headache days/month. Subjects could be on one prophylactic medication if the dose had been stable for at least 2 months prior to the start of the baseline period. Patients with medication overuse headache were excluded (defined as headaches occurring ≥ 15 days per month coinciding with regular overuse of acute headache medication). Subjects were excluded if they had any the following within 12 months of screening: myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery or revascularization.

The primary endpoint for Study 296 was the change in mean MMD from baseline to the last 3 months of the 24-week double-blind treatment phase.
Key secondary endpoints were:

- Achievement of at least a 50% reduction from baseline in mean MMD over the last 3 months of the double-blind treatment period (DBTP), i.e., a responder analysis based on the primary endpoint.
- Change from baseline in mean monthly acute migraine-specific medication treatment days over the last 3 months of the DBTP.
- Change from baseline in mean monthly average *physical impairment domain scores* over the last 3 months of the DBTP as measured by the Migraine Physical Function Impact Diary (MPFID).
- Change from baseline in mean monthly average *impact on everyday activities domain scores* over the last 3 months of the DBTP, as measured by the MPFID.

To control the overall type-1 error rate, a multiplicity adjustment was applied to the primary and key secondary endpoints in this study, with overall alpha set at 0.05, apportioned to cover the two erenumab doses and the primary and secondary endpoints. The adjustment method was prospectively planned and deemed adequate.

Efficacy analyses and analyses of the MPFID were based on the efficacy analysis set, defined as patients who received at least one dose of investigational product and completed at least one change from baseline measurement in monthly migraine days during the DBTP.

297 (Episodic Migraine)
Study 297 was a 12-week randomized, double-blind, placebo-controlled trial in patients with episodic migraine. After a four-week baseline period, patients were randomized in a 1:1 ratio to receive placebo or erenumab 70 mg SC monthly. The primary endpoint was the change in MMD from baseline to the last month of the 12-week double-blind treatment phase. Studies 297 and 296 were similar, except for the duration of the double-blind period (12 vs. 24 weeks in Studies 297 and 296, respectively), the period of assessment for the primary endpoint (1 vs. 3 months, respectively), and the lack of an erenumab 140 mg treatment arm in Study 297.

The key secondary endpoints were:

- Achievement of at least a 50% reduction from baseline in mean MMD over the last month of the DBTP.
- Change from baseline in mean monthly acute migraine-specific medication treatment days over the last month of the DBTP.
- Achievement of at least a 5-point reduction from baseline on average *physical impairment domain scores* of the MPFID .
- Achievement of at least a 5-point reduction from baseline on average *impact on everyday activities domain scores* of the MPFID.

Secondary endpoints were calculated based on change from baseline over the last month of the 12-week double-blind treatment phase. A sequential testing procedure, specifically, hierarchical gate-keeping procedures and the Hochberg method, were used to maintain the 2-sided study-wise type-I error rate at 0.05 for the primary and secondary endpoints.

295 (Chronic Migraine)

Study 295 was a 12-week randomized, double-blind, placebo-controlled trial in patients with chronic migraine. Eligible subjects were adults 18 to 65 years of age with a history of migraine with or without aura who experienced ≥15 headache days per month, with ≥8 migraine days per month. Eligible subjects were randomized in a 3:2:2 ratio to placebo, erenumab 70 mg, or erenumab 140 mg.

The primary endpoint for this study was the same as that used in Study 297, specifically, the change in MMD from baseline to the last 4 weeks of the 12-week double-blind treatment phase.

Secondary endpoints were:

- Achievement of at least a 50% reduction from baseline in MMD in the last 4 weeks.
- Change from baseline in monthly acute migraine-specific medication treatment days in the last 4 weeks.
- Change from baseline in cumulative monthly headache hours in the last 4 weeks.

The MPFID was not measured in this trial.

The efficacy analysis set was defined in the same way as described above for Study 296 and 297. A multiplicity adjustment method was pre-specified and deemed adequate by Dr. Liu.

Results

In the three efficacy studies, the median age of the subjects was 41 to 45 years. Seventy-nine to 87% of subjects were female, and 87 to 97% were Caucasian. Demographics were generally balanced between treatment groups, although in the CM trial, 21% of subjects were male in the placebo arm, and 13-16% of subjects were male in the active treatment arms.

Baseline disease characteristics were balanced between treatment groups in all three trials. The mean number of MMD at baseline was 8 days in the EM population and 18 days in the CM population.

Treatment groups were also generally balanced with respect to prior use of prophylactic medications and concomitant use of prophylactic medication, which was allowed in the EM trials, but not in the CM trial. On average, 39 to 43% of patients in the EM studies had prior use of a prophylactic medication. Importantly, only 3-7% of patients in the EM studies were taking a prophylactic medication during the trial. Seventy-two to 76% of CM patients had prior use of prophylaxic medications.

Change in Mean Monthly Migraine Days from Baseline (Primary Efficacy Endpoint)

Study 296 (Episodic Migraine)

For Study 296, Dr. Liu reports that treatment with erenumab at both doses resulted in a significantly greater change from baseline in mean MMD, as compared with placebo. Refer to Table 2, below.

