CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761077Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761077
Priority or Standard	Standard
Submit Date(s)	5/17/2017
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Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Laura Jawidzik, MD
Review Completion Date	5/15/2018
Established Name	Erenumab
(Proposed) Trade Name	Aimovig
Applicant	Amgen
Formulation(s)	Subcutaneous
Dosing Regimen	1 injection of 70mg SC or 2 injections of 70mg SC
Applicant Proposed Indication(s)/Population(s)	Prevention of migraine
Recommendation on Regulatory Action	Approval of 70mg SC monthly and 140mg SC monthly
Recommended Indication(s)/Population(s) (if applicable)	For preventive treatment of migraine in adults age 18 or older

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Glossary

AC	advisory committee
ADaM	analysis data model
AE	adverse event
AHS	American Headache Society
AI	auto-injector
AAN	American Academy of Neurology
BID	twice a day
BLA	biologics license application
BOCF	baseline observation carried forward
BRF	Benefit Risk Framework
CGRP	calcitonin gene-related peptide
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
COA	clinical outcomes assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography scan
CV	cardiovascular
DBF	dermal blood flow
DBP	diastolic blood pressure
DBTP	double-blind treatment phase
DCRP	Division of Cardiovascular and Renal Products
DM	demographics
DMC	data monitoring committee
DME	designated medical event
DNP	Division of Neurology Products

ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
eDiary	electronic diary
EEG	electroencephalography
EOP2	end of phase 2
ETASU	elements to assure safe use
ETT	exercise treadmill test
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HIV	human immunodeficiency virus
HLT	high level term
ICH	International Conference on Harmonization
ICHD-2	International Classification of Headache Disorders 2nd edition
ICHD-3	International Classification of Headache Disorders 3rd edition
IEC	independent ethics committee
IHS	International Headache Society
IND	Investigational New Drug
ID	identification
IP	investigational product
IR	information request
IRB	institutional review board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
IVC	inferior vena cava
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMDs	monthly migraine days
MPFID	Migraine Physical Function Impact Diary
MPPRC	Medical Policy and Program Review Council (MPPRC)
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NNT	number needed to treat
OCS	Office of Computational Science

OCP	oral contraceptive pill
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	pre-filled syringe
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PT	preferred term
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QID	four times a day
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneously
SCS	Summary of Clinical Safety
SDTM	study data tabulation model
SGE	special government employee
SMQ	standard MedDRA queries
SOC	standard of care
SY	subject-years
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TID	three times a day
VAI	voluntary action indicated

1 Executive Summary

1.1. Product Introduction

Erenumab (previously AMG 334) is a monoclonal antibody that antagonizes the calcitonin gene-related peptide (CGRP) receptor. CGRP is a potent vasodilator in the cerebral, coronary, and renal vascular beds (Russell et al. 2014). CGRP has been shown to have a role in migraine pathophysiology. Plasma CGRP levels increase during migraine attacks and infusion of CGRP has been shown to induce migraine-like attacks in susceptible people (Hansen et al. 2010). Erenumab competes with the binding of CGRP and inhibits the function of CGRP at its receptor.

The sponsor has proposed a dose of 140mg subcutaneously (SC) to be given monthly as two injections of 70mg via a pre-filled syringe (PFS) or auto-injector (AI). Both 70mg and 140mg have been studied in pivotal clinical efficacy trials. The product is intended to be prescribed for the preventive treatment of both episodic and chronic forms of migraine.

Erenumab is a new molecular entity (NME). There are no FDA approved drugs in this class.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support approval. The applicant provided data from three adequate and well controlled studies that demonstrated that erenumab reduces the frequency of migraine as compared to placebo for both the 70mg and 140mg dose. The applicant has shown this consistently across trials for episodic and chronic migraine. The primary endpoint was statistically significant for all three studies, and key secondary endpoints were also statistically significant consistently across all three trials. The treatment effect observed in these trials was comparable to what has been accepted in other FDA approved drugs for migraine prophylaxis.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Erenumab is a monoclonal antibody that antagonizes the calcitonin gene-related peptide (CGRP) receptor. It is indicated for the for the preventive treatment of migraine in patients with episodic and chronic migraine. Erenumab is given once monthly by subcutaneous injection.

Migraine is a very common, chronic neurological condition with a broad spectrum of frequency and severity. It is characterized by recurrent attacks of headache with accompanying symptoms of nausea, vomiting, photophobia, and phonophobia. These attacks are generally of moderate to severe intensity and can at times be disabling and impact the quality of patients' lives. There are several FDA approved drugs for the preventive treatment of migraine. They have limitations related to tolerability and to their frequency or route of administration.

The efficacy of erenumab was demonstrated in three randomized clinical trials. Two trials were conducted in episodic migraine and one trial was conducted in chronic migraine. Both erenumab 70mg and 140mg demonstrated reduction in monthly migraine days as compared to placebo. In episodic migraine trials, patients had a baseline of about 8 migraines per month. Erenumab reduced monthly migraine days by about 1 to 2 days compared to placebo. In the chronic migraine trial, patients had a baseline of about 18 migraines per month. Erenumab reduced monthly migraine days by about 2 to 3 days compared to placebo. Reduction of the number of monthly migraine days a patient experiences may lead to decreased disability, fewer days in bed, and a reduction in the use of acute migraine treatments that have their own side effects and risks.

The safety profile of erenumab was characterized in three pivotal trials and one dose-ranging trial. No major, serious toxicities were identified in these trials that were definitively drug related. Adverse events in clinical trials included muscle cramps, constipation, viral infections, injection site reactions, cough, and pruritus. Clinical trials included generally young, healthy patients and excluded patients over age 65. Patients with major pre-existing cardiovascular disease were effectively excluded. A few events suggestive of ischemia were identified in the review including transient ischemic attack (TIA), myocardial ischemia, ischemic colitis, worsening Raynaud's syndrome, and two cardiac deaths. Due to the mechanism of action of erenumab, these cases were examined carefully and did not appear to be drug related.

I recommend a postmarketing requirement (PMR) to study safety in patients over age 65. I recommend a PMR for a pregnancy registry study. These PMRs combined with enhanced pharmacovigilance, and product labeling will address the risks associated with erenumab in the postmarket setting.

I recommend approval of both the 70mg and 140mg dose of erenumab. Erenumab represents an additional therapeutic option for patients with migraine headache. The efficacy of the product is similar to other products approved for the preventive of migraine. The tolerability of the product appears to be an improvement over other approved products. The product is given once monthly which may improve compliance over drugs that need to be taken daily.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Migraine is a very common, chronic neurological disease with a broad spectrum of frequency, and severity. It is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. The attacks tend to be unilateral headaches associated with other symptoms such as nausea, vomiting, phonophobia, or photophobia. A typical migraine can be exacerbated by even minor physical activity and may last anywhere from 4 hours to 72 hours. Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache. Typically, migraine is experienced on an episodic basis. However, some patients experience more frequent migraine. The International Classification of Headache Disorders (ICHD) published by the International Headache Society (IHS) recognizes a type of migraine called chronic migraine. Patients with chronic migraine have headaches on 15 or more days per month of which at least 8 have the features of migraine Migraine is more frequent in females than in males. In a large U.S. population based study, the one-year prevalence of migraine was 18% in females and 7% in males and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007).	Migraine can be a serious and at times disabling condition that can impact the quality of patients' lives.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are several FDA approved therapies for migraine prophylaxis, as well as many other drugs that are used off-label. The FDA approved therapies include propranolol, timolol, divalproex/sodium valproate, and onabotulinumtoxinA (approved for chronic migraine only). There are many other drugs and supplements that are used off-label as well for migraine prophylaxis. The currently FDA-approved treatments all have some limitations. They have a modest effect at reducing the frequency of migraine headaches. Except for onabotulinumtoxinA, all must be taken at least daily and up to three times daily for propranolol. OnabotulinumtoxinA requires 31 injections in the head and neck, and needs to be administered every three months. The biggest limitation in the current armamentarium for migraine prophylaxis is the absence of a drug that completely or nearly completely ameliorates the condition. Most patients will continue to have migraines even on therapeutic doses of effective medications. The currently approved treatments reduce the number of monthly migraines days a patient experiences by 1 to 2.5 days monthly as compared to placebo. Several of the available prophylactic medications have some intolerable side effects making it difficult for patients to justify continuing to take a daily medication that does not completely prevent migraines.	A drug that is better tolerated and taken monthly as opposed to daily may improve compliance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	There are three pivotal trials that demonstrate the efficacy of erenumab given once monthly subcutaneously. Two of these studies are in episodic migraine and one is in chronic migraine. All three of the studies demonstrate the efficacy of the 70mg dose and two of the studies demonstrate the efficacy of the 140mg dose. The primary endpoint in all three studies is the reduction in monthly migraine days from baseline as compared to placebo. In patients with episodic migraine, erenumab has been shown to reduce monthly migraine days by 1 to 2 days as compared to placebo. In patients with chronic migraine, erenumab has been shown to reduce monthly migraine days by about 2.5 days as compared to placebo. The findings of the primary endpoint were statistically significant in both the episodic and chronic migraine trials. Two key secondary endpoints were also statistically significant and consistent with the findings of the primary endpoint. These key secondary endpoints were "≥50% reduction from baseline in monthly migraine days" and "change from baseline in acute migraine specific medication treatment days." These key secondary endpoints were statistically significant in both the episodic and chronic migraine trials. Those patients with episodic migraine may be able to appreciate a 1 to 2-day per month reduction in monthly migraine days. For those patients with chronic migraine, the clinical meaningfulness is less clear. A two to three-day reduction per month in migraines may be harder for patients to appreciate when they are experiencing near daily migraines.	Erenumab 70mg and 140mg were both found to be effective in reducing monthly migraine days in patients with episodic and chronic migraine. The treatment effect seen in these trials is similar to the treatment effect seen in clinical trials of other approved products for migraine prophylaxis. Fewer monthly migraine days may translate to fewer days of disability. Reduction in use of acute medication may lead to reduced risk of medication overuse headache and reduced risk of side effects related to the use of acute treatments for migraine. Erenumab may be a more convenient option for patients since it is administered monthly rather than daily.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	No serious safety issues related to the use of erenumab were identified in this review. Several theoretical safety issues related to the use of CGRP antagonists were reviewed in detail. Cardiovascular (CV) events: Two CV deaths were observed in clinical trials. Both cases had plausible alternative causes of death. A relationship between erenumab and these events cannot be entirely ruled out, but is not considered likely. Liver toxicity: One case of acute liver injury was identified. Erenumab is unlikely to be the cause of the acute liver injury, and review of the entire database showed no other cases. Other ischemic events: Included 1 case of ischemic colitis, 1 case of TIA, 2 cases of myocardial ischemia, and 2 cases of worsening Raynaud's syndrome. All cases were seen in patients treated with erenumab primarily during open-label treatment. Common adverse events in clinical trials included muscle cramps, constipation, viral infections, injection site reactions, cough, and pruritus. Clinical trials included generally young, healthy patients and effectively excluded patients with major cardiovascular disease and explicitly excluded patients over age 65.	Erenumab has an acceptable safety profile for the migraine population. Safety issues have not been adequately evaluated in the population 65 and older, or in patients with major cardiovascular disease.
Risk Management	A meeting with the Medical Policy and Program Review Council (MPPRC) was conducted to review the theoretical cardiovascular risk of CGRP antagonism. The Council concluded that the nonclinical evidence of cardiovascular risk was not compelling enough to warrant inclusion of a theoretical cardiovascular risk in labelling. A Medication Guide does not appear to be needed. A pregnancy registry study will be a postmarketing requirement. I recommend a safety study in patients age 65 and older.	Enhanced pharmacovigilance may address the safety issues associated with erenumab such as the liver toxicity and cardiovascular concerns. Labeling will not include the theoretical cardiovascular risk associated with CGRP receptor antagonism.

2 Therapeutic Context

2.1. Analysis of Condition

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

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

Typically, migraine is experienced on an episodic basis. However, some patients experience more frequent migraine. The International Classification of Headache Disorders (ICHD) published by the International Headache Society (IHS) recognizes a type of migraine called chronic migraine. Patients with chronic migraine have headaches on 15 or more days per month, of which, at least 8 have the features of migraine.

Migraine is more frequent in females than in males. In a large U.S. population based study, the one-year prevalence of migraine was 18% in females, 7% in males, and 12% overall (Lipton et al. 2001). Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton et al. 2007). Although the prevalence of migraine declines with age, prevalence estimates in the population age 60+ is about 5% for females, and 1.6% for males (Lipton et al. 2007). Another estimate by Bigal and Lipton (2006) shows that the prevalence of migraine in the age 70+ population is about 4% with a 2% prevalence for males, and 5% prevalence for females.

2.2 Analysis of Current Treatment Options

There are several FDA approved therapies for migraine prophylaxis, as well as many other drugs that are used off-label. The American Headache Society (AHS) in conjunction with the American Academy of Neurology (AAN) published two guidelines in 2012 with recommendations for use of certain drugs and complementary therapies in the prevention of episodic migraine (Silberstein et al. 2012). These guidelines include both therapies that are FDA approved and those that are off label use. It is limited to prophylactic therapy for episodic migraine, and does not address chronic migraine. The guidelines recommend the following drugs as having Level A

evidence (established as effective): divalproex/sodium valproate, metoprolol, butterbur, propranolol, timolol, and topiramate. The following drugs are considered by this guideline to have Level B evidence (probably effective): amitriptyline, fenoprofen, feverfew, histamine, ibuprofen, ketoprofen, magnesium, naproxen, riboflavin, venlafaxine, and atenolol. The following drugs are considered to have Level C evidence (possibly effective): candesartan, carbamazepine, clonidine, guanfacine, lisinopril, nebivolol, pindolol, flurbiprofen, mefenamic acid, coenzyme Q10, and cyproheptadine.

Table 1 Summary of FDA-Approved Treatments for Migraine Prophylaxis

Product Name	Year of Approval for Migraine	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Propranolol	1970s	20-80mg TID-QID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Timolol	1980s	10-15mg BID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Divalproex/sodium valproate	1996	250 -500mg BID	Treatment effect: 1.5 to 2.2-day reduction in monthly migraine days	Boxed warning for hepatotoxicity	Neural tube defects
Topiramate	2004	50mg BID	Treatment effect: 1.0 to 1.3-day reduction in monthly migraine days	Paresthesias, weight loss	Cleft lip and palate
OnabotulinumtoxinA	2010	Total dose 155 units divided across 7 muscles; administered every 12 weeks	Treatment effect: 1.4 to 2.3-day reduction in monthly headache days from baseline	Transient weakness may occur in muscles that are injected	Approved for chronic migraine only; administered intramuscularly by a physician

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

The biggest limitation in the current armamentarium for migraine prophylaxis is the absence of a drug that completely or nearly completely ameliorates the condition. As it stands, migraine prophylaxis reduces the frequency of migraine headaches, but does not prevent them entirely. Patients often discontinue migraine prophylactic medication because of 'lack of efficacy' even if the drug is performing as expected. It is difficult for patients to justify taking a daily medication when they perceive that the 'medication isn't helping' and they continue to have migraines. In addition, several of the available prophylactic medications have some intolerable side effects making it even more difficult for patients to justify continuing to take a daily medication that does not completely prevent migraines.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application 116098 was opened for AMG 334 (erenumab) on September 17, 2012 for the prophylaxis of episodic migraine. After several interactions with the Division, the indication was broadened to prophylaxis of migraine.

In March 2013, the Division had a Type C face-to-face meeting with the sponsor that focused on the discussion of the design of the phase 2 and phase 3 protocols and the requirements to support the indication prophylaxis of migraine. The Division agreed that the primary endpoint "change from baseline in monthly migraine days in the last 4-week period of the 12-week

double-blinded treatment phase compared to placebo" would be acceptable. The Division stated that the indication would reflect the population studied so to get a claim for global migraine prophylaxis both populations of episodic and chronic migraine would need to be studied. At that time the Division recommended stratifying by frequency of migraine. Alternatively, the Division stated that one adequate and well-controlled study in episodic migraine and one adequate and well-controlled study in chronic migraine could be supportive of the indication prophylaxis of migraine.

In June 2014, the Division had another Type C meeting with the sponsor to discuss the development of their patient reported outcomes (PRO) assessment. The Division provided feedback and guidance on the development of the PRO.

In March 2015, the Division had an end of phase 2 (EOP2) meeting with the sponsor. At that time the sponsor proposed to study the 70mg dose in the phase 3 studies. The Division recommended that the sponsor add an additional arm to the phase 3 studies to include a 140mg dose. At EOP2, the Division noted that the sponsor's simulations suggested that patients with higher body mass may experience reduced efficacy and that weight-based dosing might be more appropriate for those of higher body mass. The Division agreed that a single trial in episodic migraine combined with data from a single trial in chronic migraine that both utilized the 140mg dose could be supportive of approval of the 140mg dose. The Division also agreed that the change from baseline in the mean monthly migraine days would be an acceptable primary endpoint.

At EOP2, the Division expressed concern that patients over the age of 65 were being excluded from the pivotal trials and recommended that a sufficient number of patients over the age of 65 be included to characterize the safety profile in that population. The sponsor stated they would study safety and pharmacokineteics (PK) in 25 patients age 65 and older in their treadmill study.

At EOP2, there was also discussion regarding cardiovascular safety of erenumab. The sponsor asked what they would need to avoid class labeling associated with triptans. The Division recommended including at least 20% of patients with pre-existing cardiovascular disease, and obtaining long-term data on 40 to 50 patients with cardiovascular disease. The sponsor did not think this would be possible. The Division stated that in the absence of specific nonclinical or clinical findings of cardiovascular concern, then triptan type labeling would be unlikely. However, if the cardiovascular risks associated with the mechanism of action remain theoretical, then this would be conveyed in the warnings and precautions section of the product label. In a post-meeting minutes note, the Division suggested an in vitro coronary artery study to assess for potential coronary artery constriction or reduced coronary blood flow.

In October 2016, the Division had a Type C meeting with the sponsor regarding the ongoing development of the sponsor's PRO. The Division emphasized that it was not sufficient to have statistically significant findings on the endpoints of the PRO, but that there needed to be demonstration of a clinically meaningful change as well.

The pre-BLA meeting was held January 31, 2017. At this meeting the Division agreed to accept the final analysis of the treadmill study 20140254 at the 120-day safety update. The sponsor stated that at the time of the BLA filing, analyses of the primary objective would be available, but that safety data at the week 12 follow-up visit would not be available.

Summary of dates for regulatory interactions:
Initial IND: September 17, 2012
End of phase 2 meeting: March 4, 2015
Pre-BLA meeting: January 31, 2017
BLA filing: May 17, 2017

3.3. Foreign Regulatory Actions and Marketing History

Erenumab is not approved or marketed in any country.

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

4.1. Office of Scientific Investigations (OSI)

Two U.S. sites were inspected: one in Santa Monica, California, and one in St. Louis, Missouri. OSI has noted under-reporting of adverse events (AEs) at one of the inspected sites (Santa Monica) for study 20120297, but not for study 201202095. There were five unreported adverse events in 4 of 30 randomized patients. Two of the unreported AEs occurred in the double-blind phase and 3 occurred in the open-label phase. The adverse events were documented in study visit progress notes, but were not transcribed to the AE log and not entered into the electronic case report form (eCRF). The adverse events that were not recorded on the eCRFs were swollen glands, fall, right knee pain, intermittent right flank pain, and edema ankle/hands/feet. There was no evidence of under-reporting of serious adverse events (SAEs).

No under- reporting of AEs was noted at the St. Louis site (studies 20120295 and 20120296).

Two foreign sites were inspected: one in Germany and one in Denmark. Form FDA 483 was

issued to a site in Denmark for under-reporting of adverse events. At this site, under-reported AEs were from patients who were monitored centrally. Per OSI, central monitoring cannot review source documents, and is limited in its ability to detect under-reporting of AEs. There was no evidence of under-reporting of AEs at the German site.