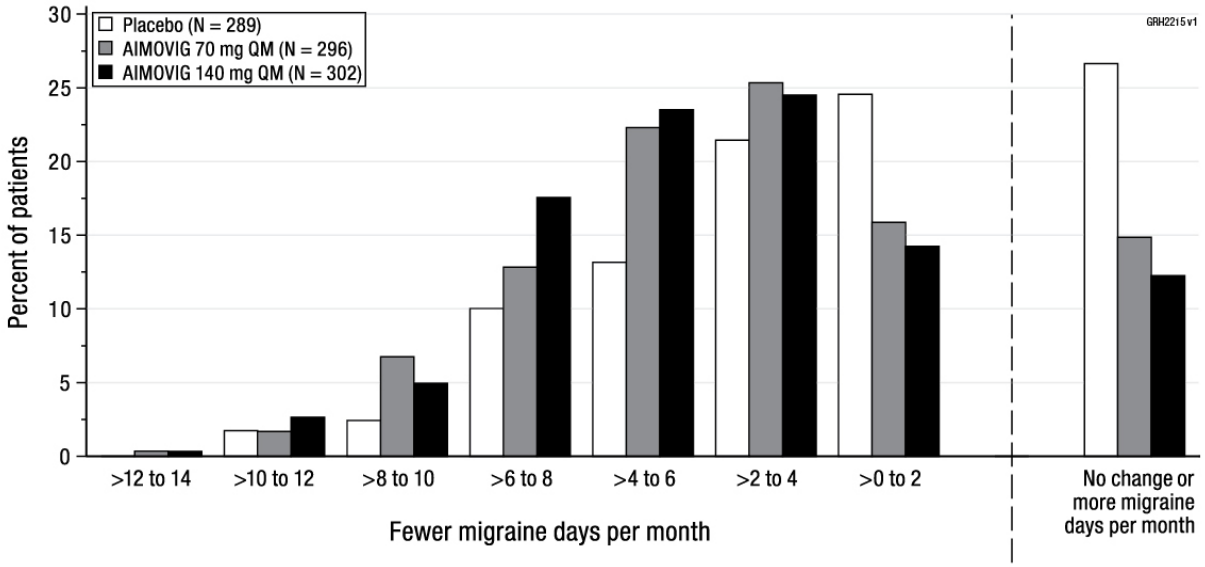
Table 2: Study 296 – Change from baseline in mean monthly migraine days (adapted from applicant's Table 10-1, clinical study report)

	Placebo (n=316)	Erenumab 70 mg (n=312)	Erenumab 140 mg (n=318)
Mean monthly migraine days (MMD) at baseline	8.25	8.31	8.33
Mean MMDs over Month 4, 5, and 6	6.33	4.95	4.48
Change from baseline in mean MMD	-1.95	-3.36	-3.83
Adjusted analysis			
LSM estimates	-1.83	-3.23	-3.67
95% CI of LSM	(-2.18, -1.48)	(-3.58, -2.88)	(-4.02, -3.33)
Difference in LSM		**-1.40**	**-1.85**
95% CI of the difference		(-1.88, -0.92)	(-2.33, -1.37)
p-value		< 0.001	< 0.001

Dr. Jawidzik also notes in her review that the treatment effect was consistent throughout all 6 months of the trial.

Figure 2 shows a distribution of changes from baseline in mean MMD in bins of 2 days, by treatment group. A leftward shift (toward improvement) is evident for both doses of erenumab relative to placebo. The visual representation of the treatment effects provides little suggestion that 140 mg is more effective than 70 mg.

Figure 2: Study 296 – Distribution of change from baseline in MMD in the last 3 months of the treatment period (source: from applicant, verified by FDA)



Study 297 (Episodic Migraine)

For Study 297, Dr. Liu reports that treatment with erenumab resulted in a significantly greater change from baseline in the mean MMD, as compared with placebo. The difference in LSM (95% CI) was -1.04 (–1.61, –0.47) days for erenumab 70 mg vs. placebo ($p < 0.001$).

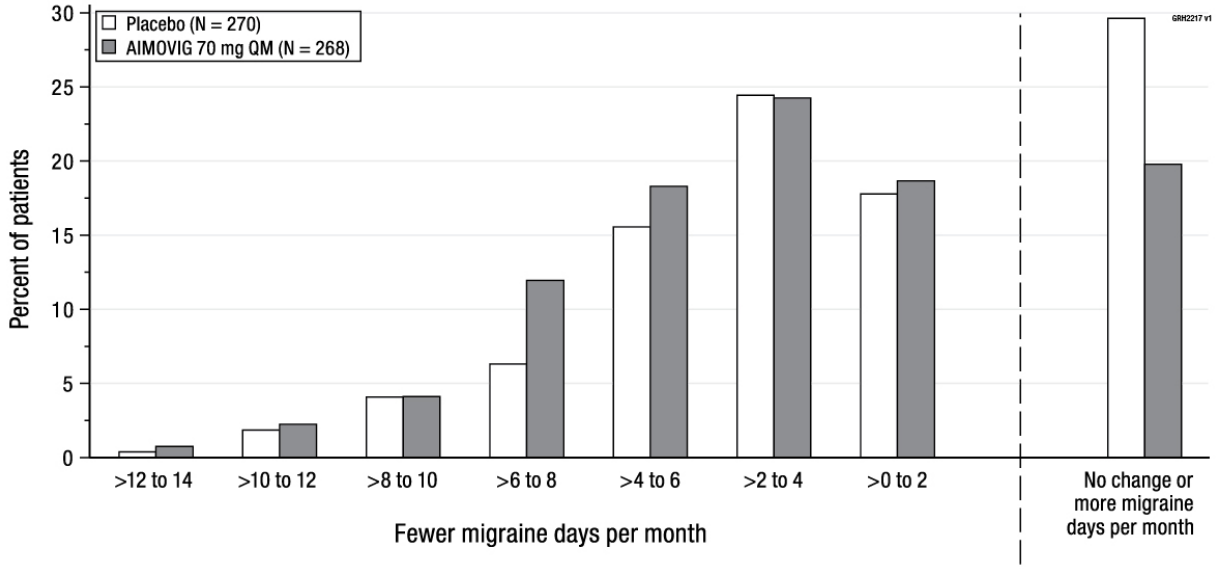
Table 3: Study 297 – Change from baseline in mean MMD (adapted from applicant's Table 10-1 of clinical study report)

	Placebo (n=288)	**Erenumab 70 mg (n=282)**
Mean monthly migraine days (MMD) at baseline	8.38	8.13
Mean MMDs over last 4 weeks of treatment	6.49	5.24
Change from baseline	-1.96	-2.89
Adjusted analysis		
LSM estimates	-1.84	-2.88
95% CI of LSM	(-2.25, -1.43)	(-3.3, -2.47)
Difference in LSM		**-1.04**
95% CI of the difference		(-1.61, -0.47)
p-value		< 0.001

The distribution of change in MMD from baseline to the last month of the treatment period for Study 297 is shown in Figure 3. As in Study 296, a leftward shift (towards improvement) is

evident, although it is visually less striking than in Study 296 (consistent with the smaller overall treatment effect).

Figure 3: Study 297 – Distribution of change from baseline in MMD in the last month of the treatment period (source: applicant, verified by FDA)



Study 295 (Chronic Migraine)

For Study 295, Dr. Liu reports that treatment with erenumab at both doses resulted in a significantly greater change from baseline in mean MMD as compared with placebo. The difference in LSM (95% CI) was the same for both doses: −2.46 (−3.52, −1.39) days for erenumab 70 mg vs. placebo and −2.45 (−3.52, −1.38) days for erenumab 140 mg vs. placebo ($p < 0.001$ for both, Table 4).

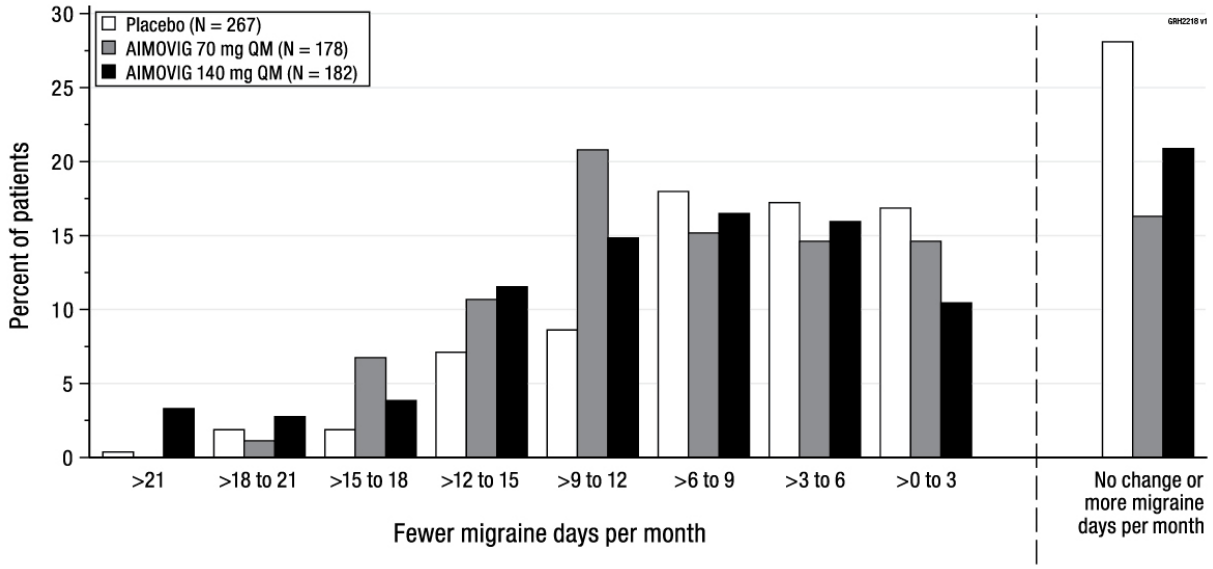
Table 4: Study 295 – Change from mean MMD (source: adapted from applicant's Table 10-1 of CSR)

	Placebo (n=281)	**Erenumab 70 mg (n=188)**	**Erenumab 140 mg (n=187)**
Mean monthly migraine days (MMD) at baseline	18.24	17.94	17.78
Mean MMDs over last 4 weeks of treatment	14.03	11.34	11.28
Change from baseline	-4.24	-6.63	-6.53
Adjusted analysis			
LSM estimates	-4.18	-6.64	-6.63
95% CI of LSM	(-4.86, -3.50)	(-7.47, -5.81)	(-7.45, -5.80)
Difference in LSM		**-2.46**	**-2.45**
95% CI of the difference		(-3.52, -1.39)	(-3.51, -1.38)
p-value		< 0.001	< 0.001

Dr. Jawidzik notes that the treatment effect was consistent through all 3 months of the study.

The distribution of change in monthly migraine days from baseline to the last month of the treatment period for Study 295 is shown in
Figure 4 (using 3-day bins, as the number of monthly migraine days is greater in this patient population). As in the episodic migraine studies, a treatment effect for erenumab is evident across a range of changes in migraine days from baseline, and in particular in patients with the largest reductions in monthly migraine days (-12 days and greater).

Figure 4: Study 295 – Distribution of change in MMD from baseline to the last 4 weeks of the 12 week treatment period by treatment group (source: applicant, verifiewd by FDA)



50% Reduction from Baseline in Mean Monthly Migraine Days
In Study 296, Dr. Liu reports that the proportions of subjects who achieved at least a 50% reduction in mean MMD from baseline to the last 3 months (Month 4, 5, and 6) of the 24-week double-blind treatment phase were 26.6%, 43.3%, and 50.0% for the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively; results were statistically significant for both erenumab treatment groups vs. placebo ($p < 0.001$ for both).

In Study 297, the proportions of subjects who achieved at least a 50% reduction in MMD from baseline to the last month of the 12-week double-blind treatment phase was 29.5% for the placebo group and 39.7% for the erenumab 70 mg treatment group ($p = 0.010$).

In Study 295, Dr. Liu reports that the proportions of subjects with at least a 50% reduction in MMD from baseline to the last 4 weeks of the 12-week double-blind treatment phase were 23.5%, 39.9%, and 41.2% for the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively; results were statistically significant for both erenumab treatment groups vs.

placebo ($p < 0.001$ for both). Please refer to Table 5 for a comparison of results for the three efficacy trials on this secondary endpoint.

Table 5: Studies 295, 296 and 297 – Reduction of at least 50% from baseline in MMDs (adapted from Table 50 of Dr. Jawidzik's review and Tables 7, 13, and 20 of Dr. Liu's review)

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295			
% responders	23.5	39.9	41.2
Odds ratio		2.18	2.34
p-value		<0.001	<0.001
Difference from placebo (%)		16.4	17.7
Study 296			
% responders	26.6	43.3	50.0
Odds ratio		2.13	2.81
p-value		<0.001	<0.001
Difference from placebo (%)		16.7	23.4
Study 297			
% responders	29.5	39.7	N/A
Odds ratio		1.59	
p-value		0.010	
Difference from placebo (%)		10.2	N/A

There was a consistent erenumab treatment effect across studies on the proportion of subjects with a 50% reduction from baseline in mean MMD. There was a small numerical advantage of the 140-mg dose over the 70-mg dose in the two trials that included both doses.