The OSI reviewers issued a voluntary action indicated (VAI) to the site in Santa Monica, and have concluded that the unreported adverse events would be unlikely to affect the overall analysis.

4.2. Product Quality

The drug substance contains (b) (4) Erenumab is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection in either a pre-filled syringe (PFS) or a pre-filled auto-injector. The auto-injector (AI) is a disposable, handheld mechanical, (b) (4) delivery device that is pre-assembled with the PFS. Both the autoinjector and the PFS deliver a volume of 1ml with 70mg/ml of erenumab. Stability data has been provided for the 70mg/ml PFS and the 70mg/ml AI.

4.3. Clinical Microbiology

Please see the review by Dr. Dupeh Palmer, product quality microbiology reviewer.

4.4. Nonclinical Pharmacology/Toxicology

Erenumab has a high affinity for the monkey and human CGRP receptor. General toxicology studies were conducted exclusively in monkeys due to a lack of pharmacological activity in another species. Safety pharmacology and toxicology studies in monkeys showed no adverse cardiovascular, pulmonary, neurobehavioral, developmental, or general toxicity concerns and exposures that exceed ten times the human values. The only drug related finding was minimal to mild injection site hemorrhage and infiltrate.

Please see the review by Dr. Edmund Nesti, nonclinical reviewer.

4.5. Clinical Pharmacology

Please see the review by Dr. Girish Bende, clinical pharmacology reviewer and Gopichand Gottipati, pharmacometrics reviewer. I have summarized some of the major findings from their review in this section.

4.5.1. Mechanism of Action

Erenumab is a monoclonal antibody that is a competitive inhibitor of the native ligand CGRP. Erenumab binds to the CGRP receptor, which inhibits the CGRP ligand from binding. CGRP levels have been show to rise during migraine attacks, and infusion of CGRP triggers migraine in susceptible people. Erenumab binds the CGRP receptor preventing the CGRP ligand from binding, and preventing the activation of the trigeminal-vascular system.

4.5.2. Pharmacodynamics

The inhibition of capsaicin-induced dermal blood flow (DBF) in healthy volunteers was used to help inform early dose selection. The reduction in capsaicin-induced DBF is an indirect measure of CGRP receptor inhibition. Capsaicin is applied topically to the arm to stimulate the release of CGRP which results in vasodilatation and an increase in DBF. Phase 1 studies showed that treatment with erenumab resulted in dose-dependent inhibition of capsaicin-induced DBF. Phase 2 clinical trials showed that migraine efficacy was achieved at doses and systemic exposures that were higher than required for maximal inhibition of DBF. See section 6.1.1 Rationale for Dose Selection for more detail.

4.5.3. Pharmacokinetics

Erenumab exhibits nonlinear PK following a single SC dose over the range of doses 1mg through 210mg. From 1mg to 70mg, erenumab exposure increases more than dose proportionally. Exposure is approximately dose proportional from 70mg to 210mg following a single administration SC. The mean AUC increased (3.8-fold) from 171 to 652 µg·day/mL and mean Cmax increased (2.4-fold) from 6.25 to 15.2 µg/mL following a dose increase from 70mg to 210mg.

Following SC administration, peak serum concentration is reached between four and eleven days post-dose with doses ranging from 1mg to 210mg. Bioavailability is about 82% with the 140mg dose. Steady state is usually reached by week 12 with minimal accumulation. Per clinical pharmacology reviewer, Dr. Girish Bende, the mean terminal elimination half-life is 21 days.

A DDI study with CYP450 substrates was not conducted as part of the development program because erenumab is unlikely to affect drug metabolizing enzymes or transporters. The sponsor did conduct a DDI study with the oral contraceptive combination norgestimate/ethinyl estradiol. The sponsor also conducted a dedicated DDI study with sumatriptan. No renal or hepatic impairment studies were conducted because monoclonal antibodies are not eliminated by the kidney or liver. The metabolism of erenumab is through catabolism into amino acids.

4.6. Devices and Companion Diagnostic Issues

The drug product for the initial clinical studies was supplied in glass vials containing 70mg/ml of erenumab. Later in development, the drug product was suppled in glass pre-filled syringes containing 70mg/ml of erenumab. The pre-filled syringes were used for injection and for loading into the "SureClick" auto-injector. However, most of the clinical development was conducted using the pre-filled syringe only and not the "SureClick" auto-injector. The sponsor conducted a clinical home use study assessing self-administration of erenumab 70mg/ml given in 2 injections in the open-label phases of studies 20130255 and 20120178.

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Clinical Trials Relevant to Migraine Prophylaxis

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up*	No. of patients completing study	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
20120178	Randomized, double-blind, placebo controlled (dose-ranging)	7, 21, or 70mg SC monthly	Reduction in monthly migraine days	12 weeks/ 8 weeks	448	Episodic migraine (18 to 60 years)	59 and 7
20120295	Randomized, double-blind, placebo controlled (pivotal efficacy trial)	70 or 140mg SC monthly	Reduction in monthly migraine days	12 weeks/ 12 weeks	631	Chronic migraine (18 to 65 years)	69 and 10
20120296	Randomized, double-blind, placebo controlled (pivotal efficacy trial)	70 or 140mg SC monthly	Reduction in monthly migraine days	24 weeks/ 12 weeks	858	Episodic migraine (18 to 65 years)	121 and 13
20120297	Randomized, double-blind, placebo controlled (pivotal efficacy trial)	70mg SC monthly	Reduction in monthly migraine days	12 weeks/ 8 weeks	546	Episodic migraine (18 to 65 years)	69 and 8
Studies to Support Safety							
20130255	Open-label extension for trial 20120295	70 or 140mg SC monthly	Safety/tolerability	52 weeks/ 12 weeks	225	Chronic migraine	64 and 10
20140254	Randomized, double-blind, placebo controlled	140mg IV	Exercise time during a treadmill test	Single dose/ 12 weeks	88	Stable angina	35 and 10

*For study 20120178 patients could enter an open label active treatment phase lasting up to 256 weeks. For studies 20120296 and 20120297 patients could enter the 28-week open label active treatment phase after completion of the double-blind treatment period. The follow up period for the patients in these three studies would follow the completion of the additional treatment.

5.2. Review Strategy

The sponsor has proposed the 140mg SC monthly dose as the to-be-marketed dose. There are two pivotal studies assessing this dose (20120295, and 20120296). There is an additional pivotal study (20120297) that assesses only the 70mg dose along with a dose-ranging study (20120178) that looks at doses 7mg, 21mg, and 70mg. This review will evaluate the data supporting both the 70mg and 140mg doses to determine whether 70mg or 140mg or both doses are approvable based on their efficacy and safety profiles.

For efficacy, the three pivotal studies will be reviewed in detail (20120295, 20120296, 20120297) and study 20120178 will be reviewed to inform dosing. For safety, all four studies will be reviewed. In addition, study 20130255 that rolled patients over from study 20120295 will be included.

Note: Throughout this review, I will use the term 'treatment effect' to refer to the effect that remains after subtracting out the placebo effect. Negative numbers indicate improvement and positive numbers represent worsening. In this review, one month refers to 4 weeks or 28 days.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 20120296: A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Episodic Migraine Prevention

6.1.1. Study Design

Overview and Objective

The primary objective is to evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly migraine days in patients with episodic migraine and to evaluate the safety and tolerability of AMG 334.

Trial Design

Study 20120296 is a multinational, randomized, double-blind, placebo-controlled, parallel group study of patients with episodic migraine. Patients were initially screened, and then if qualified, entered a four-week baseline period. After completion of the four-week baseline period, patients were then randomized in a 1:1:1 ratio to receive placebo, AMG 334 70mg SC, or AMG 140mg SC monthly. Randomization was stratified by region and treatment status with

migraine prophylactic medication. The patients were treated with investigational product (IP) during the double-blind treatment period (DBTP) for 6 months (24 weeks). This was followed by an additional 28-week treatment period, and a 12-week safety follow up. No IP was administered during the safety follow up period. Patients were re-randomized to either 70mg or 140mg in the 28-week treatment period, and were blinded to the actual dose received.

In study 20120296 and study 20120297 patients completed a daily eDiary that collected data for a novel patient-reported outcomes (PRO) called the Migraine Physical Functional Impact Diary (MPFID). Description of the MPFID and the secondary endpoints associated with the MPFID will be included below in the trial design section.

Basic Study Design

Screening phase: up to 3 weeks
Baseline: 4 weeks
Randomization
Double-blind treatment phase: 24 weeks (placebo, 70mg, 140mg SC monthly)
Additional treatment: 28 weeks (70mg or 140mg SC monthly)
Follow-up: 12 weeks (16 weeks after the last dose of IP)

The study was conducted from July 17, 2015 through September 5, 2016 (data cutoff date) at 121 centers in Canada, Austria, Belgium, Czech Republic, Finland, Germany, Poland, Slovakia, Sweden, the United Kingdom, Turkey, the Netherlands and the U.S.

Diagnostic Criteria

The sponsor utilized the ICHD-3 for the diagnosis of migraine with or without aura. For this study, patients had to have a history of migraine meeting this definition for at least one year. These patients had to experience a ≥4 and <15 migraines per month on average during the three months prior to screening.

ICHD-3 diagnostic criteria for migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity

D. During the headache, at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

ICHD-3 diagnostic criteria for migraine with aura

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal

C. At least two of the following four characteristics:
   1. At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. Each individual aura symptom lasts 5 to 60 minutes
   3. At least one aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes by headache

Key Inclusion Criteria

- Adults 18≥ to ≤65 years of age
- History of migraine for ≥ 12 months prior to screening
- Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening and < 15 headache days per month on average across the 3 months prior to screening
- If only one prophylactic medication was used, the dose had to be stable within 2 months prior to the start of the baseline period and throughout the study

Key Exclusion Criteria

- Older than 50 years of age at migraine onset
- History of cluster headache or hemiplegic migraine
- No therapeutic response with >2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial
- Use of a prohibited medication, device, or procedure within 2 months prior to the start of the baseline period
- Taken ergotamines or triptans on ≥ 10days per month during the 2 months prior to the start of

the baseline period
- Taken simple analgesics on ≥15 days per month during the 2 months prior to the start of the baseline period
- Taken opioids or butalbital containing analgesics on ≥ 4 days per month during the 2 months prior to the start of the baseline period
- Excluded medical conditions: chronic pain syndromes, major psychiatric disorders, seizure disorders, malignancies, HIV infection, or hepatic disease
- Excluded medical conditions within 12 months of screening: myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, revascularization, drug or alcohol abuse

To be randomized into the study after the completion of the baseline period, patients had to have demonstrated at least 80% compliance with the eDiary.

Reviewer Comment: Study 20120296 initially excluded patients who were taking concurrent migraine prophylaxis. However, an amendment was later added to allow inclusion of patients taking only one medication for migraine prophylaxis. Overall, relatively few patients were on concurrent migraine prophylaxis.

Study 20120296 did not explicitly exclude all patients with major cardiovascular or other vascular disease. Patients with recent cardiovascular and vascular events were excluded. Effectively, however, patients with major cardiovascular disease were not included in this study.

Rationale for Dose Selection

Dose selection in this study was determined from preclinical and phase 1 safety data as well as pharmacodynamics data in humans using the capsaicin-induced dermal blood flow (DBF) model (Sinclair et al. 2010). Blockade of CGRP is expected to inhibit capsaicin-induced increases in dermal blood flow. In early studies, 7mg produced 39% inhibition, 21mg produced 75% inhibition, 70mg produced 90%, and 140mg produced 95% inhibition of capsaicin-induced increases in dermal blood flood. Study 20120178, a phase 2 dose-ranging study evaluated 7mg, 21mg, and 70mg in terms of clinical efficacy. Only 70mg showed statistically significant findings on the primary endpoint therefore the 70mg dose was carried over into the pivotal studies. The 140mg dose was added into studies 20120296 and 20120295 at the suggestion of the Division at the EOP2. The rationale for this was not indicated in the meeting minutes from the EOP2. However, per clinical pharmacology reviewer Dr. Girish Bende, the higher dose (140mg) was included in phase 3 studies because an analysis of exposure-response data at that time indicated that potentially greater efficacy could be observed with a higher dose. The Division also suggested that the sponsor consider weight-based dosing as the sponsor's simulations suggested that patients with higher body mass would be expected to experience a smaller

reduction in migraine days. The sponsor did not incorporate weight-based dosing into the development plan, but did include the 140mg dose in two of the pivotal efficacy studies.

Study Treatments

IP was administered monthly for 6 months by SC injection. The doses in the study were placebo, 70mg, or 140mg. The 140mg dose was given via two SC injections of 70mg. Throughout the double-blind treatment phase and active treatment phase, two SC injections were given for each IP administration to maintain the blind. IP was administered into the upper arm, upper thigh, or abdomen. The injection site location was the same for both injections. Patients were observed for 30 minutes following IP injection. All doses of IP were administered in the clinic by the investigator or other authorized personnel.

Assignment to Treatment

All patients who entered screening were assigned a unique subject identification (ID) number prior to completing any study procedures. The subject ID number was assigned by an interactive voice response or interactive web response system (IVR/IWR).

Patients were initially randomized in a ratio of 1:1:1. A patient was randomized to treatment for the double-blind treatment period (DBTP) if the patient met all the screening and baseline eligibility criteria. The DBTP was stratified by region, and treatment status with migraine prophylactic medication. The stratification for region was North America versus all other locations. The stratification for treatment status with migraine prophylactic medication was current treatment, prior treatment only, or no treatment.

After completion of the DBTP, patients were re-randomized into the open-label treatment in a 1:1 ratio to 70mg or 140mg SC monthly and were blinded to the dose. The re-randomization was stratified by treatment group assigned during the DBTP. The dose level remained blinded.

Reviewer Comment: Per the SAP for study 20120296, the sponsor planned to combine the 'current migraine prophylactic medication treatment group' with the 'prior migraine prophylactic treatment group' if the number of patients in the 'current migraine prophylactic medication treatment group' was less than 10% of the total population. Because the amendment to allow patients on current prophylactic treatment came late in development, the sponsor did not have many patients in the 'current migraine prophylactic treatment group' so these groups were in fact combined.

Blinding

This was a double-blind placebo controlled trial. Patients, site personnel, and Amgen study personnel were blinded to the randomized treatment group assignment. The independent global safety and independent biostatistics group with Amgen had access to treatment assignments and provided unblinded results to the data monitoring committee (DMC) for safety monitoring.

Dose Modification/Dose Discontinuation

The dosage for IP was fixed for all patients and could not be adjusted. At any time during the study, the investigator could discontinue the IP administration for any patient who experienced a severe or life threatening adverse events. Patients who permanently discontinued IP during the DBTP phase were to continue to return for all other study procedures until the end of the DBTP and the completion of the safety follow up visit. Patients who discontinued treatment in the open-label period completed the 12-week safety follow up visit which was 16 weeks after the last dose of IP.

Procedures and Schedule

The schedule of trial procedures and assessments is summarized in Table 3**.** I have modified this table from the sponsor's materials to include only key assessments.

Table 3 Schedule of Procedures and Assessments for Study 20120296

Period (duration)	Screening (3 weeks)	Baseline (4 weeks)	Double-Blind Treatment Phase (24 weeks)						
			Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Vitals signs	x	x	x	x	x	x	x	x	x
IP administration			x	x	x	x	x	x	
ECGs	x		x	x	x	x			x
Pregnancy testing	x	x	x	x	x	x	x	x	x
Chemistry, hematology	x		x	x		x			x
Anti-AMG 334 antibodies			x	x		x			x
C-SSRS	x	x	x	x	x	x	x	x	x
Adverse Event Recording	x	x	x	x	x	x	x	x	x

Period (duration)	Active Treatment Phase (28 weeks)								Safety Follow-up
	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	
Vitals signs	x	x	x	x	x	x	x	x	x
IP administration	x	x	x	x	x	x	x		
ECGs	x	x		x				x	
Pregnancy testing	x	x	x	x	x	x	x	x	x
Chemistry and hematology	x	x		x				x	x
Anti-AMG 334 antibodies	x	x		x				x	x
C-SSRS	x	x	x	x	x	x	x	x	x
Adverse Event Recording	x	x	x	x	x	x	x	x	x

Note: Randomization occurred after the completion of the baseline period. Patients who completed the double-blind treatment period could be re-randomized into the active treatment phase. The safety follow up visit occurred 16 weeks after the last dose of IP.

Concurrent Medications

Throughout the study and while the patients were receiving IP, the investigators could prescribe concomitant medications or treatments deemed necessary for the general health and well-being of the patient. However, the following medications related to migraine treatment could not be newly prescribed:

- botulinum toxin in the head and/or neck
- ergots, steroids, or triptans for migraine prophylaxis
- devices and procedures for migraine prophylaxis

Upon initial entry into the study, patients could be using up to one medication with possible migraine-prophylactic effects. The dose had to be stable for at least the two months prior to the start of the baseline period, and had to remain stable throughout the study. The allowed prophylactic medications were as follows:

- divalproex sodium, sodium valproate, topiramate, carbamazepine, or gabapentin
- all beta blockers
- all tricyclic antidepressants
- flunarizine, lomerizine, or verapamil

- venlafaxine, desvenlafaxine, duloxetine, or milnacipran
- butterbur, feverfew, magnesium, or riboflavin
- lisinopril or candesartan
- clonidine, guanfacine, cyproheptadine, methysergide, or pizotifen

Reviewer Comment: Studies 20120296 and 20120297 allowed for patients to be on one stable dose of a prophylactic migraine medication. However, this allowance was made in a protocol amendment that came very late in development. Therefore, very few patients were taking a prophylactic treatment during the study.

Treatment Compliance

Treatment compliance was not measured in this trial. All doses of IP were administered in the clinic by the investigator or other authorized personnel.

Patient completion, discontinuation, or withdrawal

A patient who discontinued IP during the double-blind treatment period remained in the study and should have completed the remaining study procedures and study visits. The safety follow up visit for these patients occurred 16 weeks after the last dose of IP was given. A patient who declined IP or other protocol related procedures was to continue participation in the study. The investigator was instructed to document any changes in the schedule of assessments, and was to document the level of follow-up to which the patient agreed.

Migraine Physical Function Impact Diary (MPFID)

The MPFID is a self-administered, thirteen question PRO that was developed by the sponsor with scientific and regulatory feedback provided by DNP and Clinical Outcomes Assessment staff (COA). The MPFID is composed of two domains: "Impact on Everyday Activities" (7 questions), and "Physical Impairment" (5 questions). There is also one question that asks about an overall, global assessment of function. Patients' responses to the questions are scored on a 5-point scale. There is one score for each of the two domains, and a third score for the global question. Patients are asked to respond how they were feeling over the past 24 hours. The MPFID was completed every day in the eDiary, whether or not the patient had a headache. Per the sponsor, the MPFID was designed to be used in patients with both EM and CM. However, it was evaluated only in the two EM studies (20120296 and 20120297).

Each item is scored on a scale of 1 to 5 with 5 being a more negative impact on function. Raw scores for the "Impact of Everyday Activities" domain range from 7 to 35, and 5 to 25 for the

domain "Physical Impairment." Each MPFID domain score is then transformed and scaled to a 100-point score. The score for the MPFID is calculated by averaging the daily MPFID score over a 28-day period. Studies 20120296 and 20120297 each have secondary endpoints relating to the MPFID. The questions and scoring rubric are in Appendix 13.3.

Study Endpoints

Primary Endpoint

The primary endpoint for this study is the change from baseline in mean monthly migraine days (MMDs). The MMDs were calculated using the monthly migraine days from the last three months (months 4, 5, and 6) of the 24-week double-blind treatment phase.