Acute Migraine-specific Medication Treatment Days

In all 3 studies, there were significantly greater reductions from baseline in the mean number of days (per month) with use of acute migraine-specific drugs in erenumab-treated patients than in placebo-treated patients (Table 6).

Table 6: Studies 295, 296 and 297 – Change from baseline in mean number of acute migraine-specific medication treatment days (adapted from applicant's Tables 4, 5, and 6 from 2.7.3, summary of clinical efficacy)

	Placebo	Erenumab 70 mg	Erenumab 140 mg
Study 295			
Baseline (days)	9.4	8.8	9.7
Mean over 3 months (days)	7.9	5.7	5.6
Raw difference over 3 months	-1.5	-3.1	-4.1
p-value		< 0.001	< 0.001
Study 296			
Baseline-mean	3.4	3.2	3.4
Mean over months 4-6 (days)	3.3	2.3	1.8
Raw difference over months 4-6	-0.1	-1.0	-1.7
p-value		< 0.001	< 0.001
Study 297			
Baseline (days)	3.4	3.8	N/A
Mean over 3 months (days)	3.0	2.6	N/A
Raw difference over 3 months	-0.4	-1.2	N/A
p-value		0.002	N/A

The results from the three efficacy trials demonstrate a 1- to 2-day difference (vs. placebo) in mean number of days with use of acute migraine-specific medications. The 140-mg dose shows a numerical advantage over the 70-mg dose in the two trials that included both doses.

Change from Baseline in Cumulative Monthly Headache Hours

In the CM study, change from baseline in cumulative monthly headache hours was a key secondary endpoint. As Dr. Jawidzik reports, patients on placebo had a reduction of about 55 hours, compared with a 65-hour reduction for erenumab 70 mg ($p = 0.28$) and a 75-hour reduction for erenumab 140 mg ($p = 0.03$). After adjustment to control for the type-1 error rate, neither comparison was statistically significant.

Migraine Physical Function Impact Diary

Dr. Kovacs, from the Clinical Outcome Assessment (COA) staff in OND, reviewed the Migraine Physical Function Impact Diary (MPFID), a patient reported outcome (PRO) instrument developed by the applicant to assess the impact of migraine on physical impairment and everyday activities. The MPFID contains 13 items evaluating the impact of migraine

during the previous 24 hours on two concepts of interest: impact on everyday activities (7 items) and physical activity (5 items), as well as one global item assessing the overall difficulty doing activities. Patients report the impact or difficulty associated with migraine on a daily basis and monthly MPFID scores are averaged over 28 days; higher scores indicate worse impact on both domains. The COA staff found the content validity, domain structure, and psychometric properties of the MPFID acceptable, but noted high floor effects for more than half of the items, which would be expected to reduce its sensitivity to detect treatment effects. As discussed in greater detail in the reviews, the impact on everyday activities and on physical impairment were considered separately, and the score for both subscales were normalized to a 0 to 100 scale, where 100 represents greater impact of migraine on any day of the month, and 0 represents lesser impact. The applicant included the MPFID in Study 297 and Study 296. The applicant used a responder definition in Study 297 (based on a 5-point score change), and a comparison of mean changes in Study 296. The results were numerically in favor of erenumab in Study 297, but did not achieve statistical significance (see Table 7). In Study 296, the MPFID results achieved high statistical significance (see Table 8). In addition, a comparison based on the 5-point responder definition was also nominally significant. There was extensive discussion among the review team with respect to the threshold for a clinically meaningful change on the MPFID, and whether the change observed in Study 296 was clinically meaningful. It is important to consider the baseline MPFID scores to interpret the clinical importance of score changes. (b) (4)

(b) (4) the applicant's prospective definition of a nge that is clinically meaningful.

Table 7: MPFID Results for Study 297 (adapted from applicant's table in the clinical study report)

	Placebo	Erenumab 70 mg
Physical impairment domain (points)		
Baseline (mean)	11.5	10.7
Mean over month 3	9.3	7.5
Change from baseline	-1.9	-3.3
Difference from placebo (*p*-value[+])		-1.3 (0.02)
5-point change from baseline* (*p*-value vs. placebo)	27.1%	33.0% (0.13)
Impact on everyday activity domain (points)		
Baseline (mean)	13.1	12. 6
Mean over month 3	9.7	8.2
Change from baseline	-3.3	-4.4
Difference from placebo (*p*-value[+])		-1.1 (0.06)
5-point change from baseline* (*p*-value vs. placebo)	35.8%	40.4% (0.26)

*prespecified MPFID endpoint in Study 297 [+] nominal *p*-value

Table 8: MPFID Results for Study 296 (Adapted from applicant's table in the clinical study report)

	Placebo	Erenumab 70 mg	Erenumab 140 mg
			(b) (4)

Efficacy by Subgroups
Males, patients over the median age and non-white patients had a smaller treatment response in all 3 trials; however, the small numbers of subjects in these subgroups limit the interpretability of this observation.

Efficacy Based on the Presence of ADA
There were 94 patients (5.9%) exposed to any erenumab dose (7, 21, 20 or 140 mg) who developed ADA. Of the patients who received the to-be-marketed doses (70- or 140-mg), 69 (8.6%) developed ADA. Erenumab appears to maintain a treatment effect in patients with ADA, but the data are too limited to make a definitive conclusion on the effect of ADA on efficacy.

Dose-finding
As Dr. Jawidzik describes, the applicant used the capsaicin induced dermal blood flow (DBF) model to determine the doses to take into their clinical dose-finding trial. The applicant estimated that a 21-mg dose would be efficacious, because it produced near maximal inhibition of capsaicin-induced DBF, and then selected the 7-mg dose as the minimally efficacious dose and 70 mg as the high dose. The applicant conducted a 12-week phase 2 dose-finding randomized, double-blind, placebo-controlled trial in patients with episodic migraine (20120178). In that trial, patients were randomized to one of four arms (placebo, erenumab 7 mg, erenumab 21 mg, or erenumab 70 mg) and received monthly SC injections. The primary

endpoint was the change in MMD between baseline and the last four weeks of treatment. In this trial, only the 70-mg dose of erenumab demonstrated a nominally significant change (p = 0.021) from baseline, as compared with placebo. In addition, the proportion of subjects with at least a 50% reduction in MMD from baseline showed a nominally significant (p = 0.011) difference from placebo for the 70-mg dose only. Based on these results, FDA recommended that the applicant add a 140-mg dose arm in phase 3.

Efficacy Conclusions

The applicant has provided substantial evidence of effectiveness of erenumab based on three adequate and well-controlled investigations. Two trials in episodic migraine and one trial in chronic migraine demonstrated significant reductions in mean MMD from baseline in patients treated with erenumab, compared with those who received placebo. In addition, treatment benefits were demonstrated in secondary outcomes, i.e., the proportion of subjects with at least a 50% reduction in mean monthly migraine days, and the use of rescue medication. The magnitude of change in the reduction in mean MMD from baseline is relatively small (1-2 days/month over the placebo effect), but consistent with the magnitudes of treatment effects for previously approved migraine prophylaxis drugs. As expected, some patients receive a substantially larger treatment effect, but there is no method to identify such patients prospectively. The 70-mg dose is clearly effective, and is appropriate as the recommended starting dose. The 140-mg dose shows small numerical advantages on the primary and key secondary endpoints in one study (296), and on the secondary endpoint of the proportion of subjects with at least a 50% reduction in MMD from baseline in another study (295). Although superiority of the 140-mg dose has not been established over the 70-mg dose, it is possible that some patients may benefit from an increase from 70 to 140 mg.

8. Safety

Dr. Laura Jawidzik conducted the clinical safety review.

As discussed by Dr. Jawidzik, the overall exposure to erenumab exceeds the minimum numbers of patients recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 3150 subjects have been exposed to at least one dose of erenumab (including 613 healthy volunteers), 2128 subjects to erenumab 70 mg and 1223 to erenumab 140 mg. (Some patients received both 70 and 140 mg; therefore, the total numbers of patients exceed 3150.) One-thousand eight-hundred and eleven patients were exposed to erenumab 70 mg for ≥ 6 months and 707 patients for ≥ 12 months. One-thousand forty-one patients were exposed to erenumab 140 mg for ≥ 6 months and 176 patients for ≥ 12 months. There is significantly more exposure data for the 70-mg dose than the 140-mg dose. Dr. Jawidzik notes that there are very few patients with cardiovascular disease or significant cardiovascular risk factors in this database. She also notes that there is limited information on patients over 65 years of age.

Deaths

There were two deaths in the erenumab database for this application; both occurred during the open-label treatment phase, and both were cardiovascular-related sudden deaths. The first patient was a 54 year-old white male with a history of hypertension. The patient received 3

doses of erenumab 7 mg and 21 doses of erenumab 70 mg in the study. He was found dead in his apartment 9 days after taking the last dose of study drug. At autopsy, the patient was found to have a 90% stenosis of the right and left coronary arteries with 60% stenosis of the left anterior descending artery. His toxicology screen was positive for ethanol, phenylpropanolamine, and norpseudoephedrine. Of note, the patient's father died at age 39 of a heart attack. The second patient was a 43 year-old male who received 6 doses of erenumab 70 mg and 4 doses of erenumab 40 mg. He was found dead 22 days after taking the last dose of erenumab. The autopsy report noted grade 1 atherosclerosis, fatty infiltration of the myocardium and left ventricular hypertrophy. Genetic testing revealed that the patient was heterozygous for a frameshift mutation in the SCN5A gene. The autopsy diagnosis was heart failure due to arrhythmogenic cardiomyopathy.

Both deaths were cardiovascular in nature and occurred in relatively young males. The first case is difficult to interpret; there was ingestion of cardiac stimulants in the setting of severe atherosclerosis. The second case is confounded by the underlying genetic disease (SCN5A mutation) and the cardiomyopathy presumed to be related to his genetic mutation. Dr. Jawidzik states that although the applicant asserts that both deaths are unrelated to the investigational products, and that both deaths are confounded, it is possible to consider that chronic CGRP antagonism may have had a role in the death of the first case. Dr. Preston Dunnmon from the Division of Cardiology and Renal Products evaluated both cases and concluded that both cases had a plausible cause of death other than the use of erenumab; he did not believe these cases alone impacted approvability or labeling decisions. The review team agrees with Dr. Dunnmon's conclusions.

Serious Adverse Events (SAEs)

Dr. Jawidzik notes that there were 56 SAEs in the controlled studies. The most commonly reported SAEs were infections, musculoskeletal disorders, and nervous system disorders. The only imbalances noted in SAEs between placebo and active treatment are in the infection and infestation system organ class (SOC) for the 140-mg dose, when all controlled trials are pooled. This may be a chance finding.

At the time of the 120-day safety update, 162 SAEs had been reported in 126 patients (5%) who received erenumab 70 or 140 mg. Dr. Jawidzik reports that there was no SAE SOCs that contained ≥ 1% patients. SAEs related to vascular events were of special interest and were closely examined (see cardiovascular discussion below). There were several isolated cases of possible vascular events that mapped to the following preferred terms: myocardial ischemia (n=2), arrhythmogenic right ventricular dysplasia (n=1), non-cardiac chest pain (n=4), syncope (n=5), ischemic colitis (n=1), and thromboses (n=8 in 5 patients), including two cases of cerebral venous thrombosis. In most cases, a clear relationship to erenumab could not be made, but some cases had no clear alternate etiology to the event, which is not unusual in clinical studies. The rate of these events in erenumab trials, however, does not exceed the background rate in migraine patients. Select events are discussed in more details in other sections of this memo.