Secondary Endpoints

- Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last 3 months of the DBTP
- 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 double-blind treatment phase 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

Reviewer Comment: In October 2016, Amgen notified the Division that their secondary endpoints related to the MPFID failed to meet statistical significance in study 20120297. Several exploratory endpoints in study 20120297 relating to the MPFID had nominal significance without formal type-I error control. Amgen amended their statistical analysis plan in October 2016. Two exploratory endpoints from study 20120296 were elevated to key secondary endpoints after the sponsor completed the analysis of study 20120297. After a teleconference between the sponsor and the Division, and in consultation with our statisticians, it was determined that the sponsor could change the secondary endpoints in study 20120296 based on the results from study 20120297. This was predicated on the sponsor's assurance that the data in study 20120296 had not yet been analyzed at the time of the change.

Definition of Qualifying Migraine Day for the Primary and Secondary Endpoints

Migraine day: Any calendar day in which the patient experienced a qualified migraine headache. A qualified migraine headache was a migraine with or without aura, lasting for ≥30 minutes, and meeting at least one of the following criteria (a and/or b):

a. ≥2 of the following features: unilateral, throbbing, moderate to severe, exacerbated by exercise/physical activity
b. ≥1 of the following associated symptoms: nausea and/or vomiting; photophobia and phonophobia

If the patient took a migraine-specific medication (triptan or ergotamine) to treat a headache, then it was to be counted as a migraine day regardless of the duration of the pain.

Definition of Headache Day

Any calendar day in which the patient experienced one of the following: a qualified migraine headache, a non-migraine headache that lasted continuously for ≥30 minutes, or a headache of any duration for which acute treatment was administered.

Statistical Analysis Plan

Analysis Populations

Table 4 Analysis Sets for Study 20120296

Analysis Set	Definition	Analyses Performed
Full Analysis Set	All patients randomized	Patient disposition, demographics, baseline characteristics, protocol deviations
Efficacy Analysis Set	Patients who received at least 1 dose of IP and completed at least 1 post-baseline monthly eDiary measurement	Efficacy endpoints
Safety Analysis Set	All randomized patients who received at least 1 dose of IP	Safety endpoints
Per Protocol Set	Patients who received the IP and did not have important protocol deviations	Sensitivity analyses on primary and secondary efficacy endpoints

Sample Size Estimation

The sponsor assumed a treatment effect compared to placebo of -1.12 days for the 70mg group with a standard deviation of 3.78. The planned sample size of 284 patients per group was to provide 90% power using a t-test with a 2-sided significance level of 0.04. The sponsor assumed a treatment effect of -1.30 days for the 140mg group and a standard deviation of 3.78. The planned sample size of 284 patients per group was to provide 90% power using a t-test with a 2-sided significance level of 0.01. The sponsor projected that this sample size would provide 95% power to detect a difference of 15.5% in the proportion of patients with 50% response on the change in monthly migraine days compared to placebo. The power calculations assumed a 10% dropout rate. The assumed treatment effect of the 70mg dose was calculated from the mean difference compared to placebo and common standard deviation observed in study 20120178.

Stratification Factors

The randomization was stratified by region: North America versus other. It was also stratified by prior treatment versus no prior treatment with migraine prophylactic medication.

Planned Covariates and Planned Subgroup Analyses

All analyses of efficacy endpoints were adjusted for the effect of the stratification factors of region (North America vs other) and treatment with migraine prophylactic medication (current migraine prophylactic medication treatment vs prior migraine prophylactic medication treatment only vs no prior or current migraine prophylactic medication treatment) and the baseline value.

The primary and secondary endpoints were analyzed by the subgroups defined by the stratification factors. Additional subgroup analyses were based on baseline monthly migraine days (< 8 days vs ≥ 8 days), prior prophylactic failure status, and BMI (< median vs ≥ median).

Hypothesis Testing

The primary endpoint of the study tested 70mg and 140mg compared to placebo with an alpha of 0.04 and 0.01, respectively.

Null Hypothesis

In patients with episodic migraine, the treatment group is the same as placebo in terms of reduction of the mean monthly migraine days from baseline.

Alternative Hypothesis

In patients with episodic migraine, the treatment group is different from placebo in terms of reduction of the mean monthly migraine days from baseline.

Pre-specified Methods of Handling Missing Data

Baseline: Missing baseline data were not to be imputed.
Primary Endpoint: Missing eDiary data for the primary analysis in the calculations of monthly measurements about patients' migraine and non-migraine headaches were to be handled by the following method.

1. For monthly intervals with eDiary compliance ≥ 50% (i.e., ≥ 14 days of eDiary days out of 28 days for DBTP):

    a) Monthly frequency measurements (including migraine days and headache days, hours of migraine headaches, acute medication use) were to be prorated to 28-day equivalents.

    b) Monthly average severity of migraine pain, migraine related symptoms and monthly average scale of migraine interference with daily activity were to be calculated as the average of observed scores.

2. For monthly intervals with eDiary compliance < 50% (i.e., < 14 days of eDiary days out of 28 days), all monthly measurements were to be set as missing.

Last observation carried forward (LOCF): post-baseline missing continuous efficacy endpoints during the DBTP were to be imputed using the last observed value.

Reviewer Comment: Because the MMDs were prorated if the eDiary were incomplete, this led to MMDs sometimes being reported as fractions of a day rather than full days for individual patients.

Statistical Methodology Used for Adjusting for Multiplicity

The hierarchical gate-keeping procedures and Hochberg method were used to maintain the two-sided family-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints (Figure 1). The test for the superiority of AMG 334 for the primary endpoint was tested at significance level 0.04 for the 70mg arm, and 0.01 for the 140mg arm. If the primary

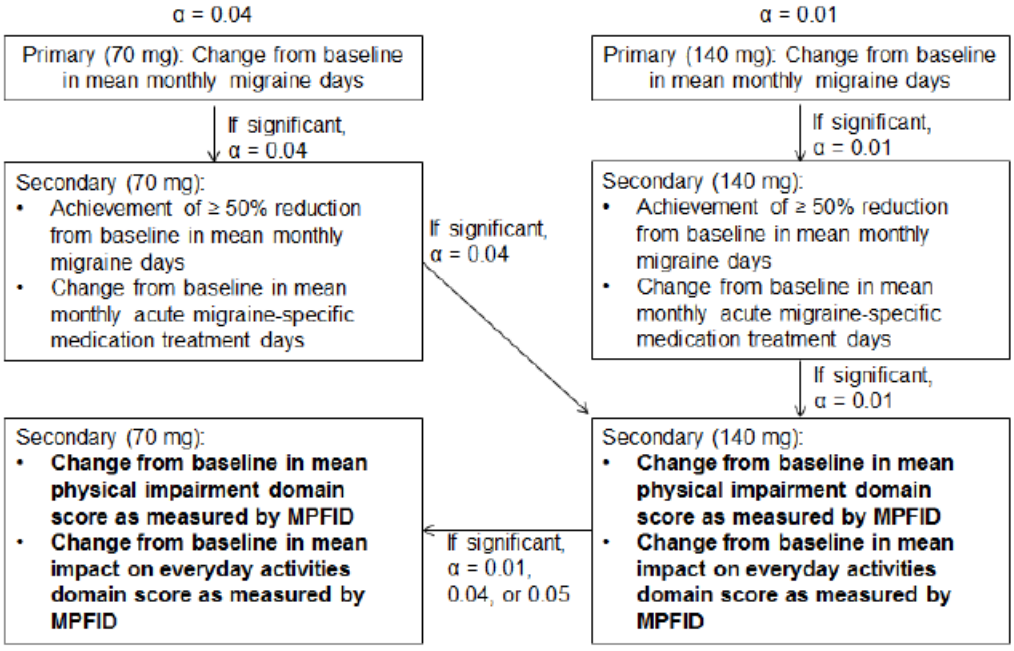
endpoint were statistically significant, using a gate-keeping strategy, the first two secondary endpoints would be tested at significance level 0.04 for the 70mg arm, and 0.01 for the 140mg arm, separately.

If the first two secondary endpoints were statistically significant for both arms, the other two secondary endpoints for the 140mg arm would be tested using the Hochberg method at significance level 0.05. If the first two secondary endpoints are not significant then the two secondary endpoints for the 140mg arm would be tested either at 0.04 or 0.01 significance level. The 0.04 level would be used if the secondary endpoints for the 70mg dose are significant, and 0.01 would be used if the secondary endpoints for the 140mg dose are significant.

If the second set of secondary endpoints for the 140mg arm is statistically significant, then the last two secondary endpoints will be tested for the 70mg arm.

For the 50% responder rate, a stratified Cochran-Mantel-Haenszel (CMH) test was used after missing data was imputed as non-response.

Figure 1 Statistical Method Used for Adjusting Multiplicity for Study 20120296



Note: This figure was taken from the sponsor's material from study 20120296

Protocol Amendments

Two protocol amendments were made to the original protocol which was released on March 24, 2015. At the time of the release of the first amendment, 759 patients had been enrolled. The first amendment was released on October 20, 2015. This amendment allowed patients taking one stable migraine prophylactic treatment to be enrolled in the study when previously they were excluded. After the first amendment was released, an additional 196 patients enrolled.

A second amendment was released on June 3, 2016. This amendment revised the secondary endpoints that included the MPFID. An unblinded, interim analysis of safety data was added.

A third amendment changed the two MPFID-related secondary endpoints again. Two exploratory endpoints were elevated to secondary endpoints after the analysis of study 20120297 showed that the initial secondary endpoints did not have statistical significance in that study.

The original statistical analysis plan (SAP) was released July 23, 2015 and was amended one time. The sponsor asserts that these changes were made before any analyses were performed. The final SAP was released October 18, 2016. These changes included updating exploratory objectives, stratification factors, and study definitions.

Data Quality and Integrity: Sponsor's Assurance

The sponsor has stated that study centers were visited at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol, compliance with good clinical practice (GCP), and for accuracy of the data. Investigator staff training was provided by Amgen during investigator meetings, and routine monitoring visits. An independent audit of the study was conducted by Amgen's Global R&D Compliance and Audit Organization.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor asserts that this study was conducted in accordance with ICH GCP regulations; the GCPs applicable to the regions where the study was conducted; and in accordance with the ethical principles in the Declaration of Helsinki.

The sponsor asserts that the study protocol, amendments, and informed consent were reviewed and approved by an IEC or an IRB as appropriate for the country in which the study was conducted.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Date of first patient randomized: July 17, 2015
Date of last patient randomized: March 16, 2016
Date of last patient completing double-blind treatment phase (DBTP): September 5, 2016

Screened: 1492
Randomized: 955 (placebo: 70mg: 140mg 319:317:319)
Received 1 or more doses of IP: 952
Efficacy analysis set: 946
Per protocol analysis set: 808

The efficacy analysis set consisted of patients who received at least one dose of IP and completed at least one post-baseline monthly eDiary measurement. Of the 955 patients who were randomized, nine were not included in the efficacy analysis set leaving a total of 946 for the efficacy analysis set. Three of these nine patients did not receive a dose of IP and the other six did not have at least one post-baseline measurement in MMDs during the DBTP.

The per protocol analysis set was used to perform sensitivity analyses on the primary and secondary endpoints. Of the 955 patients who were randomized, 808 were included in the per protocol set and 147 were excluded. Of these 147, 107 were excluded from the per protocol analysis set because data on the primary endpoint were incomplete. The others were excluded for a variety of reasons (not mutually exclusive) including, but not limited to the following: migraine frequency at baseline did not meet eligibility criteria, deviation from eligibility criteria, receiving excluded therapies, not receiving IP at the primary time point.

Reviewer Comment: *A total of 9 patients (0.9 % of randomized patients) were excluded from the primary efficacy analysis set. Three did not receive IP, and 6 did not have a post-baseline measurement. The small number would not influence the results of the primary efficacy analysis.*

Two of the 6 patients who did not have post-baseline measurements in MMDs actually completed the trial, and went into the open-label phase. An IR was sent to the sponsor to clarify

why these two patients had no eDiary data, yet completed the trial and had data obtained at all trial visits. The sponsor clarified that the two patients were a married couple, and had inadvertently entered data into each other's eDiary. The site was not able to determine at which time points these errors occurred. The sponsor decided that the eDiary data were unreliable and elected not to transfer that data. Instead the eDiary data from these two patients were invalidated. The sponsor states that this occurred prior to unblinding.

Protocol Violations/Deviations

There were 64 patients of the 955 randomized patients who had what the sponsor considered to be important protocol deviations. Of these 64 patients, 20 patients were in the placebo arm, 26 were in the 70mg arm, and 18 were in the 140mg arm. The most common protocol deviation was inclusion of patients who did not meet study entry criteria. The most frequent inclusion/exclusion deviation was "used prohibited migraine prophylactic therapy pre-baseline." There were equal percentages of patients in all three arms who did not meet study entry criteria yet were enrolled in the study.

Reviewer Comment*: Patients who had protocol violations were included in the primary efficacy analysis, but not in the per protocol analysis. Based on the type of protocol violations, it is unlikely that patients included in the primary efficacy analysis who had protocol violations would influence the results. There are overall very few patients with what I would consider a significant protocol deviation, and they are distributed similarly over all three arms. One of the largest groups who was included in the primary efficacy analysis were patients with incomplete data on the primary endpoint. Patients with incomplete data on the primary endpoint were distributed evenly between placebo and treatment groups, and was addressed by sensitivity analyses on the per protocol analysis set. For a detailed listing of patient disposition and protocol deviations see Appendix Tables 134 and 135.*

Table of Demographic Characteristics

No baseline imbalances in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 5).

Table 5 Demographic Characteristics of All Randomized Patients for Study 20120296

Demographic Parameters	Placebo	Treatment Group	
	(N=319) n (%)	70mg (N=317) n (%)	140mg (N=319) n (%)
Sex			
Male	45 (14.1)	49 (15.5)	47 (14.7)
Female	274 (85.9)	268 (84.5)	272 (85.3)
Age			
Mean years (SD)	41.3 (11.2)	41.1 (11.3)	40.4 (11.1)
Median (years)	41	42	41
Min, max (years)	18, 65	18, 63	19, 65
Age Group			
18-40	152 (47.6)	139 (43.8)	149 (46.7)
41-55	129 (40.4)	146 (46.1)	143(44.8)
56-65	38 (11.9)	32 (10.1)	27 (8.5)
Race			
White	277 (86.8)	281 (88.6)	293 (91.8)
Black or African American	24 (7.5)	24 (7.5)	18 (5.6)
Asian	8 (2.5)	5 (1.6)	4 (1.3)
American Indian or Alaska Native	2 (0.6)	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.3)
Other or multiple	8 (2.5)	7 (2.2)	2 (0.6)
Ethnicity			
Hispanic or Latino	32 (10.0)	26 (8.2)	22 (6.9)
Not Hispanic or Latino	287 (90.0)	291 (91.8)	297 (93.1)
Body Mass Index (BMI) kg/m^2			
Mean (SD)	27.1 (6.3)	27.3 (5.9)	27.0 (6.2)
Median	25.6	26.6	25.5
Min, Max	16.6, 53.0	16.7, 48.4	18.0, 54.7
Region			
North America (USA/CAN)	158 (49.5)	159 (50.2)	160 (50.2)
Rest of the World	161 (50.5)	158 (49.8)	159 (49.8)

Table 5 was created by the reviewer in JMP using the DM (demographics) and VS (vital signs) STDM datasets for study 20120296. This dataset included demographic data for all randomized patients.

***Reviewer Comment**: Migraine is more prevalent in females than males. In the population, there is approximately a 3:1 ratio of females to males experiencing migraine. However, in this study, females are somewhat over-represented in a ratio of 6:1 instead of 3:1. The percentage of blacks and Hispanics in this study is lower than the percentage of blacks and Hispanics in the U.S. This may have occurred because more than half of the patients were from non-US*

locations. This may affect the generalizability of the study to the U.S. population. The study only allowed for enrollment of patients up to age 65. Patients over age 65 therefore are not represented. While it is true that migraine prevalence decreases with age, it still occurs in the population age 65 and older.

No baseline imbalances in the disease severity or baseline use of migraine medications were noted between placebo and treatment groups (Table 6).

Table 6 Other Baseline Characteristics for All Randomized Patients for Study 20120296

	Placebo	**Treatment Group**	
Baseline Characteristics	(N=319) n (%)	70mg (N=317) n (%)	140mg (N=319) n (%)
Disease Duration			
Mean in years (SD)	20.1 (12.2)	19.8 (12.3)	19.7 (12.3)
Median	19	18	18
Min, Max	1, 56	0.9, 52	1, 56
Monthly Migraine Days			
Mean (SD)	8.2 (2.5)	8.3 (2.5)	8.3 (2.5)
Median	8	8	8
Min, Max	3, 14.9	2.7, 14.5	3.2, 16
Monthly Headache Days			
Mean (SD)	9.3 (2.6)	9.1 (2.6)	9.3 (2.5)
Median	9	9	9
Min, Max	4, 14.5	2.7, 15.4	4, 17
Treatment with migraine prophylactic medication			
Naive	178 (55.8)	175 (55.2)	187 (58.6)
Prior Use Only	131 (41.1)	133 (42)	124 (38.9)
Current Use	10 (3.1)	9 (2.8)	8 (2.5)
Acute headache medications used			
None	4 (1.3)	11 (3.5)	7 (2.2)
Any acute medication	315 (98.7)	306 (96.5)	312 (97.8)
Migraine specific	191 (59.9)	179 (56.5)	192 (60.2)
Non specific	244 (76 5)	243 (76 7)	256 (80 3)
Acute migraine specific medication use			
Mean (days)	3.4	3.2	3.4

Median	3.2	3	3
Min, Max	0, 12	0, 14	0, 12.6
MPFID Global Item (Raw)*			
Mean (SD)	1.6 (1.0)	1.6 (1.0)	1.5 (0.9)
Median	1	1	1
Min, Max	1, 5	1,5	1, 5
MPFID Global Item **			
Mean	10.5	8.1	7.5
Median	6.3	4.6	4.5
Min, Max	0, 59	0, 74	0, 50
MPFID everyday activity**			
Mean	13.7	14.0	13.1
Median	11.9	11.6	11.0
Min, Max	0, 49.4	0.1, 52.3	0, 46.2
MPFID physical impairment**			
Mean	12.2	12.6	12.0
Median	10.2	10.2	10.3
Min, Max	0.3, 51.2	0, 62.2	0, 47.3

The figures in this chart were taken from the sponsor's materials from the clinical study report for study 20120296.
*Reviewer calculated using ADaM dataset ADMPFID (range 1-5). **MPFID everyday activity and physical impairment domains are reported as transformed scores (range 0-100).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not assessed because the IP was administered by the investigator or other study authorized personnel.

The most frequently used concomitant medications were acute headache medications, which were used during the baseline (Table 6) and DBTP (Table 7). The two most commonly used categories of these medications were non-opioid acute headache medications, and triptan-based migraine medications.

Table 7 Use of Concomitant Medications (Rescue Medication) in Study 20120296

Medication Category	**Placebo** (N=319) n (%)	**Treatment Group**	
		70mg (N=314) n (%)	140mg (N=319) n (%)
Triptan-based (any use)	199 (62.4)	192 (61.1)	197 (61.8)
Used at baseline and not used in DBTP	3 (0.9)	8 (2.5)	7 (2.2)
Not used baseline and used in DBTP	8 (2.5)	15 (4.8)	8 (2.5)

Non-opioid (any use)	255 (79.9)	252 (80.3)	270 (84.6)
Used at baseline and not used in DBTP	7 (2.2)	6 (1.9)	9 (2.8)
Not used baseline and used in DBTP	22 (6.9)	26 (8.3)	21 (6.6)
Ergotamine (any use)	0	2 (0.6)	4 (1.3)
Used at baseline and not used in DBTP	0	0	0
Not used baseline and used in DBTP	0	1 (0.3)	1 (0.3)
Opioid-based (any use)	19 (6.0)	24 (7.6)	21 (6.6)
Used at baseline and not used in DBTP	1 (0.3)	4 (1.3)	1 (0.3)
Not used baseline and used in DBTP	6 (1.9)	9 (2.9)	8 (2.5)
Non-opioid containing butalbital (any use)	3 (0.9)	6 (1.9)	5 (1.6)
Used at baseline and not used in DBTP	0	0	0
Not used baseline and used in DBTP	1 (0.3)	2 (0.6)	3 (0.9)
Opioid containing butalbital (any use)	2 (0.6)	0	0
Used at baseline and not used in DBTP	0	0	0
Not used baseline and used in DBTP	0	0	0

*These figures were taken from the sponsor's materials from the CSR for study 20120296. This table was created by the sponsor from the safety analysis population.