There was one reported SAE coded as drug-induced liver injury in a female who had received a single dose of erenumab 140 mg in a PK study. Ten days after she was dosed, the patient

developed elevated transaminases and bilirubin with a clinical picture consistent with hepatocellular injury. The patient experienced full resolution of this event approximately two months after presentation. The Division of Gastroenterology and Inborn Errors Products was consulted to review this case, and concluded that the event was unlikely to be related to erenumab. There was one SAE of constipation reported in the open-label treatment period. Dr. Jawidzik believes that this was likely related to study drug.

AEs Leading to Study Discontinuation

Dr. Jawidzik reports a dose-related increase in the rate of adverse dropouts in controlled studies (1.2, 1.7, and 2.4% for placebo, erenumab 70 mg, and erenumab 40 mg, respectively). The SOCs that showed a dose-response for adverse dropouts were cardiac (placebo 0%, erenumab 70 mg 0.1%, erenumab 140 mg 0.4%), gastrointestinal (placebo 0.1% , erenumab 70 mg 0.4 %, erenumab 140 mg 0.6%), and psychiatric disorders (placebo 0.1%, erenumab 70 mg 0.3%, erenumab 140 mg 0.4%). Given the low numbers of events overall, it is difficult to draw clear conclusions from these small differences.

Notable cases of adverse dropouts in controlled studies were one patient with cerebral venous thrombosis (also reported as SAE), one patient with constipation, one patient with worsening irritable bowel syndrome, two patients with palpitations, and one patient with ventricular extrasystoles, compared to none on placebo. There was one patient on active treatment and one on placebo who discontinued because of hypertension. Again, with small numbers of events, it is not possible to draw conclusions about the relationship of these events to erenumab. Select events are discussed in more details in other sections of this memo.

In the open-label studies, there were 61 adverse events reported by 57 patients leading to withdrawal of study medication. Notable is one patient with worsening Raynaud's phenomenon (see further discussion below).

Adverse Events of Any Severity

The adverse events with an incidence at least 1% greater in erenumab-treated patients than in placebo-treated patients over the first three months of treatment in the controlled efficacy trials include injection site reaction, constipation, and cramps/muscle spasms (see Table 9).

Table 9: AEs of Any Severity in the Pivotal Efficacy Trials over the 3-month Double-Blind Treatment Period Occurring ≥2% Over Placebo: (Adapted from Table 74 of Dr. Jawidzik's review)

	Placebo (n=890)	Erenumab 70 mg (n=787)	Erenumab 140 mg (n=507)
Injection site reaction	3%	6%	5%
Constipation	1%	1%	3%
Cramps, muscle spasms	0%	0%	2%

Table 10 shows the 6-month pooled data from the controlled clinical trials, which included the same items as in the first 3 months of treatment, with the addition of groupings of infection-all and infection-viral, as well as arthralgia.

Table 10: AEs and Groupings of AEs of Any Severity in the Pivotal Efficacy Trials Occurring ≥2% Over Placebo. (inclusive of 6 month data) (Adapted from Table 77 of Dr. Jawidzik's review)

	Placebo (n=890)	Erenumab 70 mg (n=787)	Erenumab 140 mg (n=507)
Infection, all	25%	25%	27%
Injection site reaction	3%	6%	5%
Infection, viral	3%	5%	5%
Constipation	1%	1%	4%
Arthralgia, arthritis, arthrosis	2%	2%	3%
Cramps, muscle spasms	0%	0%	2%

Vital signs

Dr. Jawidzik reports that there were no clinically significant changes from baseline in mean heart rate, systolic blood pressure, or diastolic blood pressure (DBP) on active treatment as compared to placebo at Week 12 in the pooled controlled studies (178, 295, 296, and 297). There was a small dose-related increase in the number of patients who had a ≥ 10 mm Hg increase from baseline in DBP at multiple time points (Weeks 4 to 24) in the pooled data from the double-blind treatment period of Study 295 and 296 (Table 11). Changes in DBP were not observed in Study 297 (70 mg and placebo only), but were identified in Study 178 when the placebo and 70 mg doses were compared. There was no increase in the fraction of patients who had a ≥ 10 mm Hg increase from baseline in systolic blood pressure (SBP).

Table 11: Studies 295 and 296 – Increases in DBP by ≥ 10 mm Hg from baseline in the double-blind treatment period (source: Table 102 of Dr. Jawidzik's review)

	Placebo (%)	Erenumab 70 mg (%)	Erenumab 140 mg (%)
Week 4	6.2	9.1	9.6
Week 8	6.1	8.5	9.8
Week 12	8.1	8.4	10.5
Week 24*	7.7	7.3	10.0

*Study 296 only

ECG changes

Dr. Jawidzik reports that the applicant provided an analysis of the double-blind placebo-controlled pool that showed an imbalance between placebo and active treatment in ectopic supraventricular rhythms. In the 6-month pooled controlled trial data, the rates of ectopic supraventricular rhythms were 0.3% for placebo, 1.3% for erenumab 70 mg and 2.2% for erenumab 140 mg. The applicant defined ectopic supraventricular rhythms as premature atrial complexes, premature junctional complexes, ectopic atrial tachycardia, multifocal atrial tachycardia, paroxysmal supraventricular tachycardia, and junctional escapes. Dr. Dunnmon from DCRP reviewed the ECG information and concluded that there was no evidence of excessive tachycardia or bradycardia in erenumab-treatment patients.

Dr. Jawidzik reports that there were no dose-dependent changes in the PR, QRS, or QT intervals from baseline to the end of the double-blind period. Because this product is a biologic, a thorough QT study was not required, but the QT data were obtained from summary statistics from the pooled controlled trial data. Dr. Jawidzik reports that no patients on erenumab had a QTcF > 500 msec. One patient in the 70-mg group had a QTcF interval increase from baseline > 60 msec.

Safety Areas of Special Interest

Cardiac Effects

Multiple published reports state that CGRP is a potent vasodilator. A theoretical concern has been raised in the literature that inhibition of CGRP could impair protective vasodilation in patients with ischemia. To address these concerns, the applicant submitted an *in vitro* human coronary artery study to assess the potential for erenumab to induce vasoconstriction and a review of the relevant published literature on the biology of CGRP and its role in the cardiovascular system (see Nonclinical Pharmacology/Toxicology above). There are also reassuring data in healthy men that nitroglycerin-induced vasodilatation is not CGRP-dependent; therefore, patients with CGRP blockade should remain responsive to sublingual nitrates. Our review of cardiovascular events, ECGs, and vital signs measurements in the erenumab database does not identify a cardiovascular risk to patients. As noted above, two cardiac-related deaths were reported in the erenumab database, but the deaths did not appear to be erenumab-related. There were isolated cases of ischemic events reported in the database, but the rate of these cases was no greater than the background rate in this patient population. There were no clear signals related to changes in heart rate or ECG. There was a small increase identified in the number of patients with a 10 mm Hg increase in DBP in the active treatment groups, as compared to placebo, but no such change in regard to SBP. This finding is plausibly drug-related, but unlikely to be clinically significant. In addition, the applicant conducted a treadmill study in 88 patients with stable angina to evaluate the effect of erenumab on exercise time following a single intravenous injection of erenumab 140 mg. The primary endpoint was change from baseline in total exercise time, and the secondary endpoints were time to onset of exercise-induced angina and time to onset of $\geq$ 1 mm ST segment depression. Although the study was unable to establish that erenumab does not affect exercise capacity in patients, it is reassuring that no patient experienced a significant vascular event in the study. The Medical Policy and Program Review Council (MPPRC) discussed the theoretical risk of worsened ischemia with erenumab on April 20, 2018 following a presentation of the nonclinical data by Dr. John Koerner (from DCRP) and unanimously concluded that nonclinical data do not raise substantial concern about the potential for cardiovascular risk in humans.

Thrombosis

Dr. Jawidzik reports that there were 3 cases of thrombosis on active treatment in controlled studies, as compared to none on placebo. One of the 3 cases had no clear alternative etiology for this event. There were an additional 5 patients in open-label studies who reported 8 thrombotic events. In all cases but one, the patients had an alternate risk factor for thrombosis. The drug causality is unclear at this time, considering the small number of cases, and the background rate for thrombosis.

Raynaud's phenomenon

Dr. Jawidzik reports that there were 11 patients with a diagnosis of Raynaud's phenomenon in the erenumab database. Two of these patients reported a worsening of symptoms. One patient was receiving erenumab 140 mg but did not discontinue from the study. Another patient who was receiving 70 mg of erenumab had symptoms consistent with Raynaud's phenomenon. These symptoms were severe enough to lead the patient to discontinue the investigational product. It has been reported that a deficiency of CGRP release can result in a lack of reflex vasodilatation observed in Raynaud's phenomenon, and that administration of CGRP has a beneficial effect (Bunker et al 1993, and Russell et al 2014). However, most patients with a history of Raynaud's phenomenon (9/11) tolerated erenumab treatment well, and the worsening noted in the other two patients is compatible with a fluctuation in disease severity. Drug causality remains uncertain.

Gastrointestinal Effects

Dr. Jawidzik notes in her review that nonclinical data suggest that CGRP may reduce gastric acid secretion. Therefore, gastrointestinal disorders was considered a safety area of interest. Dr. Jawidzik notes that there was no imbalance in the incidence of reports of AEs in the gastrointestinal SOC between treatment groups, but there was an imbalance in constipation, with a dose-related increase in constipation events (Table 9). In addition, there were three adverse dropouts (one reported as SAE) related to constipation. There was one case of ischemic colitis in the database, but this patient continued treatment with erenumab.

Analysis of Liver Transaminase and Bilirubin Elevations

There was one patient in a single-dose phase 1 trial who developed a pattern of transaminase elevation consistent with acute liver injury. This case is described above, and does not appear drug-related. The erenumab safety database does not suggest a signal for hepatotoxicity.

Suicidality

The applicant performed the the Columbia Suicide Severity Rating Scale on all patients in the efficacy trials and Dr. Jawidzik notes that no safety signal for suicidality was identified.

Injection Site Reactions

Dr. Jawidzik reports that injection site reactions were reported more frequently in erenumab-treated patients than in placebo-treated patients in controlled studies. The frequencies of injection site reactions in controlled studies were 3.3% for placebo, 5.9% for erenumab 70 mg, and 4.9% for erenumab 140 mg. Description of this information in Section 6 of labeling is appropriate.

Immunogenicity

Dr. Jawidzik reports that at the time of the 120-day safety update, 224/2515 patients (8.9%) had developed anti-drug antibodies (ADAs); no patients had developed neutralizing ADAs. When safety was evaluated in ADA-positive patients, the profile of AEs was in line with the most common AEs reported in the overall database, according to Dr. Jawidzik. Overall, the rate of development of erenumab antibodies was low, and no safety concern was identified in ADA-positive patients.

Safety conclusions
No serious safety issues related to the use of erenumab were identified. The most frequent adverse events in the controlled database were injection site reactions and constipation.

Dr. Jawidzik noted that patients over 65 years of age, who may have additional cardiovascular risk factors, were not recruited into the clinical trials, and recommended requiring a safety study in that population. In the absence of a safety signal for a vascular risk with erenumab, that study is not justified, and would be highly unlikely to contribute useful information, as it would lack assay sensitivity.

Given that other drugs approved for migraine pose cardiovascular risks, it was extremely important to consider carefully the cardiovascular risks of erenumab. Erenumab is a first-in-class drug, thus there are no data on cardiovascular risks from other drugs in its class. As noted previously, there is a body of nonclinical literature, predominantly from the 1980s and 1990s, suggesting that inhibition of CGRP could impair protective or compensatory vasodilation in patients with tissue ischemia, inhibit collateral perfusion, and/or decease cardiac preconditioning. The applicant made an attempt to study cardiovascular risks by performing treadmill exercise testing in 88 patients with known coronary artery disease, with and without pre-treatment with intravenous erenumab. They also studied erenumab's vasomotor effects on coronary artery rings *in vitro*. These results were somewhat reassuring, but in no way definitive. And although we had encouraged the applicant to enroll older patients with cardiovascular risk factors in their migraine trials, when the database was locked, there were very few of these patients.