Reviewer Comment: These concomitant medications could also be considered 'rescue' medications. The general trend in the table above is that a slightly greater percentage of patients receiving erenumab than placebo needed to add acute migraine treatments (triptans, non-opioids, ergotamines, and butalbital) in the DBTP. At the same time, however, a slightly greater percentage of patients receiving erenumab than placebo could stop using acute treatments (triptans, opiates) in the DBTP. This suggests that treatment with erenumab does not have much effect on reducing the percentage of people needing acute migraine medications.

However, a formal analysis on reduction in monthly use of acute migraine medications when looking specifically at triptan and ergot usage shows a small, but statistically significant reduction in the use of acute migraine medications (see Efficacy Results-Secondary Endpoints).

Efficacy Results - Primary Endpoint

The primary endpoint for this study is the change from baseline in mean monthly migraine days as compared to placebo. There was a statistically significant mean reduction in the change from baseline in monthly migraine days for both the 70mg and 140mg dose as compared to placebo (Table 8). The treatment effect was -1.4 days for 70mg and -1.9 days for 140mg. The sponsor's table (Table 8) was verified by our statistician, Dr. Jinnan Liu.

Table 8 Results for the Primary Endpoint for Study 20120296 (Sponsor's Table)

	Placebo	Treatment Group	
		70mg	140mg
Baseline*			
n	316	312	318
Mean MMD (SD)	8.3 (2.5)	8.3 (2.5)	8.3 (2.5)
Mean of MMDs over months 4, 5, 6			
n	289	296	302
Mean (SE)	6.3 (0.2)	5.0 (0.2)	4.5 (0.2)
Median	5.7	4.3	3.8
Min, max	0, 20.7	0, 19	0, 15.6
Change from baseline in mean over months 4, 5, 6			
n	289	296	302
Mean MMD (SE)	-2.0 (0.2)	-3.4 (0.2)	-3.8 (0.2)
Median	-2.0	-3.7	-4.0
Min, Max	-12, 12.4	-13.4, 9	-13, 6.6
Adjusted analysis			
LSM estimates	-1.8	-3.2	-3.7
95% CI of LSM	(-2.2, -1.5)	(-3.6, -2.9)	(-4., -3.3)
Difference in LSM		**-1.4**	**-1.9**
95% CI of the difference		(-1.9, -0.9)	(-2.3, -1.4)
p-value		<0.001	<0.001

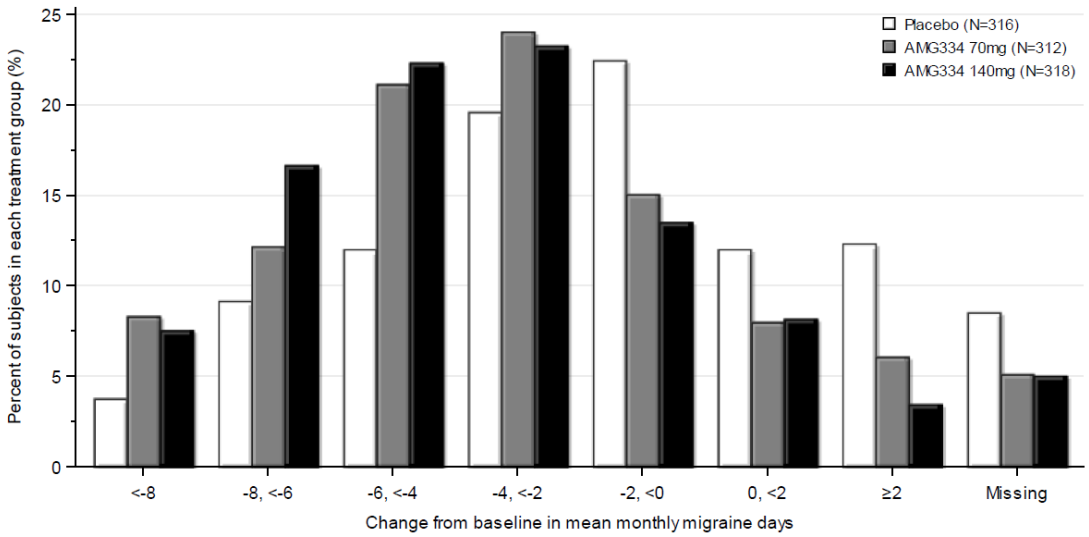
*This table is taken from the sponsor's materials from the CSR for study 20120296. The adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction stratification factors, and baseline values as covariates.

Reviewer Comment: The unadjusted calculation of the primary endpoint is essentially the same as the sponsor's adjusted calculation. The sponsor's point estimate for each dose falls within the 95% confidence interval of the other dose suggesting there is no difference in efficacy between the 70mg and the 140mg dose.

The sponsor was asked to provide a distribution of the change from baseline in mean monthly migraine days in bins of 2-day change from baseline (Figure 2). Negative numbers represent a reduction in the number of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo except in the (-2, 0) bin. In comparing the doses, there is little separation between 70mg and 140mg except for the (-8, -6) bin, and in fact 70mg has a

slightly higher percentage of patient experiencing greater than 8-day reduction in MMD as compared to 140mg. There is a slight but overall shift in treatment groups as compared to placebo towards negative values (i.e., improvement).

Figure 2 Distribution of Change from Baseline in Mean Monthly Migraine Days over Month 4, 5, and 6 by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017.

In study 20120296 the primary endpoint was assessed over the last three months of the 6-month double-blind treatment period. The Division requested that the sponsor perform analyses of the primary endpoint over the entire treatment period. I have summarized the mean monthly migraine days, change from baseline, and difference from placebo at each month during the DBTP (Table 9). My calculations are similar to the sponsor's analyses even though my analyses were unadjusted. These monthly time points show consistency with the primary endpoint.

Table 9 Study 20120296: Mean Monthly Migraine Days, Change from Baseline, and Difference from Placebo over Time

	Placebo		70mg			140mg		
	MMD	Change from Baseline	MMD	Change from Baseline	Difference from PBO	MMD	Change from Baseline	Difference from PBO
Baseline	8.2	-	8.3	-	-	8.3	-	-
Month 1	7.3	-1.0	5.9	-2.4	1.4	5.5	-2.8	1.9
Month 2	6.8	-1.4	5.3	-3.0	1.6	5.2	-3.2	1.8
Month 3	6.5	-1.7	5.3	-3.0	1.3	4.8	-3.6	1.9
Month 4	6.3	-2.0	5.2	-3.1	1.2	4.8	-3.6	1.6
Month 5	6.3	-1.9	5.0	-3.4	1.4	4.6	-3.8	1.9
Month 6	6.5	-1.7	5.0	-3.3	1.6	4.5	-3.8	2.1

*Reviewer calculated, unadjusted analysis using dataset ADMONPRI from the ISE for study 20120296 where BASETYPE=DOUBLE-BLIND and PARAMCD=MMD; analysis of AVAL by AVIST and TRT01AN, and analysis of CHG by AVISIT and TRT01AN

Reviewer Comment: There is consistency of effect at each time point during the 6 months of treatment in the DBTP. The 70mg and 140mg doses perform better than placebo at all time points.

Overall the sponsor reports about 5.1% missing data for monthly migraine days in the double-blind treatment period. Per the statistical reviewer, Dr. Jinnan Liu, the plan for handling missing data was pre-specified, and adequate and the overall rate of missing data was very low. The sponsor performed sensitivity analyses of the primary endpoint using various ways to handle missing data: last observation carried forward (LOCF), generalized linear mixed effect model for the per protocol analysis set, multiple imputation-missing at random, multiple imputation-missing not at random, and baseline observation carried forward (BOCF). The results of these sensitivity analyses showed consistency of the treatment effect. The treatment effect for 70mg was about -1.4 and for 140mg ranged from -1.8 to -1.9 in reduction of MMD as compared to placebo utilizing the various models for handling missing data. Per Dr. Liu, the results of the sensitivity analyses and per-protocol analysis were consistent with the primary efficacy analysis.

Data Quality and Integrity - Reviewers' Assessment

No major data quality and integrity issues were identified during the review of study 20120296.

Efficacy Results - Secondary and other relevant endpoints

Please see section 6.1.1 for the description of the key secondary endpoints and the type I error control for these endpoints. The results of these endpoint analyses can be found in Tables 10 through 13 below.

The proportion of patients who achieved at least a 50% reduction in MMDs from baseline to the last three months of the DBTP was greater in both treatment groups than in the placebo group. The common odds ratio for percentage of patients with a 50% reduction in MMD compared to placebo was statistically significant (Table 10). The sponsor's analyses of the secondary endpoints (Table 10) were verified by our statistician, Dr. Jinnan Liu.

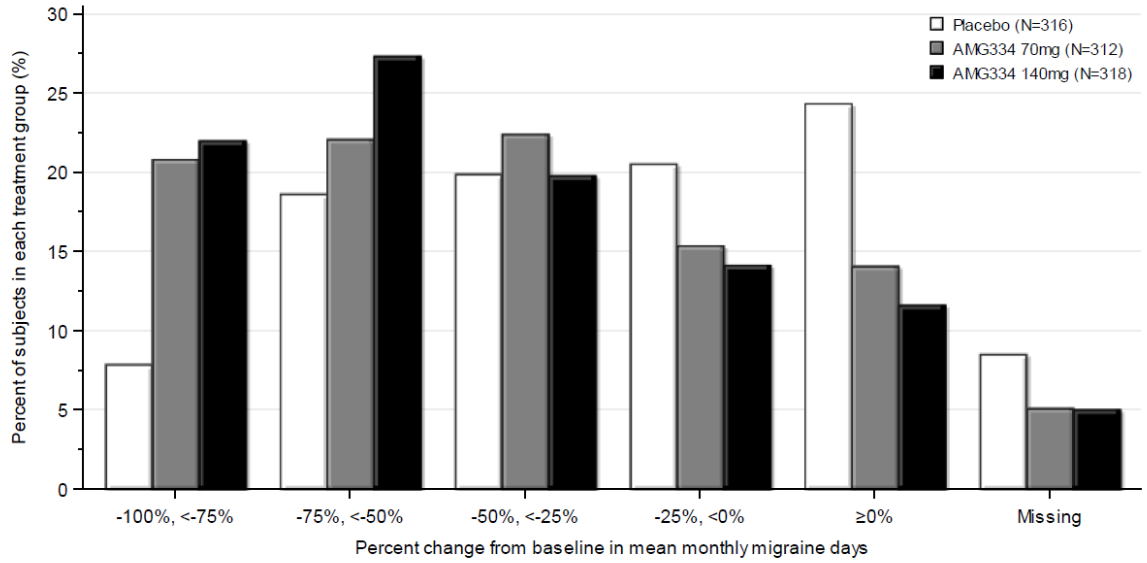
Table 10 Study 20120296: Results from Key Secondary Endpoint
Achievement of ≥50% Reduction in Mean Monthly Migraine Days from Baseline

	Placebo	**Treatment Group**	
	N=316	70mg N=312	140mg N=318
****Months 4, 5, 6**			
≥50% Response	26.6	43.3	50.0
Difference in responder (Treatment less placebo)		16.7%	23.4%
***NNT**		6.0	4.3
****Common Odds Ratio**		2.1	2.8
95% CI		(1.5, 3.0)	(2.0, 3.9)
p-value		<0.001	<0.01

* The NNT was calculated by the reviewer.
**These figures were taken from the sponsor's materials for study 20120296. The common odds ratio and p-values were calculated using CMH, using stratification factors region, and prior migraine prophylaxis.

The sponsor was asked to provide a distribution of the percentage change from baseline in mean monthly migraine days in bins of 25% change from baseline (Figure 3). Negative numbers represent a reduction in the percentage of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo except in the (0, -25%) bin. In comparing the doses, there is little separation between 70mg and 140mg. There is a slight but overall shift in treatment groups as compared to placebo towards negative values (i.e., improvement).

Figure 3 Distribution of Percentage Change from Baseline in Mean Monthly Migraine Days Over Month 4, 5, and 6 by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017

The sponsor also measured the baseline use of acute migraine-specific medication in days per month, and compared the baseline to the last three months of the double-blind treatment period. There was a small, but statistically significant change in the use of acute-migraine specific medication (Table 11). The sponsor's table (Table 11) was verified by our statistician, Dr. Jinnan Liu.

Table 11 Change from Baseline in Use of Monthly Acute Migraine-Specific Medication in Study 20120296 (Sponsor's Table)

	Placebo	Treatment Group	
		70mg	140mg
Baseline*			
N	316	312	318
Mean in days (SD)	3.4 (3.4)	3.2 (3.4)	3.4 (3.5)
Median	3.3	3.0	3.0
Min, max	0, 12	0, 14	0, 12.6
Mean over months 4, 5, 6			

n	289	296	302
Mean in days (SD)	3.3 (3.7)	2.3 (2.9)	1.8 (2.4)
Median	2.3	1.0	0.4
Min, max	0, 14.2	0, 13.4	0, 11.8
Change from baseline in mean over months 4, 5, 6			
Mean (SE)	-0.3	-1.1	-1.6
Median	0	0	-0.4
Min, Max	-8.3, 7.5	-7.8, 6.3	-9.3, 2.9
Adjusted analysis			
LSM estimates	-0.2	-1.1	-1.6
95% CI of LSM	(-0.4, 0.0)	(-1.3, -0.9)	(-1.8, -1.4)
Difference in LSM		**-0.9**	**-1.4**
95% CI of the difference		(-1.2, -0.6)	(-1.7, -1.1)
p-value		<0.001	<0.001

*This table is adapted from the sponsor's materials from clinical study report 20120296.

There was a small, but statistically significant change in the baseline score for both domains of the MPFID (Table 12 and Table 13). (b) (4) The scores reported in Tables 12 and 13 are the transformed scores (0 to 100) which was a linear transformation from the raw score scale (5 to 25 for Physical Impairment and 7 to 35 for Everyday Activities).

Table 12 Change from Baseline in Mean Monthly Average Impact on Everyday Activities Score as Measured by the MPFID in Study 20120296 (Sponsor's Table)

	Placebo	**Treatment Group**	
		70mg	140mg
Baseline*			
n	316	312	318
Mean (SD)	13.7 (9.1)	14.0 (8.9)	13.0 (8.2)
Median	11.9	11.7	11.0
Min, max	0, 49.4	0.1, 52.3	0, 46.2
Mean over months 4, 5, 6			
n	289	296	302
Mean	10.0 (0.6)	8.0 (0.5)	7.6 (0.5)

Median	6.76	5.44	4.75
Min, max	0, 58.5	0, 71.0	0, 52.8
Change from baseline in mean over months 4, 5, 6			
Mean (SE)	-3.7 (0.5)	-5.8 (0.5)	-5.8 (0.4)
Median	-3.4	-5.2	-5.5
Min, Max	-32.3, 25.5	-32.7, 40.0	-32.5, 35.7
Adjusted analysis**			
LSM estimates	-3.3	-5.5	-5.9
95% CI of LSM	(-4.1, -2.5)	(-6.3, -4.8)	(-6.6, -5.1)
Difference in LSM		**-2.2**	**-2.6**
95% CI of the difference		(-3.3, -1.2)	(-3.6, -1.5)
p-value		<0.001	<0.001

*These figures are adapted from the sponsor's table from study 20120296. Scores on the scale are reported here as transformed scores. The transformed score is on a scale from 0 to 100.
** The adjusted analysis uses a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors, and baseline value as covariates. P-values for pairwise comparisons are nominal without multiplicity adjustment.

Table 13 Change from Baseline in Mean Monthly Average Physical Impairment Domain Scores on the MPFID in Study 20120296 (Sponsor's Table)

	Placebo	**Treatment Group**	
		70mg	140mg
Baseline*			
n	316	312	318
Mean (SD)	12.2 (9.4)	12.6 (9.7)	12.0 (9.0)
Median	10.2	10.2	10.2
Min, max	0.3, 51.2	0, 62.2	0, 47.3
Mean over months 4, 5, 6			
n	289	296	302
Mean (SE)	9.6 (0.6)	7.9 (0.6)	7.3 (0.5)
Median	6.6	4.7	3.8
Min, max	0, 53	0, 74.3	0, 52.3
Change from baseline in mean over months 4, 5, 6			
Mean (SE)	-2.7 (0.5)	-4.4 (0.5)	-4.8 (0.5)
Median	-2.1	-3.8	-4.5
Min, Max	-31.7, 26.2	-32.1, 53.1	-32.9, 43.7

Adjusted analysis**			
LSM estimates	-2.4	-4.2	-4.8
95% CI of LSM	(-3.2, -1.6)	(-5.0, -3.5)	(-5.6, -4.0)
Difference in LSM		**-1.9**	**-2.4**
95% CI of the difference		(-3.0, -0.8)	(-3.5, -1.4)
p-value		<0.001	<0.001

*These figures are adapted from the sponsor's table from study 20120296. Scores on the scale are reported here as transformed scores. The transformed score is on a scale from 0 to 100.
** The adjusted analysis uses a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors, and baseline value as covariates. P-values for pairwise comparisons are nominal without multiplicity adjustment.

The Clinical Outcome Assessment (COA) team was consulted to review the MPFID. I will summarize the findings and conclusions here. The COA team reviews the within-subject changes in scores, while the clinical review division (DNP) and corresponding biometrics team are responsible for between-group score changes.

Per Dr. Sarrit Kovacs' review of the MPFID dossier, the sponsor demonstrated that the MPFID's content validity, domain structure, and psychometric properties exceeded the sponsor's pre-specified criteria for acceptability and was in-line with their expectations. However, Dr. Kovacs found issues with certain MPFID items that had high floor effects. Dr. Kovacs cautions against the use of the MPFID version 2.0, without modification, in future development programs because of high floor effects in more than half of the items, and an inability to detect treatment effects. Please see the consult by Dr. Sarrit Kovacs, COA reviewer for further details.

Within-subject Improvement

Based on initial estimates from a validation study, the sponsor concluded that a within-subject improvement of (b) (4) on the MPFID domain scores (on the 0 to 100 point transformed scale) is considered clinically meaningful. To develop this within-subject change threshold, the sponsor utilized these two anchors:

Primary anchor: ≥30% or ≥50% reduction from baseline in monthly migraine days
Primary anchor: ≥20% or ≥50% reduction from baseline in the MPFID global assessment of everyday activities item score

The COA team asked the sponsor to provide cumulative distribution function (CDF) curves for the anchor scales (b) (4) is clinically meaningful. After reviewing these CDF curves, Dr. Kovacs feels that the within-subject improvement thresholds are (b) (4) on the MPFID domain scores. She estimates that the thresholds are closer to 8 to

9 points for the Impact on Everyday Activities domain, and 6 to 7 points on the Physical Impairment domain.

Between-group Difference

To develop the between-group change threshold, the sponsor utilized a 1-day difference in monthly migraine days as an anchor to define clinically distinct groups. Per the sponsor's estimation provided in a prior interaction with the Division in a Type C meeting briefing document dated March 7, 2016, the between-group estimate for the treatment effect was -3.1 for the Impact of Everyday Activities domain and -3.5 points for the Physical Impairment domain. Results in 20120296 were statistically significant but failed to meet this threshold (Tables 12 and 13). The treatment effect for the Impact of Everyday Activities domain was -2.2 points for 70 mg and -2.6 points for 140mg. For the Physical Impairment domain, the treatment effect was -1.9 points for 70mg and -2.4 points for 140mg.