The Warnings and Precautions section of labeling can include serious or otherwise clinically significant adverse reactions that have not been observed but are nevertheless *anticipated* to occur, if animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans. Having discussed the animal studies at length with consultants from the Division of Cardiovascular and Renal Products and with the Medical Policy and Program Review Council, we reached the unanimous conclusion that, considered as a whole, the animal data do not raise substantial concern with respect to human risk; therefore, there will not be a warning/ precaution in labeling with respect to cardiovascular risk, and a post-marketing safety study will not be required.

Routine pharmacovigilance is appropriate for erenumab.

9. CDRH

Dr. Robert Meyer conducted the CDRH review and Dr. John McMichael was the Team leader. They both recommend approval. Erenumab is proposed for administration in a prefilled syringe, using an autoinjector. Both devices were found acceptable by CDRH.

Bioequivalence study for Autoinjector
The applicant conducted a bioequivalence study showing similar C_{max}, T_{max} and AUC when erenumab is administered with the autoinjector or with the prefilled syringe.

Human Factor Review
The summative human factor testing for the prefilled syringe and auto injector adequately validates the function of the device.

Compliance with Quality System Requirements
Daniel Ramsey from the CDRH Office of Compliance evaluated the applicant's compliance with applicable quality system requirements and concludes that this submission should be approved. He reports that inspections were waived at the applicant's two manufacturing sites because previous inspections conducted within the last 2 years classified as Voluntary Action Indicated (VAI). He also reports that established procedures for management responsibility, design controls and design control responsibilities, design development, verification and risk management, purchasing controls and corrective and preventive actions for combination products have been adequately addressed by the applicant. Daniel Ramsey reports on the manufacturing and states that the applicant confirmed that all drug product manufacturing, including filling, is conducted at the Amgen Manufacturing Limited facility for both the prefilled syringe and the autoinjector.

10. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because it was clear that the applicant had provided substantial evidence of effectiveness from three adequate and well controlled studies, using clinical trial designs similar to those of trials for previously approved migraine drugs. Moreover, the safety profile was deemed acceptable for the treatment of migraine, without controversial issues.

11. Pediatrics

Erenumab was discussed at a PeRC meeting on April 4, 2018. Agreement was reached with the applicant's plan for requesting a partial waiver for patients 0 to less than 6 years of age and deferral for patients 6 to 17 years of age. Please refer to Section 14 of this memo for the planned pediatric postmarketing studies.

12. Other Relevant Regulatory Issues

Office of Scientific Investigations
Dr. Cara Alfaro conducted the review for the Office of Scientific Investigations. Four clinical sites were inspected. Dr. Alfaro reports that the studies appear to have been conducted adequately and the data generated by those sites appear acceptable. There was some evidence of underreporting of non-serious adverse events at two sites, but the frequency was low, and most occurred in subjects randomized to placebo or in subjects participating in the open-label phase of the trial. Therefore, this underreporting is unlikely to affect the overall safety analyses. There was no underreporting of serious adverse events at any of the inspected clinical sites. The final compliance classification of two inspections were No Action Indicated

(NAI) and the final compliance classification of the two inspections where underreporting was noted was a VAI.

Controlled Substance Staff
The Controlled Substance Staff reviewer for this application was Dr. Joshua Hunt. Dr. Hunt concludes that there is no abuse signal or data requiring further review of this application. (b) (4)

Division of Medication Error Prevention and Analysis
Dr. Whaley reviewed the human factors validation study, prescribing information, instructions for use (IFU), container labels, and carton labeling to determine if they are acceptable from a medication error perspective. Dr. Whaley describes that the objective of the simulated use human factor (HF) validation study was to evaluate whether the intended user could safety and effectively use the 70-mg autoinjector. A total of 286 representative users were evaluated. Dr. Whaley reviewed the root cause analysis provided by the applicant for each failure related to critical tasks and recommended revisions to the IFU to provide additional clarity. She does not recommend additional HF validation testing. She also recommended changes to the Prescribing Information, carton labeling, and container labels. The applicant agreed to these changes.

Dr. Morris reviewed the proposed proprietary name, Aimovig, and concluded that this name is acceptable.

Dr. Whaley reviewed the nonproprietary name suffix. The applicant's proposed suffix –aooe is acceptable and Dr. Whaley recommends that the nonproprietary name be revised throughout draft labels and labeling to erenumab-aooe.

13. Labeling

Agreement was reached with the applicant on labeling. (b) (4)

14. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
A REMS is not necessary for this product.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR 3392-1 Juvenile monkey toxicology study to evaluate effects of erenumab-aooe on growth, reproductive development, and neurological and neurobehavioral development.

PMR 3392-2 An open-label pharmacokinetic, safety, and tolerability study in pediatric migraine patients ages 6 through 11 years. Dosing will depend on body weight,

according to two weight bands: <40 kg and ≥40 kg. The study should identify doses that provide exposures that match those observed with the 70-mg and 140- mg doses of Aimovig in adults.

PMR 3392-3 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 (of at least 12 weeks duration), with an open-label extension (of at least 40 weeks duration). Two weight bands should be utilized for dosing. In each weight band, two different dosing levels of Aimovig should be tested. Dosing should provide exposures matching those observed with the 70-mg dose and with the 140-mg dose of Aimovig in adults. This study is to be submitted as a special protocol assessment (SPA).

PMR 3392-4 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 (of at least 12 weeks duration), with an open-label extension (of at least 40 weeks duration). Two weight bands should be utilized for dosing. In each weight band, two different dosing levels of Aimovig should be tested. Dosing should provide exposures matching those observed with the 70- mg dose and with the 140-mg dose of Aimovig in adults. This study is to be submitted as a special protocol assessment (SPA).

PMR 3392-5 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 Aimovig during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Aimovig 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 3392-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3392-5 (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 Aimovig during pregnancy compared to an unexposed control population.

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

/s/

HEATHER D FITTER
05/17/2018

ERIC P BASTINGS
05/17/2018

ELLIS F UNGER
05/17/2018