Reviewer Comment: Although the MPFID score change in study 20120296 is statistically significant, I do not think that the magnitude of the change is clinically significant. For both domains on the MPFID, the score difference (between-group difference) from baseline is about a 2 to 2.5-point change on a 100-point scale. For between-group differences in scores, (b) (4)

I agree with Dr. Kovacs assessment that the threshold for within-subject improvement is (b) (4) *on the MPFID.*

At prior interactions with the sponsor, the Division in conjunction with the COA staff felt that the thresholds for clinical meaningfulness are (b) (4) *for within-subject improvement, and* (b) (4) *for between-group differences. However, the scale did not meet the sponsor's proposed changes which the Division felt were* (b) (4) *at the outset.*

Dose/Dose Response

This will be addressed in section 7.1.4.

Additional Analyses Conducted on the Individual Trial

The sponsor performed some additional analyses on the primary endpoint to include subgroup analyses by the stratification factors: region and use of prior or current prophylactic

medications. The treatment effect in the sponsor's subgroup analyses were consistent with the findings of the primary analysis (Table 14).

Table 14 Study 20120296: Primary Endpoint: Summary of Treatment Effect by Subgroup

	Treatment effect (95% CI)	
Subgroup	70mg	140mg
North America	-1.2 (-1.9, -0.5)	-1.5 (-2.2, -0.8)
All other regions	-1.6 (-2.2, -0.9)	-2.1 (-2.8, -1.4)
Current or prior use of migraine prophylaxis	-1.9 (-2.6, -1.1)	-2.4 (-3.2, -1.6)
Treatment naive	-1.0 (-1.7, -0.4)	-1.4 (-2.0, -0.8)
<8 baseline MMD	-1.5 (-2.1, -0.9)	-1.9 (-2.5, -1.3)
≥8 baseline MMD	-1.4 (-2.1, -0.6)	-1.8 (-2.5, -1.1)

*These figures are summarized from the sponsor's tables from the CSR for study 20120296. Region, and use of prophylaxis were stratification factors. Baseline MMDs was not a stratification factor.

Reviewer Comment: Subgroup analyses by the region stratification factor and the baseline number of migraine days showed little effect on the analysis of the primary endpoint and was consistent overall with the treatment effect observed in the entire population. Subgroup analyses on use of prior/current migraine prophylaxis does show some evidence of a larger treatment effect in patients who have current/prior use of migraine prophylaxis as compared to those who have no prior or current use. The point estimate for both the 70mg and 140mg doses lie outside of the confidence intervals for the 'no prior/current use' and the confidence intervals of these subgroups are not overlapping suggesting that the treatment effect might be slightly larger in those who have been on prior or current prophylactic medication. I do not think the use of current prophylactic medication influenced that difference in treatment effect. There were very few people in the study who were actually taking migraine prophylaxis, and the dose had to be stable prior to entry in the study, and throughout the study. When examining this group of patients who had prior use of migraine prophylaxis, their difference from placebo appears larger primarily due to a diminished placebo effect in patients who had taken prior migraine prophylaxis.

I conducted two exploratory analyses on study 20120296 looking at responder rates ≥75% and the 100% responder rate. I examined the data in two ways. First, I looked at how many patients were free of migraine or nearly free of migraine at the end of the study (Table 15), and then I looked at the same responder rate over the last three months of the study consistent with the way the primary endpoint was analyzed (Table 16). For both analyses, treatment with

erenumab resulted in a greater proportion of patients who achieved ≥75% or 100% reduction in their monthly migraines.

Table 15 Achievement of ≥75% and 100% Reduction in Mean Monthly Migraine Days from Baseline at Month 6

	Placebo	**70mg**	**140mg**
	N=316	N=312	N=318
Month 6			
≥75% Response n (%)	48 (15.2)	79 (25.3)	78 (24.5)
Difference in responder (Treatment less placebo)		10.1	9.3
NNT		9.9	10.8
100% Response n (%)	18 (5.7)	38 (12.2)	30 (9.4)
Difference in responder (Treatment less placebo)		6.5	3.7
NNT		15.4	27.0

*This table was created by the reviewer from ADMONPRI for study 20120296 from the ISE where PARAMCD= MMDRD100, or MMDRDC75, BASETYPE=DOUBLE-BLIND, AVISIT=WEEK 24, analysis of AVALC by TRT01PN.

Table 16 Achievement of ≥75% and 100% Reduction in Mean Monthly Migraine Days from Baseline at Months 4, 5, 6

	Placebo	**70mg**	**140mg**
	N=316	N=312	N=318
Month 4, 5,6			
≥75% Response n (%)	25 (7.9)	65 (20.8)	70 (21.9)
Difference in responder (Treatment less placebo)		12.9	14.0
NNT		7.8	7.1
100% Response n (%)	9 (2.8)	10 (3.2)	16 (5.0)
Difference in responder (Treatment less placebo)		0.4	2.2
NNT		250	45.5

*This table was created by the reviewer from ADMONPRI for study 20120296 from the ISE where PARAMCD= MMDRD100, or MMDRDC75, BASETYPE=DOUBLE-BLIND, AVISIT=Endpoint: Mean of Month 4 to 6, analysis of AVALC by TRT01PN.

6.2. Study 20120297: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Episodic Migraine Prevention

6.2.1. Study Design

Study 20120297 has many similarities to study 20120296. The differences between the two studies will be highlighted below in the trial design section.

Trial Design

Study 20120297 included a placebo and a 70mg arm while 20120296 had an additional arm evaluating 140mg. Study 20120297 treated patients with IP for 3 months versus 6 months in study 20120296. In the open-label period, there was a single arm with 70mg. The safety follow-up period in study 20120297 was shorter than in study 20120296. Because the studies were of different lengths, the primary endpoint was measured at a different time point in each of the two studies. The primary endpoint for study 20120297 was measured at the last 4 weeks of the DBTP vs study 20120296 which was measured over the last 3 months of the 6-month DBTP. Secondary endpoints differed between the two studies and will be highlighted under each trial separately.

Diagnostic criteria, concurrent medications, inclusion and exclusion criteria, definition of qualifying migraine for the primary endpoint all were the same between the two studies. Patients in this study also completed the MPFID using their eDiary in this study. Please see section 6.1.1 Study Design for study 20120296.

Basic Study Design

Screening phase: up to 3 weeks
Baseline: 4 weeks
Randomization
Double-blind treatment phase: 12 weeks (placebo or 70mg SC monthly)
Additional treatment: 28 weeks (70mg SC monthly)
Follow-up: 8 weeks (12 weeks after the last dose of IP)

The study was conducted from July 20, 2015 through July 11, 2016 (data cutoff date) at 69 centers in Denmark, France, Greece, Portugal, Russian Federation, Spain, Switzerland, and the U.S.

Study Treatments

IP was administered for 3 months by subcutaneous injection. The treatments in this study were placebo or 70mg given as a single SC injection.

Procedures and Schedule

The schedule of trial procedures and assessments is summarized in Table 17. I have modified this table from the sponsor's materials to include only pertinent assessments.

Table 17 Schedule of Procedures and Assessments for Study 20120297

Period (duration)	Screening (3 weeks)	Baseline (4 weeks)	Double-Blind Treatment Phase (12 weeks)			
			Day 1	Week 4	Week 8	Week 12
Vitals signs; pregnancy testing; C-SSRS; adverse event recording	x	x	x	x	x	x
IP administration			x	x	x	
ECGs	x		x	x	x	x
Chemistry, hematology	x		x	x		x
Anti-AMG 334 antibodies			x	x		x

Period (duration)	Active Treatment Phase (28 weeks)								Safety Follow up
	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	
Vitals signs; pregnancy testing; C-SSRS; adverse event recording	x	x	x	x	x	x	x	x	x
IP administration	x	x	x	x	x	x	x		
ECGs	x	x		x				x	
Chemistry and hematology	x	x		x				x	x
Anti-AMG 334 antibodies	x	x		x	x	x		x	x

Note: Randomization occurred after the completion of the baseline period. Patients who completed the double-blind treatment period could be entered the active treatment phase. The safety follow up visit occurred 8 weeks after the end of the study which is 12 weeks after the last dose of IP.

Study Endpoints

Primary Endpoint

The primary endpoint for this study is the change from baseline in monthly migraine days in the last month of the 3-month double-blind treatment phase.

Secondary Endpoints

- Achievement of at least a 50% reduction from baseline in mean monthly migraine days 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 in mean impact on everyday activities domain score over the last month of the double-blind treatment phase as measured by the MPFID
- Achievement of at least a 5-point reduction from baseline in mean physical impairment domain score over the last month of the double-blind treatment phase as measured by the MPFID

Statistical Analysis Plan

For analysis populations, sample size estimation, stratification factors, planned covariates, planned subgroup analyses, handling of missing data, and sponsor's assurance of data quality, please see study 20120296 in section 6.1.1 Study Design.

Hypothesis Testing

The primary endpoint tested the 70mg dose compared to placebo with a type I error of 0.05.

Null Hypothesis

In patients with episodic migraine, the treatment group is the same as placebo in terms of reduction of the monthly migraine days from baseline.

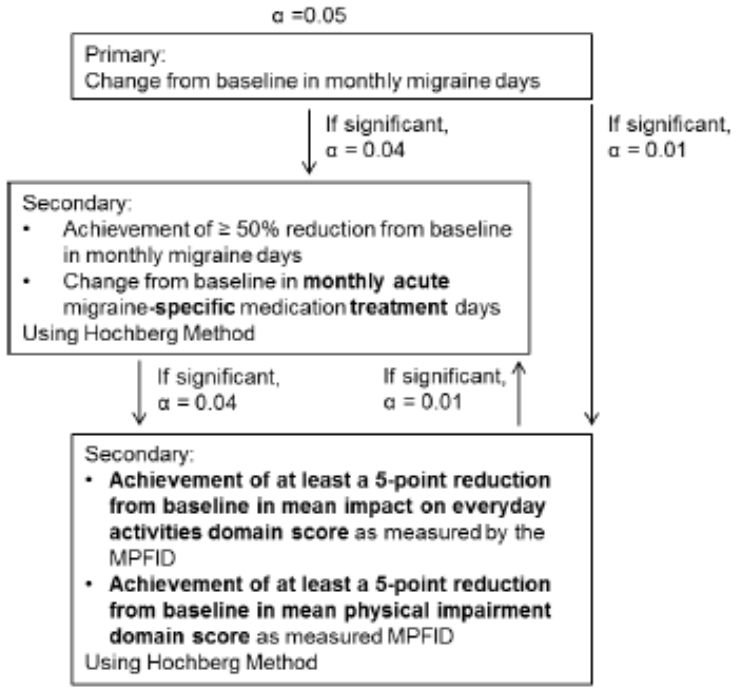
Alternative Hypothesis

In patients with episodic migraine, the treatment group is different from placebo in terms of the reduction of monthly migraine days from baseline.

Statistical methodology used for adjusting multiplicity

A sequential testing procedure was used to maintain the family-wise type I error at 0.05 between the primary and secondary endpoints. If the primary endpoint were statistically significant, then the secondary efficacy endpoints would be tested using a gate-keeping process. The first two secondary endpoints were to be tested using the Hochberg method at a significance level of 0.04. If the first two secondary endpoints were statistically significant, the last two secondary endpoints would be tested at a level of 0.05 otherwise they would be tested at a significance level of 0.01.

Figure 4 Statistical Method Used for Adjusting Multiplicity for Study 20120297



Note: This figure was taken from the sponsor's materials from the protocol for study 20120297.

Protocol Amendments

Two protocol amendments were made to the original protocol which was released on April 15, 2015. From the time of original protocol release to the first amendment, 154 patients had been enrolled. The first amendment was released on October 20, 2015. This amendment allowed patients taking a stable migraine prophylactic treatment to be enrolled into the study when previously they were excluded. This amendment also added a blinded interim analysis to evaluate the MPFID PRO. After the first amendment was released, an additional 423 patients enrolled. A second amendment was released on May 26, 2016. This amendment refined two of the MPFID-related secondary endpoints.

The original statistical analysis plan was released on August 30, 2015 and was amended one time. The sponsor asserts that these changes were made before any analyses were performed. The final SAP was released on July 14, 2016. These changes updated the secondary and exploratory endpoints, sensitivity analyses, stratifications factors, and study definitions.

Data Quality and Integrity: Sponsor's Assurance

The sponsor has stated that study centers were visited at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol, compliance with good clinical practice (GCP), and for accuracy of the data. Investigator staff training was provided by Amgen during investigator meetings, and routine monitoring visits. An independent audit of the study was conducted by Amgen's Global R&D Compliance and Audit Organization.

6.2.2. Study Results

Compliance with Good Clinical Practices

The sponsor asserts that this study was conducted in accordance with ICH GCP regulations, the GCP's applicable to the regions where the study was conducted, and in accordance with the ethical principles in the Declaration of Helsinki.

The sponsor asserts that the study protocol, amendments, and informed consent were reviewed and approved by an IEC or an IRB as appropriate for the country in which the study was conducted.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Date of first patient randomized: July 20, 2015
Date of last patient randomized: April 19, 2016
Date of last patient completing double-blind treatment phase (DBTP): July 11, 2016

Screened: 887
Randomized: 577 (placebo: 70mg 291:286)
Received 1 or more doses of IP: 572
Efficacy analysis set: 570
Per protocol analysis set: 522

The efficacy analysis set consisted of patients who received at least one dose of IP and completed at least one post-baseline monthly eDiary measurement. Of the 577 patients who were randomized, seven were not included in the primary efficacy analysis set leaving a total of 570 for the efficacy analysis set. Five of these seven patients did not receive a dose of IP and the other two did not have at least one post-baseline measurement in MMDs in the DBTP.

The per protocol analysis set was used to perform sensitivity analyses on the primary and secondary endpoints. Of the 577 patients who were randomized, 522 were included in the per protocol analysis set and 55 were excluded. Of the 55 patients who were excluded from the per protocol analysis, 39 were excluded because of incomplete data on the primary endpoint.

Reviewer Comment: About 1.2% of randomized patients were excluded from the primary efficacy analysis set. It is unlikely that this small number would influence the results.

Protocol Violations/Deviations

There were 21 patients of the 577 randomized patients who had what the sponsor considered to be important protocol deviations. Of these 21 patients, 15 patients were in the placebo arm, and six were in the 70mg arm.

The most common protocol deviation was inclusion of patients who did not meet study entry criteria. There were eleven patients in the placebo arm and four in the 70mg arm who did not meet study entry criteria, but entered the study anyway. Overall, none of the study entry criteria were violated by more than three patients.

Reviewer Comment*: Patients who had protocol violations were included in the primary efficacy analysis, but not in the per protocol analysis. Based on the type of protocol violations, it is*

unlikely that patients included in the primary efficacy analysis who had protocol violations will influence the results. However, if there were any influence of these protocol violations on the primary efficacy analysis, this would be addressed in the sensitivity analyses of the per protocol analysis set. For a detailed listing of patient disposition and protocol deviations see Appendix Tables 136 and 137.

Table of Demographic Characteristics

No baseline imbalances in the demographics were noted between placebo and treatment groups in the demographic characteristics (Table 18).

Table 18 Demographic Characteristics of All Randomized Patients for Study 20120297

Demographic Parameters	**Placebo** (N=291) n (%)	**70mg** (N=286) n (%)
Sex		
Male	44 (15.1)	41 (14.3)
Female	247 (84.9)	245 (85.7)
Age		
Mean years (SD)	42.2 (11.5)	42.3 (11.4)
Median (years)	43	43.5
Min, max (years)	18, 65	19, 65
Age Group		
18-40	124 (42.6)	120 (42.0)
41-55	123 (42.3)	125 (43.7)
56-65	44 (15.1)	41 (14.3)
Race		
White	259 (89.0)	259 (90.6)
Black or African American	27 (9.3)	24 (8.4)
Asian	0	2 (0.7)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	1 (0.3)	0
Other or multiple	4 (1.4)	1 (0.3)
Ethnicity		
Hispanic or Latino	34(11.7)	23 (8.0)
Not Hispanic or Latino	257 (88.3)	263 (92.0)
BMI (kg/m^2)		
Mean (SD)	27.4 (6.1)	27.4 (6.3)
Median	25.8	26.3
Min, Max	16, 49.3	16.6, 54.7
Region		

USA	170 (58.4)	168 (58.7)
Rest of the World	121 (41.6)	118 (41.3)

This table was created by the reviewer in JMP using the DM and VS STDM datasets for study 20120297. This dataset included demographic data for all randomized patients.

Reviewer Comment: Migraine is more prevalent in females than males in a ratio of approximately 3:1. In this study, the ratio approaches 6:1 which is disproportionate to the expected ratio in the migraine population. The percentage of blacks and Hispanics in this study is lower than the percentage of blacks and Hispanics in the U.S. This may have occurred because 40% of the patients were from non-U.S. locations. This may affect the generalizability of the study to the U.S. population. The study only allowed for enrollment of patients up to age 65. Patients over 65 are not represented in this study. While it is true that migraine prevalence decreases with age, it does still occur in this population.

No baseline imbalances in the disease severity or use of migraine medications were noted between placebo and treatment groups (Table 19).

Table 19 Other Baseline Characteristics for All Randomized Patients for Study 20120297

Baseline Characteristics	**Placebo** (N=291) n (%)	**70mg** (N=286) n (%)
Disease Duration		
Mean in years (SD)	20.0 (12.1)	21.7 (12.6)
Median	18	22
Min, Max	1, 55	1, 62
Monthly Migraine Days		
Mean (SD)	8.4 (2.6)	8.1 (2.7)
Median	8.2	8.0
Min, Max	2.8, 16.6	0, 16.3
Monthly Headache Days		
Mean	9.3 (2.7)	9.1 (2.7)
Median	9	9
Min, Max	2.8, 18.9	2.9, 16.3
Treatment with migraine prophylactic medication		
Naive	150 (51.5)	144 (50.3)

Prior Use Only	125 (43.0)	123 (43.0)
Current Use	16 (5.5)	19 (6.6)
Acute headache medications used		
None	8 (2.7)	6 (2.1)
Any acute medication	283 (97.3)	280 (97.9)
Migraine specific	174 (59.8)	178 (62.2)
Non-specific	236 (81.1)	224 (78.3)
Acute migraine specific medication use		
Mean (days)	3.4	3.7
Median	2.6	3.5
Min, Max	0, 12.4	0, 13.5
MPFID Global Item*		
Mean	13.6	13.1
Median	12.1	11.4
Min, Max	0, 100	0, 100
MPFID everyday activity**		
Mean (SD)	13.2 (8.9)	12.6 (8.6)
Median	11.1	10.5
Min, Max	0, 53.7	0.2, 48.3
MPFID physical impairment**		
Mean (SD)	11.5 (9.2)	10.8 (9.1)
Median	8.75	8.61
Min, Max	0, 53.8	0, 53.2

The figures in this chart were adapted from the sponsor's materials from the CSR for study 20120297. Some baseline figures were verified in JMP by the reviewer. *Reviewer calculated using ADaM dataset ADMPFID (reported as transformed scores). **MPFID everyday activity and physical impairment domains are reported as transformed scores (range 0-100).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not assessed because the IP was administered by the investigator or other study authorized personnel.

The most frequently used concomitant medications were acute headache medications, which were used during the baseline (Table 19) and the DBTP (Table 20). The two most commonly used categories of these medications were non-opioid acute headache medications, and triptan-based migraine medications.

Table 20 Use of Concomitant Medications (Rescue Medications) in Study 20120297

Medication Category	Placebo (N=288) n (%)	70mg (N=283) n (%)
Triptan-based (any use)	183 (63.3)	184 (65.0)
Used at baseline and not used in DBTP	7 (2.4)	6 (2.1)
Not used baseline and used in DBTP	10 (3.5)	7 (2.5)
Non-opioid (any use)	247 (85.5)	235 (83.0)
Used at baseline and not used in DBTP	12 (4.2)	9 (3.2)
Not used baseline and used in DBTP	17 (5.9)	20 (7.1)
Ergotamine (any use)	1 (0.3)	0
Used at baseline and not used in DBTP	0	0
Not used baseline and used in DBTP	0	0
Opioid-based (any use)	14 (4.8)	13 (4.6)
Used at baseline and not used in DBTP	1 (0.3)	2 (0.7)
Not used baseline and used in DBTP	4 (1.4)	5 (1.8)
Non-opioid containing butalbital (any use)	7 (2.4)	8 (2.8)
Used at baseline and not used in DBTP	2 (0.7)	0
Not used baseline and used in DBTP	1 (0.3)	1 (0.4)
Opioid containing butalbital (any use)	0	0
Used at baseline and not used in DBTP	0	0
Not used baseline and used in DBTP	0	0

*These figures were taken from the sponsor's materials from the CSR for study 20120297. The sponsor created this table using the safety analysis set.

Reviewer Comment: These concomitant medications could also be considered 'rescue' medications. They are being used at relatively the same rate amongst those in the placebo and treatment arm. There seems to be a general trend that slightly more placebo patients then erenumab treated patients could discontinue acute treatments (triptans, non-opioids, butalbital) in the DBTP. In some categories, more placebo patients required addition of acute medications (triptans), and in some situations, more erenumab treated patients needed addition of acute medications (non-opioid, opioid, butalbital). This suggests overall that erenumab does not have much effect on the percentage of people needing acute migraine medications.

However, a formal analysis on reduction in monthly use of acute migraine medications when looking specifically at triptan and ergot usage shows a small, but statistically significant reduction in the use of acute migraine medications (see Efficacy Results-Secondary Endpoints).

Efficacy Results - Primary Endpoint

The primary endpoint for this study is the change from baseline in mean monthly migraine days as compared to placebo. There was a small, but statistically significant mean reduction in the change from baseline in the 70mg arm as compared to placebo (Table 21). The treatment effect for the 70mg dose was -1.04 days. The sponsor's table (Table 21) was verified by our statistician, Dr. Jinnan Liu.

Table 21 Results for the Primary Endpoint for Study 20120297 (Sponsor's Table)

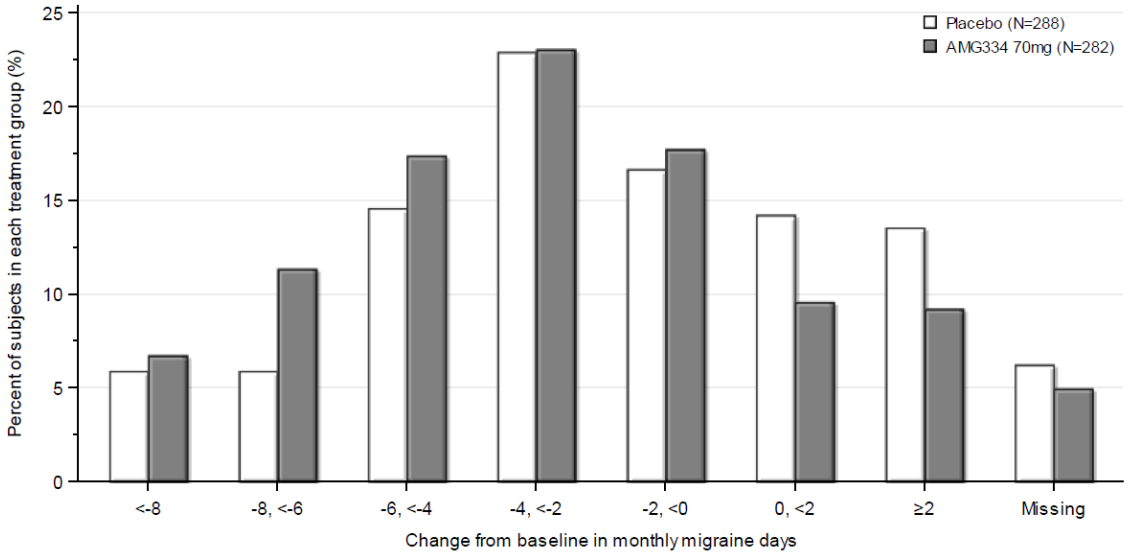
	Placebo	**70mg**
Baseline*		
n	288	282
Mean MMD (SD)	8.4 (2.6)	8.1 (2.6)
Mean of MMDs over last 4 weeks of DBTP		
n	270	268
Mean (SE)	6.5 (0.2)	5.2 (0.2)
Median	6.0	4.7
Min, max	0, 24	0, 21.5
Change from baseline in mean over last 4 weeks		
n	270	268
Mean MMD (SE)	-2.0 (0.3)	-2.9 (0.2)
Median	-2.3	-3.1
Min, Max	-12.4, 14.7	-13.5, 16.4
Adjusted analysis		
LSM estimates	-1.8 (0.2)	-2.9 (0.2)
95% CI of LSM	(-2.3, -1.4)	(-3.3, -2.5)
Difference in LSM		**-1.0**
95% CI of the difference		(-1.6, -0.5)
p-value		<0.001

* This table is adapted from the sponsor's materials from the CSR for study 20120297. The adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction stratification factors, and baseline values as covariates.

Reviewer Comment: The unadjusted calculation of the primary endpoint is essentially the same as the sponsor's adjusted calculation. The 70mg dose is an effective dose.

The sponsor was asked to provide a distribution of the change from baseline in mean monthly migraine days in bins of 2-day change from baseline (Figure 5). Negative numbers represent a reduction in the number of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo in all bins.

Figure 5 Distribution of Change from Baseline in Monthly Migraine Days in the Last Month of the Double-Blind Treatment Phase by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017.

The sponsor performed sensitivity analyses of the primary endpoint using various ways to handle missing data. Per Dr. Jinnan Liu, statistical reviewer, the sponsor prespecified how to handle missing data, and this was considered adequate. The sponsor performed sensitivity analyses using the following methods: last observation carried forward (LOCF), generalized linear mixed effect model for the per protocol analysis set, multiple imputation-missing at random, multiple imputation-missing not at random, and baseline observation carried forward (BOCF). The results of these sensitivity analyses showed consistency of the treatment effect. The treatment effect for the 70mg dose ranged from -1.0 to -1.1 days which is consistent with the planned analysis of the primary endpoint. Per Dr. Liu, the results for the sensitivity analyses and per protocol analysis were consistent with the primary efficacy analysis.

Data Quality and Integrity - Reviewers' Assessment

No major data quality and integrity issues were identified during the review of study 20120297.

Efficacy Results - Secondary and other relevant endpoints

Please see section 6.2.1 for the description of the key secondary endpoints and the type I error control for these endpoints. The results of these endpoint analyses can be found in tables 22 and 23 below. The secondary endpoints related to the MPFID were not statistically significant.

The proportion of patients who achieved at least a 50% reduction in MMDs from baseline to the month of the DBTP was greater in the 70mg treatment group than in the placebo group. The common odds ratio for percentage of patients with a 50% reduction in MMD compared to placebo was statistically significant (Table 22). The sponsor's results for the secondary endpoints were verified by our statistician, Dr. Jinnan Liu.

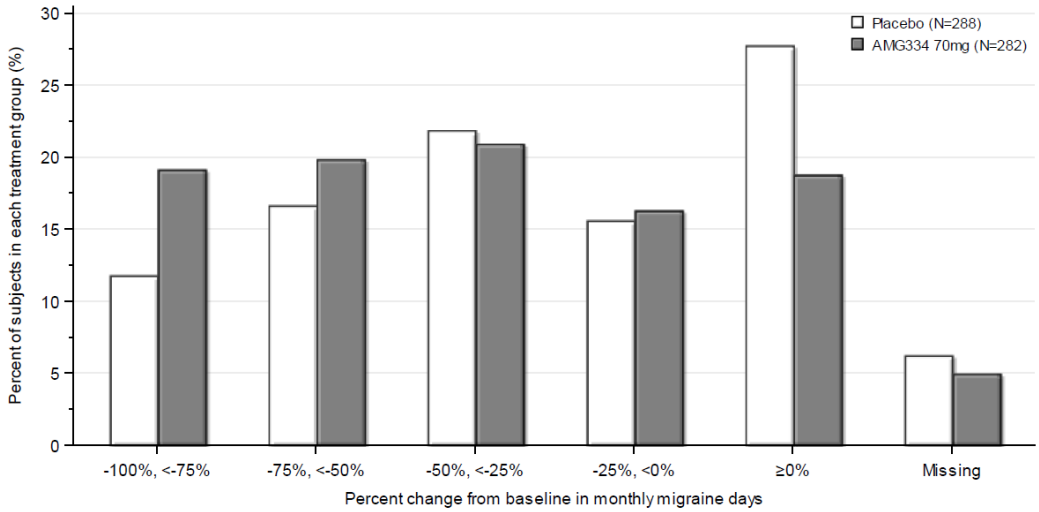
Table 22 Study 20120297: Results from Key Secondary Endpoint
Achievement of ≥50% Reduction in Mean Monthly Migraine Days from Baseline

	Placebo	**70mg**
	N=288	N=282
Month 3		
≥50% Response n (%)	85 (29.5)	112 (39.7)
Difference in responder (Treatment less placebo)		10.2%
***NNT**		9.8
Common Odds Ratio		1.6
95% CI		(1.1, 2.3)
p-value		0.010

These figures were adapted from the sponsor's materials from the CSR for study 20120297. *NNT was calculated by the reviewer.

The sponsor was asked to provide a distribution of the percentage change from baseline in mean monthly migraine days in bins of 25% change from baseline (Figure 6). Negative numbers represent a reduction in the percentage of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo except in the (-25, -50%) bin.

Figure 6 Distribution of Percentage Change from Baseline in Monthly Migraine Days in the Last Month of the Double-Blind Treatment Phase by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017

The sponsor also measured the baseline use of acute migraine-specific medication in days per month, and compared the baseline to the last month of the double-blind treatment period. There was a small, but statistically significant change in the use of migraine-specific medication (Table 23). Patients on erenumab had about a 1-day reduction per month in the use of migraine specific medication as compared to placebo patients who had about 0.5-day reduction. The sponsor's table (Table 23) was verified by our statistician, Dr. Jinnan Liu.

Table 23 Change from Baseline in Use of Monthly Acute Migraine-Specific Medication in Study 20120297 (Sponsor's Table)

	Placebo	70mg
Baseline*		
n	288	282
Mean in days (SD)	3.4 (3.6)	3.8 (3.7)
Median	2.6	3.6
Min, Max	0, 12.4	13.5
Mean over Month 3		
n	270	268
Mean (SD)	3.0 (3.5)	2.6 (3.3)

Median	1.8	1.1
Min, Max	0, 16	0, 15
Change from baseline in mean over month 3		
Mean (SE)	-0.6 (0.2)	-1.3 (0.2)
Median	0	0
Min, Max	-8.4, 7.7	-12, 8.2
Adjusted analysis		
LSM estimates	-0.6	-1.2
95% CI of LSM	(-0.9, -0.4)	(-1.5, -0.9)
Difference in LSM		-0.6
95% CI of the difference		(1.0, -0.2)
p-value		0.002

*The figures were adapted from the sponsor's materials from the CSR for study 20120297. Adjusted analyses used a generalized linear mixed model which includes treatment, visit, treatment by visit interaction, stratification factors, and baseline values as covariates.

In study 20120297, the two secondary endpoints related to the MPFID did not reach statistical significance. The sponsor defined a responder on the MPFID to be at least a 5-point reduction from baseline on the Impact on Everyday Activities domain or the Physical Impairment domain. For the Everyday Activities domain, 36% in the placebo arm and 40% of patients in the 70mg arm met the responder definition. For the Physical Impairment domain, 27% in the placebo arm and 33% in the 70mg arm met the responder definition. There was essentially no difference in the sponsor's defined responder rate between placebo and 70mg.

Dose/Dose Response

This will be addressed in section 7.1.4.

Additional Analyses Conducted on the Individual Trial

The sponsor performed some additional analyses on the primary endpoint to include subgroup analyses by the stratification factors: region and use of prior/current prophylactic medications. The sponsor also did a subgroup analysis by baseline number of monthly migraine days. Results of these subgroups analyses are similar to the findings of the overall treatment effect seen in the primary analysis (Table 24).

Table 24 Study 20120297: Primary Analysis: Summary of Treatment Effect by Subgroup

	Treatment effect (95% CI)
Subgroup	70mg
North America	-0.7 (-1.5, 0.0)
All other regions	-1.5 (-2.4, -0.6)
Current/prior use of migraine prophylaxis	-1.0 (-1.8, -0.2)
Treatment naive	-1.1 (-1.9, -0.3)
<8 baseline MMD	-1.0 (-1.8, -0.3)
≥8 baseline MMD	-1.1 (-1.9, -0.2)

These figures are summarized from the sponsor's tables from the CSR for study 20120297. Region, and use of prophylaxis were stratification factors. Baseline MMDs was not a stratification factor.

Additional exploratory endpoints conducted by the sponsor included analysis of the 75% and 100% responder rate in study 20120297 (Table 25). A very small fraction (4%) of patients achieved 100% reduction in the MMDs compared to placebo.

Table 25: Results from Exploratory Endpoints:
Achievement of ≥75% and 100% Reduction in Mean Monthly Migraine Days from Baseline

	Placebo	**70mg**
	N=288	N=282
Month 3		
≥75% Response n (%)	34 (11.8)	54 (19.1)
Difference in responder (Treatment less placebo)		7.3%
***NNT**		13.7
100% Response n (%)	7 (2.4)	18 (6.4)
Difference in responder (Treatment less placebo)		4%
***NNT**		25.0

This table was adapted from the sponsor's materials from the CSR for study 20120297. *NNT was calculated by the reviewer.

6.3. Study 20120295: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention

6.3.1. Study Design

Study 20120295 has some similarities to study 20120296. The differences between the two studies will be highlighted below in the trial design section.

Trial Design

Study 20120295 enrolled patients with chronic migraine as opposed to episodic migraine. Patients were considered enrolled in the study at the time of the screening phase whereas in the other two pivotal studies patients were considered enrolled at the time of randomization. Study 20120295 had three arms: placebo, 70mg, and 140mg. Randomization in this study was 3:2:2 as opposed to 1:1:1. Diagnostic criteria, inclusion/exclusion criteria, concurrent medications, and stratification factors differed from study 20120296.

Randomization was stratified by region and medication overuse at baseline. The patients were treated with IP for 3 months (12 weeks) as opposed to 6 months in study 20120296. Study 20120295 excluded patients taking concurrent migraine prophylaxis medications. The primary endpoint in 20120295 was measured in the last four weeks of the double-blind treatment period as compared to study 20120296 where primary endpoint was measured over the last 3 months of the 6-month DBTP. Patients who completed the DBTP of this study were eligible to enroll in an open-label extension study (study 20130255). The definition of a qualifying migraine for the primary endpoint was the same as study 20120296 except for the duration of the qualifying migraine. For 20120295, the duration had to be 4 hours as opposed to 30 minutes to count as a migraine towards the calculation of the primary endpoint. For all studies, a day when a patient treated a headache with a migraine specific medication counted as migraine day regardless of the duration of the migraine.

Patients had to have a history of migraine with or without aura for at least one year. For this study, patients additionally had to meet the criteria for chronic migraine with a history of 15 or more headache days per month of which 8 or more headaches per month needed to be migraine headaches in the three months prior to screening. Patients with a diagnosis of chronic migraine due to medication overuse of triptans, ergots, and other analgesics were allowed into the trial. This differs from study 20120296 where patients had fewer than 15 headaches per month, and medication overuse was excluded. Patients in study 20120295 could not be taking prophylactic medication.

Although study 20120295 is called a phase 2 study by the sponsor, the Division acknowledged

in prior regulatory interactions that the trial design appeared to have the features of an adequate and well-controlled trial that could potentially be used as a pivotal efficacy trial.

The study was conducted from March 5, 2014 through April 28, 2016 at 69 centers in Canada, Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, United Kingdom, and the United States.

Basic Study Design

Screening phase: up to 3 weeks
Baseline: 4 weeks
Randomization
Double-blind treatment period: 12 weeks (placebo, 70mg, 140mg SC monthly)
Follow-up: 12 weeks (16 weeks after the last dose of IP)

Key Inclusion Criteria

- History of ≥15 headache days per month of which ≥8 headache days were assessed by the patients as migraine days in each of the three months prior to screening.

Key Exclusion Criteria

- Chronic migraine where the patient was not experiencing any pain free periods
- Taken an opioid for more than 12 days during the three months prior to screening
- Taken butalbital for greater than 6 days during the 3 months prior to screening
- No therapeutic response in prophylaxis of migraine after an adequate trial of greater than 3 categories of prophylactic medications
- Used a prohibited migraine prophylactic medication within two months prior to the start of the baseline period
- Excluded medical conditions: fibromyalgia, chronic pelvic pain, major psychiatric disorders, seizure disorders, significant neurological conditions, malignancies, HIV infection, hepatic disease, Gilbert's syndrome, poorly controlled hypertension
- Excluded medical conditions within 12 months of screening: myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, revascularization, suicidal ideation, drug or alcohol abuse,
- Body mass index >40 kg/m^2

Reviewer Comment: Patients with medication overuse headache were included in the study except for patients with medication overuse due to opioid or butalbital overuse. Patients who were overusing opioids or butalbital were excluded from the study.

Study 20120295 did not explicitly exclude all patients with major cardiovascular or other vascular disease. However, one of the exclusion criteria excluded patients with recent cardiovascular and vascular issues. Effectively, however, patients with major cardiovascular disease were not included in this study.

Study Treatments

Investigational product (IP) was administered monthly for three months by subcutaneous injection. The doses in this study were placebo, 70mg, or 140mg. The 140mg dose was given via two SC injections of 70mg. Throughout the double-blind treatment phase and active treatment phase, two SC injections were given for each investigational product administration to maintain the blind. Patients were randomized in a treatment ratio of 3:2:2 (placebo: 70mg: 140mg). Patients were stratified based on medication overuse at baseline, and region (i.e., North America versus all other locations).

Definition of Medication Overuse

Medication overuse was defined during the baseline period as the following:
- ≥ 15 days of simple analgesics
- ≥ 10 days of triptans
- ≥ 10 days of ergots
- ≥ 10 days of combination therapy intake of any combination of ergots, triptans, opiates, combination-analgesic medications or simple analgesics

Procedures and Schedule

The schedule of trial procedures and assessments is summarized in Table 26. I have modified this table from the sponsor's materials to include only key assessments.

Table 26 Schedule of Procedures and Assessments for Study 20120295

Period (duration)	Screening (3 weeks)	Baseline (4 weeks)	Double-Blind Treatment Phase (12 weeks)					Safety follow up
			Day 1	Week 2	Week 4	Week 8	Week 12	
Vitals signs; adverse event recording; C-SSRS	x	x	x	x	x	x	x	x
IP administration			x		x	x		
ECGs	x		x		x	x	x	
Pregnancy testing	x	x	x		x	x	x	x
Chemistry and hematology	x		x		x	x	x	x
Anti-AMG 334 antibodies			x	x	x	x	x	x

Note: Randomization occurred after the completion of the baseline period. The safety follow up visit occurred 12 weeks after the completion of the double-blind treatment period which is 16 weeks after the last dose of IP.

Concurrent Medications

Throughout the study and while the patients were receiving IP, the investigators could prescribe concomitant medications or treatments deemed necessary for the general health and well-being of the patient. However, the following medications related to migraine treatment were excluded throughout the study and the patients had to be free of these medications for two months prior to the start of the baseline period:

- divalproex sodium, sodium valproate, topiramate, carbamazepine, or gabapentin
- all beta blockers
- all tricyclic antidepressants
- flunarizine or verapamil
- venlafaxine, desvenlafaxine, duloxetine, or milnacipran
- botulinum toxin (injected in the head and/or neck region),
- lisinopril or candesartan
- butterbur, feverfew, magnesium, or riboflavin
- clonidine, guanfacine, cyproheptadine, methysergide, or pizotifen

The following medications were excluded only if they were being used daily for the purposes of migraine prophylaxis: fluoxetine, fluvoxamine, acetazolamide, picotamide, cyclandelate, ergots, steroids, triptans, nicardipine, nifedipine, and nimodipine. If these drugs were being used for migraine prophylaxis, then the patients had to be free from them for at least two months prior

to the start of the baseline phase, otherwise the dose was to remain stable throughout the study.

Study Endpoints

Primary Endpoint

Change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase, calculated based on the following: number of migraine days during the last four weeks of the double-blind treatment phase minus the number of migraine days during the 4-week baseline period.

Secondary Endpoints

•At least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week double blind treatment phase.
•Change from baseline on monthly acute migraine specific medication treatment days in the last 4 weeks of the 12-week double-blind treatment phase.
•Change from baseline in cumulative monthly headache hours in the last 4 weeks of the 12-week double-blind treatment phase

Sponsor's Definition of a Qualifying Migraine Day for Study 20120295

Please see study 20120296 under section 6.1.1 Study Design. The definitions are the same except for the duration of the migraine or headache. For a qualifying migraine for study 20120295, the migraine or headache had to be 4 hours in duration rather than 30 minutes. Migraines of any duration treated with migraine specific medication would still qualify.

Sponsor's Definition of Qualifying Headache Day for Study 20120295

Any calendar day in which the patient experiences the following: a qualified migraine headache, a non-migraine headache that lasts continuously for ≥ 4 hours, or a headache of any duration for which acute treatment is administered.

Statistical Analysis Plan

The sponsor asserts that the analyses for the study report of 20120295 were conducted after the protocol-defined statistical analyses were detailed in the statistical analysis plan (SAP). The SAP was amended once prior to database lock.

Analysis Populations

Table 27 Analysis Sets for Study 20120295

Analysis Set	Definition	Analyses Performed
Full Analysis Set	All patients enrolled	Patient Disposition
Randomization Analysis Set	All patients randomized	Demographics, baseline characteristics, patient disposition, protocol deviations
Efficacy Analysis Set	Patients who received at least 1 dose of IP and completed at least 1 post-baseline monthly eDiary measurement	Efficacy Endpoints
Safety Analysis Set	All randomized patients who received at least 1 dose of IP	Safety endpoints
Per Protocol Set	Patients who received the IP and did not have important protocol deviations	Sensitivity analyses on primary and secondary efficacy endpoints

Sample Size Estimation

The sponsor calculated the unweighted mean difference in monthly migraine days versus placebo in three controlled trials of chronic migraine to be -1.9 days. Two of the trials were for onabotulinumtoxinA and one was for topiramate. The sponsor then assumed the same effect size for AMG 334 70mg compared to placebo. This resulted in an estimated sample size of 279 for placebo and 186 for AMG 334 70mg to provide 85% power using a two-sample t-test with a two-sided significance level of 0.04. Assuming a treatment effect compared to placebo of -2.21 days for the AMG 334 140mg group, the planned sample size of 279 for placebo and 186 for AMG 140mg was to provide 85% power using a two-sample t-test with a two-sided significance level of 0.01. The sponsor assumed a 10% dropout rate.

Stratification Factors

Randomization was stratified by region (North America or Europe) and medication overuse at baseline (yes or no). Patients with medication overuse were allowed in the study if they are overusing triptans, ergots, or other analgesics but not opiates. Medication overuse was determined in the eDiary based on the patient's acute medication use during the baseline period.

Planned Covariates

The following covariates are included in the final analysis of the efficacy endpoints: stratification factors (region and medication overuse).

Null Hypothesis

In patients with chronic migraine, neither of the two AMG 334 doses differs from placebo with respect to change in monthly migraine days from baseline.

Alternative Hypothesis

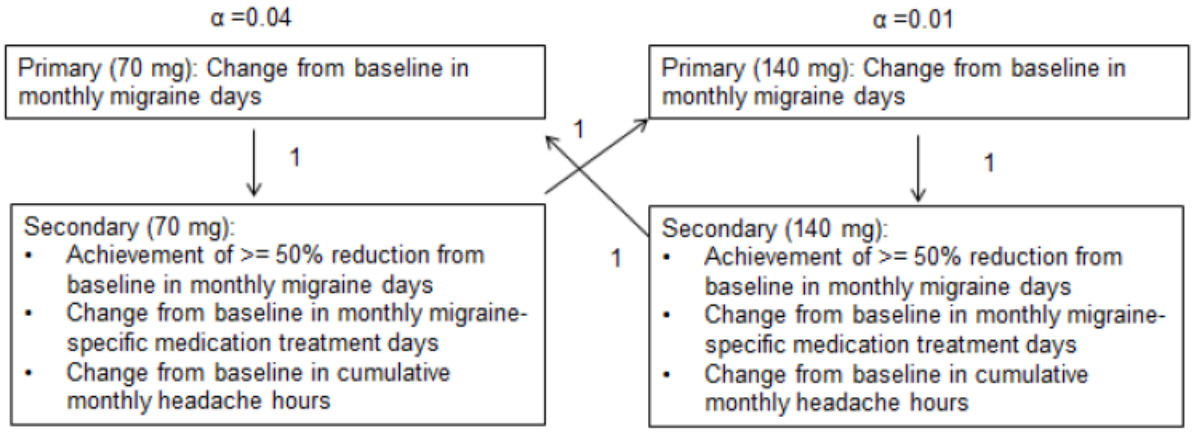
In patients with chronic migraine at least one AMG 334 dose reduces monthly migraine days from baseline than placebo.

Statistical Methodology Used for Adjusting for Multiplicity

The sponsor used a hierarchical gate-keeping procedure and Hochberg method to maintain the 2-sided family-wise type I error rate at 0.05 for the primary and secondary efficacy endpoints. The test for superiority of AMG 334 in the primary endpoint would be tested at significance level of 0.04 for the 70mg arm, and 0.01 for the 140mg arm. If the primary endpoint were statistically significant, using a gate-keeping strategy, the secondary endpoints were to be tested using the Hochberg method at 0.04 for the 70mg arm and 0.01 for the 140mg arm.

If the secondary endpoints were statistically significant for an AMG 334 treatment group, the corresponding significance level would be carried over to the hypothesis testing of the primary endpoint for the other AMG 334 treatment group, and the primary endpoint would be re-tested for the other dose. If the secondary endpoints were negatively correlated, the Holm method would be used for the corresponding tests instead of the Hochberg method.

Figure 7 Statistical Method Used for Adjusting Multiplicity for Study 20120295



Note: This figure was taken from the sponsor's material from protocol 20120295 amendment 1.

Protocol Amendments

Two protocol amendments were made to the original protocol which was released on September 6, 2013. From the time of the original protocol release to the first amendment, 135 patients had been enrolled. The first amendment was released on October 20, 2014. This amendment allowed for the DMC to review both safety data and futility analysis results. The amendment refined the plans for interim analyses. It put into place an event adjudication committee, and added an optional sub-study for the development of the MPFID, Amgen's PRO.

A second protocol amendment was released on July 23, 2015. From the time of release of amendment 1 to the release of amendment 2, an additional 365 patients had enrolled in study 20120295. Two exploratory endpoints were elevated to secondary endpoints. The number of patients randomized was increased from 490 to 651 to increase the power for each treatment arm and to adjust for multiplicity. Interim analyses for futility were removed, and plans for an administrative interim analysis was added to be performed after all randomized patients completed the double-blind treatment period. Following this amendment, 167 additional patients were enrolled.

The original SAP was dated December 9, 2013. It was amended one time prior to any analyses being performed. The SAP was finalized January 11, 2016. The changes included updating the secondary efficacy endpoints, increasing the planned sample size, adding adjustments for multiplicity, and updating study definitions.

6.3.2. Study Results

Compliance with Good Clinical Practices

The sponsor asserts that this study was conducted in accordance with International Conference on Harmonization (ICH) GCP regulations, the GCPs applicable to the regions where the study was conducted, and in accordance with the ethical principles in the Declaration of Helsinki.

The sponsor asserts that the study protocol, amendments, and informed consent were reviewed and approved by an independent ethics committee (IEC) or an institutional review board (IRB) as appropriate for the country in which the study was conducted.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Date of first patient randomized: April 3, 2014
Date of last patient randomized: December 4, 2015
Date of last patient completing double-blind treatment phase (DBTP): February 23, 2016

Screened: 953
Randomized: 667 (placebo: 70mg: 140mg 286:191:190)
Enrolled, not randomized 286
Received 1 or more doses of IP: 660
Efficacy analysis set: 656
Per protocol analysis set: 612

The efficacy analysis set consisted of patients who received at least one dose of IP and completed at least one post-baseline monthly eDiary measurement. Of the 667 patients who were randomized, 11 were not included in the efficacy analysis set leaving a total of 656 for the efficacy analysis set. Seven of these eleven patients did not receive a dose of IP and the others did not have a post-baseline measurement.

The per protocol analysis set was used to perform sensitivity analyses on the primary and secondary endpoints. Of the 667 patients who were randomized, 612 were included in the per protocol set and 55 were excluded.

Reviewer Comment: Approximately 1.6% of patients were excluded from the primary efficacy analysis set. It is unlikely that this small percentage would influence the efficacy results.

Protocol Violations/Deviations

There were 49 patients of the 667 randomized patients who had what the sponsor considered to be important protocol deviations. Of these 49 patients, 20 (7%) were in the placebo arm, 16 (8.4%) were in the 70mg arm, and 13 (6.8%) were in the 140mg arm.

The most common protocol deviation was inclusion of patients who did not meet the study entry criteria. There were equal percentages of patients in all three arms who did not meet study entry criteria yet were enrolled in the study.

Reviewer Comment: Patients who had protocol violations/deviations were included in the primary efficacy analysis, but not in the per protocol analysis. There are overall very few patients with what I would consider a significant protocol deviation, and they are distributed similarly over all three arms so it is my impression that the patients included in the study that had protocol violations will not influence the results of the primary efficacy analysis. However, if there were any influence of these protocol violations on the primary efficacy analysis, this would be addressed by analyzing the per protocol population. For a detailed listing of patient disposition and protocol deviations see Appendix Tables 138 and 139.

Table of Demographic Characteristics

There was a slightly higher percentage of male patients in the placebo group as compared to the treatment groups for the chronic migraine study (Table 28) otherwise the groups were balanced for the baseline demographics.

Table 28 Demographic Characteristics of All Randomized Patients for Study 20120295

Demographic Parameters	Placebo	Treatment Group	
	(N=286) n (%)	70mg (N=191) n (%)	140mg (N=190) n (%)
Sex			
Male	60 (21.0)	25 (13.1)	30 (15.8)
Female	226 (79.0)	166 (86.9)	160 (84.2)
Age			
Mean years (SD)	42.1 (11.3)	41.4 (11.3)	42.9 (11.1)
Median (years)	43.0	42.0	45.0
Min, max (years)	18, 66	18, 64	18, 64
Age Group			
18-40	126 (44.1)	82 (42.9)	69 (36.3)

41-55	120 (42.0)	90 (47.1)	97 (51.1)
56-65	39 (13.6)	19 (9.9)	24 (12.6)
≥ 66	1 (0.3)	0	0
Race			
White	268 (93.7)	176 (92.1)	184 (96.8)
Black or African American	11 (3.8)	10 (5.2)	6 (3.2)
Asian	4 (1.4)	4 (2.1)	0
Other	3 (1.0)	1 (0.5)	0
Ethnicity			
Hispanic or Latino	9 (3.1)	7 (3.7)	10 (5.3)
Not Hispanic or Latino	277 (96.9)	166 (86.9)	160 (84.2)
BMI (kg/m²)			
Mean (SD)	26.3 (5.1)	26.0 (5.3)	26.0 (5.4)
Median	25.7	25.0	25.2
Min, max	15.8, 39.9	15.6, 40	17.1, 40
Region			
North America (USA/CAN)	135 (47.2)	91 (47.6)	89 (46.8)
Rest of the World	151 (52.8)	100 (52.4)	101 (53.2)

This table was created by the reviewer in JMP using the DM and VS SDTM dataset for study 20120295.

Reviewer Comment: Migraine is more prevalent in females than males and this is reflected in the demographics of the study. However, generally it is reported that the prevalence of migraine in women and men is in a 3:1 ratio. The ratio in the sponsor's studies is on the order of 5:1. For chronic migraine, this might be acceptable as the prevalence estimates range from 1.7-4.0% in women and 0.6-0.7% in men. This results in a ratio ranging from 2.5-6.5 times higher in women than men (Natoli et al. 2010).

The percentage of blacks and Hispanics included in this study is even lower than the percentage included in studies 20120296 and 20120297. This may make the generalizability of study 20120295 to the general U.S. population problematic. In this study (as in all the pivotal studies), patients over 65 are not represented due to the exclusion criteria.

No baseline imbalances in the disease severity or baseline use of migraine medications were noted between placebo and treatment groups (Table 29).

Table 29 Other Baseline Characteristics for All Randomized Patients from Study 20120295

Baseline Characteristics	Placebo (N=286) n (%)	Treatment Group 70mg (N=191) n (%)	Treatment Group 140mg (N=190) n (%)
Disease Duration			
Mean in years (SD)	22.2 (12.6)	20.7 (12.8)	21.92 (11.8)
Median	20	19	21
Min, Max	0, 55	0, 52	1.2, 47
Monthly Migraine Days			
Mean (SD)	18.2 (4.7)	17.85 (4.4)	17.85 (4.4)
Median	18	17.5	17.6
Min, Max	5.6, 28	8.1, 28	11.2, 28
Monthly Headache Days			
Mean (SD)	21.1 (3.9)	20.5 (3.8)	20.7 (3.8)
Median	21	20	20
Min, Max	9.3, 28	11.2, 28	11.2, 28
Treatment with prior migraine prophylactic medication			
Yes	218 (76.2)	138 (72.3)	136 (71.6)
No	68 (23.8)	53 (27.7)	54 (28.4)
Acute headache medications used			
None	4 (1.4)	0	2 (1.1)
Any acute medication	282 (98.6)	191 (100)	188 (98.9)
Migraine specific	225 (78.7)	143 (74.9)	149 (78.4)
Non-specific	246 (86.0)	167 (87.4)	161 (84.7)
Acute migraine specific medication use			
Mean in days (SD)	9.5 (7.6)	8.8 (7.2)	9.7 (7.0)
Median	9.0	9.66	10.4
Min, Max	0, 27	0, 26	0, 23.6

The figures in this chart were adapted from the sponsor's materials from the CSR for study 20120295. Some baseline figures were verified in JMP by the reviewer using ADaM dataset ADBASE.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not assessed because the IP was administered by the investigator or other study authorized personnel.

The most frequently used concomitant medications were acute headache medications, which were used during the baseline and DBTP (Table 30). The two most commonly used categories of these medications were non-opioid acute headache medications, and triptan-based migraine medications.

Table 30 Most Commonly Used Concomitant Medications in Study 20120295

Medication Category	Placebo N=282 n (%)	Treatment Group 70mg (N=190) n (%)	Treatment Group 140mg (N=188) n (%)
Triptan-based (any use)	224 (79.4)	144 (75.8)	157 (78.2)
Used at baseline and not used in DBTP	9 (3.2)	5 (2.6)	6 (3.2)
Not used baseline and used in DBTP	4 (1.4)	2 (1.1)	1 (0.5)
Non-opioid (any use)	246 (87.2)	173 (91.1)	164 (87.2)
Used at baseline and not used in DBTP	11 (3.9)	6 (3.2)	4 (2.1)
Not used baseline and used in DBTP	9 (3.2)	8 (4.2)	7 (3.7)
Ergotamine (any use)	1 (0.4)	2 (1.1)	1 (0.5)
Used at baseline and not used in DBTP	0	0	0
Not used baseline and used in DBTP	0	1 (0.5)	0
Opioid-based (any use)	20 (7.1)	7 (3.7)	12 (6.4)
Used at baseline and not used in DBTP	2 (0.7)	0	2 (1.1)
Not used baseline and used in DBTP	7 (2.5)	2 (1.1)	5 (2.7)
Non-opioid containing butalbital (any use)	3 (1.1)	4 (2.1)	4 (2.1)
Used at baseline and not used in DBTP	0	0	1 (0.5)
Not used baseline and used in DBTP	2 (0.7)	1 (0.5)	2 (1.1)
Opioid containing butalbital (any use)	1 (0.4)	0	2 (1.1)
Used at baseline and not used in DBTP	0	0	0
Not used baseline and used in DBTP	0	0	0

*These figures were adapted from the sponsor's materials from the CSR for study 20120295. This table was created by the sponsor using the safety analysis set.

Reviewer Comment: These concomitant medications could also be considered 'rescue' medications. They are being used at relatively the same rate amongst those in the placebo and treatment arm. There seems to be about equal percentages of placebo patients and erenumab treated patients who could discontinue acute treatments in the DBTP. In some categories, more placebo patients required addition of acute medications (triptans, opioids), and in some

situations, more erenumab treated patients needed addition of acute medications (non-opioid, ergotamine). This suggests overall that erenumab does not much effect on the percentage of people needing acute migraine medications.

However, a formal analysis on reduction in monthly use of acute migraine medications when looking specifically at triptan and ergot usage shows a small, but statistically significant reduction in the use of acute migraine medications (see Efficacy Results-Secondary Endpoints).

Efficacy Results - Primary Endpoint

The primary endpoint for this study is the change from baseline in mean monthly migraine days as compared to placebo. The mean monthly migraine days was calculated using the monthly migraine days from the last month of the three month DBTP. There was a statistically significant mean reduction in the change from baseline in both the 70mg and 140mg dose as compared to placebo (Table 31). The treatment effect was -2.46 days for 70mg and -2.45 days for 140mg. The sponsor's table (Table 31) was verified by our statistician, Dr. Jinnan Liu.

Table 31 Results for the Primary Endpoint for Study 20120295 (Sponsor's Table)

	Placebo	**Treatment Group**	
		70mg	140mg
Baseline*			
n	281	188	187
Mean MMD (SD)	18.2 (0.3)	17.9 (0.3)	17.8 (0.3)
Mean of MMDs over month 3			
n	267	178	182
Mean (SE)	14.0	11.3	11.3
Median	14.0	10.0	10.4
Min, max	0, 28	0, 28	0, 28
Change from baseline in mean over month 3			
n	267	178	182
Mean MMD (SE)	-4.2 (0.4)	-6.6 (0.5)	-6.5 (0.5)
Median	-3.8	-7.3	-6.5
Min, Max	-21.8, 9	-20.3, 10.6	-26.1, 7
***Adjusted analysis**			
LSM estimates	-4.2	-6.6	-6.6
95% CI of LSM	(-4.9, -3.5)	(-7.5, -5.8)	(-7.5, -5.8)
Difference in LSM		**-2.5**	**-2.5**

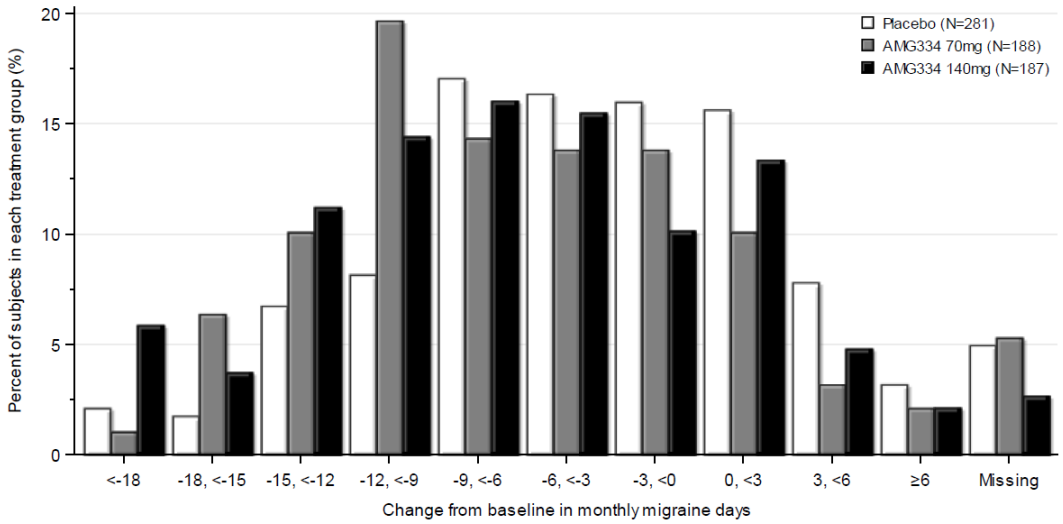
95% CI of the difference		(-3.5, -1.4)	(-3.5, -1.4)
p-value		<0.001	<0.001

*This table is adapted from the sponsor's materials from the CSR for study 20120295. The adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction stratification factors, and baseline values as covariates.

Reviewer Comment: The unadjusted calculation of the primary endpoint is essentially the same as the sponsor's adjusted calculation. The sponsor's point estimates for each dose are identical suggesting there is no difference in efficacy between the 70mg and the 140mg dose.

The sponsor was asked to provide a distribution of the change from baseline in mean monthly migraine days in bins of 3-day change from baseline (Figure 8). Negative numbers represent a reduction in the number of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo in the bins with a higher number of days of change from baseline (greater than 9-days reduction). In comparing the doses, it appears that a greater (but small) percentage of patients receiving the 140mg dose had a greater than 18-day reduction in number of MMDs.

Figure 8 Distribution of Change in Monthly Migraine Days, from Baseline to the Last 4 Weeks of the 12-Week Double-Blind Treatment Phase by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017.

In study 20120295 the primary endpoint was assessed over the last month of the DBTP. The Division requested that the sponsor perform analyses of the primary endpoint over the entire treatment period to ensure consistency of the effect of the drug. I have summarized the mean monthly migraine days, change from baseline, and difference from placebo at each month during the DBTP (Table 32). My calculations are similar to the sponsor's analyses even though my analyses were unadjusted.

Table 32 Study 20120295: Mean Monthly Migraine Days, Change from Baseline, and Difference from Placebo over Time

	Placebo		70mg			140mg		
	MMD	Change from Baseline	MMD	Change from Baseline	Difference from PBO	MMD	Change from Baseline	Difference from PBO
Baseline	18.3	-	17.9	-	-	17.8	-	-
Month 1	15.6	-2.7	12.9	-5.0	2.3	12.8	-5.1	2.3
Month 2	14.7	-3.6	11.8	-6.1	2.6	11.5	-6.3	2.8
Month 3	14.1	-4.1	11.4	-6.5	2.4	11.3	-6.6	2.4

Reviewer calculated, unadjusted analysis using dataset ADMONPRI from the ISE for study 20120295 where BASETYPE=DOUBLE-BLIND and PARAMCD=MMD; analysis of AVAL by AVIST and TRT01AN, and analysis of CHG by AVISIT and TRT01AN

Reviewer Comment: There is consistency of effect over all 3 months of treatment in the DBTP. The 70mg and 140mg doses perform better than placebo at all time points.

The sponsor performed sensitivity analyses of the primary endpoint using various ways to handle missing data. Per Dr. Jinnan Liu, the rules for handling missing data were pre-specified and adequate, and the rate of missing data was very low for this study. The sponsor performed sensitivity analyses using the following methods: last observation carried forward (LOCF), generalized linear mixed effect model for the per protocol analysis set, multiple imputation-missing at random, and multiple imputation-missing not at random. Treatment effect using each of these different methods of analysis showed a treatment effect of 2.5 days for 70mg and -2.2 to -2.6 days for 140mg. The results of these sensitivity analyses showed consistency of the treatment effect with the planned analysis of the primary endpoint. Per Dr. Liu, the results of the sensitivity analyses and the per-protocol analysis were consistent with the primary efficacy analysis.

Data Quality and Integrity - Reviewers' Assessment

No major data quality and integrity issues were identified during the review of study 20120295.

Efficacy Results - Secondary and other relevant endpoints

Please see section 6.3.1 for a description of the key secondary endpoints and of the type I error control for these endpoints. The results of these analyses are presented in Tables 33 through 35.

Key Secondary Endpoints:
•Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last month of the 3-month DBTP (Table 33).
•Change from baseline in mean monthly acute migraine-specific medication treatment days over the last month of the 3-month DBTP (Table 34).
•Change from baseline in cumulative monthly headache hours (Table 35).

The proportion of patients who achieved at least a 50% reduction in MMDs from baseline to the last month of the DBTP was greater than placebo in both treatment groups (Table 33). The adjusted odds ratio for percentage of patients with a 50% reduction in MMD compared to placebo was statistically significant. The sponsor's results for the secondary endpoints were calculated by our statistician, Dr. Jinnan Liu.

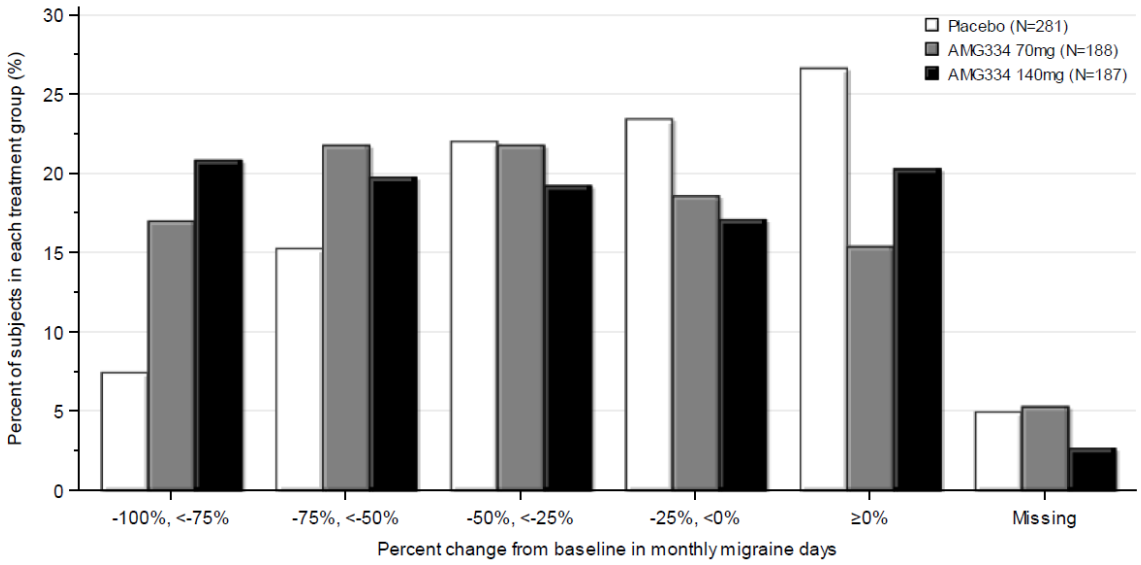
Table 33 Study 20120295: Results from Key Secondary Endpoint
Achievement of ≥50% Reduction in Mean Monthly Migraine Days from Baseline

	Placebo	**Treatment Group**	
	N=281	70mg N=188	140mg N=187
***Month 3**			
≥50% Response n (%)	66 (23.5)	75 (39.9)	77 (41.2)
Difference in responder (Treatment less placebo)		16.4	17.7
****NNT**		6.1	5.6
Adjusted Odds Ratio		2.2	2.3
95% CI		(1.5, 3.3)	(1.56, 3.5)
p-value		<0.001	<0.001

*These figures were taken from the sponsor's material from the CSR for study 20120295. **The NNT was calculated by the reviewer.

The sponsor was asked to provide a distribution of the percentage change from baseline in mean monthly migraine days in bins of 25% change from baseline (Figure 9). Negative numbers represent a reduction in the percentage of MMDs, indicating improvement. From this graphical representation of the data, it appears that a greater percentage erenumab treated patients demonstrate improvement as compared to placebo in the bins of greater than 50% improvement from baseline.

Figure 9 Distribution of Percentage Change in Monthly Migraine Days, from Baseline to the Last 4 Weeks of the 12-Week Double-Blind Treatment Phase by Treatment Group



*This figure was taken from the sponsor's materials from submission 0015, July 28, 2017

The sponsor also measured the baseline use of acute migraine-specific medication in days per month, and compared the baseline to the last month of the double-blind treatment period. There was a statistically significant change in the use of acute-migraine specific medication (Table 34). Overall use of migraine-specific medications was reduced in the both treatment groups as compared to placebo. The sponsor's table (Table 34) was verified by our statistician, Dr. Jinnan Liu.

Table 34 Change from Baseline in Use of Monthly Acute Migraine-Specific Medication for Study 20120295 (Sponsor's Table)

	Placebo	Treatment Group	
		70mg	140mg
Baseline*			
n	267	178	182
Mean in days (SD)	9.4 (0.5)	8.8 (0.5)	9.7 (0.5)
Median	9	9.83	10.4
Min, max	0, 27	0, 26	0, 23.6
Mean over month 3			
n	267	178	182
Mean (SE)	7.9 (0.5)	5.7 (0.5)	5.6 (0.5)
Median	6.0	4.3	4.0
Min, max	0, 28	0, 27	0, 25.3
Change from baseline in mean over month 3	267	178	182
Mean (SE)	-1.6 (0.3)	-3.3 (0.4)	-4.3 (0.4)
Median	-0.7	-1.6	-3.4
Min, Max	-16.5, 14.1	-16.2, 6.6	-20.3, 6.9
Adjusted analysis			
LSM estimates	-1.6	-3.5	-4.1
95% CI of LSM	(-2.1, -1.1)	(-4.0, -2.9)	(-4.7, -3.6)
Difference in LSM		-1.9	-2.6
95% CI of the difference		(-2.6, -1.1)	(-3.3, -1.8)
p-value		<0.001	<0.001

*This table was adapted from the sponsor's materials from the CSR from study 20120295.

The last key secondary endpoint, change from baseline in cumulative monthly headache hours had a numerical trend in favor of treatment, but was not statistically significant (Table 35).

Table 35 Change from Baseline in Cumulative Monthly Headache Hours for Study 20120295

	Placebo	Treatment Group	
		70mg	140mg
Baseline			
n	281	188	187
Mean in hours (SD)	235.3 (126.1)	223.6 (126.6)	215.1 (123.5)
Median	216.5	197.4	179.5
Min, max	(28.8, 657.5)	(34.6, 649.8)	(21.5, 610.0)
Change from baseline in mean at Week 12			
Mean (SE)	-59.3 (6.1)	-66.6 (7.3)	-72.4 (8.7)
Median	-50.2	-64.0	-65.9
Min, Max	(-562.4, 254.0)	-313.5, 271.7)	(-481.8, 262.4)
Adjusted analysis			
LSM estimates	-55.2	-64.8	-74.5
95% CI of LSM	(-66.4, -44.1)	(-78.3, -51.2)	(-88.1, -61.0)
Difference in LSM		-9.5	-19.3
95% CI of the difference		(-27.0, 7.9)	(-36.7, -1.9)
p-value		0.28	0.030

This data is adapted from the sponsor's materials from CSR for study 20120295.

Dose/Dose Response

This will be addressed in section 7.1.4.

Additional Analyses Conducted on the Individual Trial

The sponsor performed subgroup analyses of the primary endpoint on the stratification factors region, and presence of medication overuse headache (MOH) at baseline (Table 36). The treatment effect in patients with medication overuse at baseline was slightly higher than it was for patients who did not have medication overuse at baseline. This increase in treatment effect is primarily due to a decreased placebo effect in patients who have medication overuse at baseline. MMDs were decreased by about 6.6 days in both subgroups (region, and MOH) and in both doses. The difference from placebo was greater in the group with medication overuse. However, the point estimates of the treatment effect for both doses, and both subgroups fall into each other's 95% confidence interval suggesting that there is not a difference between the two subgroups or the dose groups. A similar trend is found in the analyses by the subgroup 'region.' MMDs are reduced by about 6 to 7 days per month in the treatment group, but placebo effect is lower in the 'Other Region' as compared to 'North America.'

Table 36 Study 20120295: Primary Endpoint: Summary of Treatment Effect by Subgroup

	Treatment effect (95% CI)	
Subgroup	70mg	140mg
Medication Overuse	-3.1 (-4.8, -1.4)	-3.1 (-4.1, -1.4)
No Medication Overuse	-2.0 (-3.4, -0.7)	-2.0 (-3.4, -0.7)
North America	-2.4 (-3.9, -0.9)	-1.8 (-3.4, -0.3)
All other regions	-2.5 (-4.0, -1.0)	-3.0 (-4.4, -1.5)
<18 baseline MMD	-3.0 (-4.4, -1.7)	-2.7 (-4.0, -1.3)
≥18 baseline MMD	-1.9 (-3.5, -0.2)	-2.3 (-4.0, -0.7)

*These figures are summarized from the sponsor's tables from the CSR for study 20120295. Region, presence of medication overuse headache at baseline were stratification factors.

I conducted an exploratory analysis on study 20120295 looking at responder rates ≥75% and the 100% responder rate (Table 37). Treatment with erenumab resulted in a greater proportion of patients who achieved ≥75% or 100% reduction in their monthly migraines.

Table 37 Study 20120295: Achievement of ≥75% and 100% Reduction in Monthly Migraine Days from Baseline at Month 3

	Placebo	**70mg**	**140mg**
	N=281	N=188	N=187
Month 3			
≥75% Response n (%)	22 (7.8)	32 (17.0)	39 (20.8)
Difference in responder (Treatment less placebo)		9.0%	12.9%
NNT		11.1	7.8
100% Response n (%)	1 (0.4)	8 (4.3)	5 (2.7)
Difference in responder (Treatment less placebo)		3.8%	2.3%
NNT		26.3	43.5

*This table was created by the reviewer from ADMONPRI join ADBASE for study 20120295 where PARAMCD= MMDRD100, or MMDRDC75, BASETYPE=DOUBLE-BLIND, AVISIT=WEEK 12, analysis of AVALC by TRT01AN.

Reviewer Comment: The 70mg dose had a slightly higher percentage of patients who achieved the 100% response rate. The numbers are so small, no definitive conclusions about the dose response can be made. Overall very few patients achieved 100% reduction in the number of MMDs.

6.4. Study 20120178: A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Please note: This study provides some information on dose ranging and is not being considered one of the pivotal efficacy studies. Data from the study are being used to inform on safety.

6.4.1. Study Design

Overview and Objective

The primary objective was to evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly migraine days in patients with episodic migraine, and to evaluate the safety and tolerability of AMG 334.

Trial Design

Study 20120178 is a multinational, randomized, double-blind, placebo-controlled, parallel group study of patients with episodic migraine. Patients were initially screened, and then, if qualified, entered a four-week baseline period. After completion of the four-week baseline period, patients were then randomized in a ratio of 3:2:2:2 to receive either placebo, 7mg, 21mg, or 70mg of AMG 334 SC monthly. The randomization was stratified by region: North America versus all other locations. Patients were treated with IP during the double-blind treatment period for 3 months (12 weeks). This was followed by an open-label treatment phase lasting up to 256 weeks, and an 8-week safety follow-up which was 12 weeks after the last dose of IP.

The study was conducted from August 6, 2013 through November 4, 2014 (data cutoff date) at 59 centers in Canada, Denmark, Finland, Germany, Norway, Sweden, and the U.S.

Basic Study Design

Screening phase: up to 3 weeks
Baseline: 4 weeks
Randomization

Double-blind treatment phase: 12 weeks (placebo, 7mg, 21mg, 70mg SC monthly)
Additional treatment: up to 256 weeks (70mg SC monthly)
Follow-up: 8 week (12 weeks after last dose of IP)

Diagnostic Criteria and Eligibility

Male and female patients ≥ 18 years to ≤60 years of age with a history of migraine with or without aura. The patients had to have a history of migraine for at least one year prior to screening per the ICHD-2. These patients had to experience a minimum of four and a maximum of fifteen migraines per month on average in the three months prior to baseline. Patients could be randomized into the study if they demonstrated at least 80% compliance on the eDiary.

Key Inclusion and Exclusion Criteria

The inclusion criteria are most similar to study 20120296 and study 20120297 except for the age limit. Study 20120296 and study 20120297 allowed patients to enter the study up to age 65 rather than age 60 as allowed in study 20120178.

The exclusion criteria for 20120178 are mostly similar to study 20120295. Studies 20120296 and 20120297 allowed patients to be on one stable dose migraine prophylactic drug. However, studies 20120295 and 20120178 both excluded patients on those drugs.

Rationale for Dose Selection

The sponsor chose three dose levels of AMG 334 (7 mg, 21 mg, and 70 mg) for this phase 2 study with the intention to characterize the dose-response relationship and to aid in dose selection for the phase 3 studies.

CGRP receptor antagonist activity was evaluated by inhibition of the DBF increase induced by topical application of capsaicin in healthy volunteers. This capsaicin-induced DBF model has been used to demonstrate proof of pharmacological activity for small molecule CGRP antagonists (Sinclair et al. 2010). AMG 334 has demonstrated dose-dependent inhibition of capsaicin-induced DBF. The sponsor predicted that the middle dose of 21mg would be efficacious as that dose produces nearly maximal inhibition of capsaicin-induced DBF. The sponsor chose 70mg to be the high dose and expected it to be efficacious as well. The sponsor expected the low dose of 7 mg to be minimally efficacious and provide additional dose-ranging information to characterize the dose-response relationship. It was thought that the low dose might provide efficacy information on CGRP receptor binding dynamics at below receptor saturation levels.

Study Treatments

IP was administered monthly for 3 months (12 weeks) by subcutaneous injection. The doses in the study were placebo, 7mg, 21mg, and 70mg. During the double-blind treatment phase, three SC injections were given per IP administration. After completion of the DBTP, patients could continue treatment with open-label AMG 334 70mg SC every month. During open-label treatment only one SC injection was given per IP administration.

Assignment to Treatment

A patient was randomized to treatment for the double-blind treatment period if the patient met all the screening and baseline eligibility criteria. Randomization was stratified by region: North America versus all other locations.

Blinding

This was a double-blind placebo controlled trial. Patients, site personnel, and Amgen study personnel were blinded to the randomized treatment group assignment.

Dose modification/Dose discontinuation

The dosage for IP was fixed for all patients and could not be adjusted. At any time during the study, the investigator could discontinue the IP administration for any patient who experienced a severe or life threatening adverse events. Patients who permanently discontinued IP during the DBTP phase were to continue to return for all other study procedures until the end of the DBTP and the completion of the safety follow up visit.

Procedures and Schedule

The schedule of trial procedures and assessments is summarized in Table 38. I have modified this table from the sponsor's materials to include only key assessments.

Table 38 Schedule of Procedures and Assessments for Study 20120178

Period (duration)	Screening (3 weeks)	Baseline* (4 weeks)	Double-Blind Treatment Phase (12 weeks)					Safety follow up
			Day 1	Week 2	Week 4	Week 8	Week 12	
Vitals signs; adverse event recording; C-SSRS	x	x	x	x	x	x	x	x
IP administration			x		x	x		
ECGs	x		x		x	x	x	
Pregnancy testing	x	x	x		x	x	x	x
Chemistry and hematology	x		x		x	x	x	x
Anti-AMG 334 antibodies			x	x	x	x	x	x

*Randomization occurred after the completion of the baseline period.

Period (duration)	Open-label Treatment Phase*											Safety Follow up
	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	
Vitals signs; pregnancy testing; C-SSRS	x	x	x	x	x	x	x	x	x	x	x	x
IP administration	x	x	x	x	x	x	x	x	x	x	x	
ECGs	x	x		x			x				x	x
Pregnancy testing	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry and hematology	x	x		x							x	x
Anti-AMG 334 antibodies	x						x					x

*Note: Patients could enter the open-label treatment phase and receive AMG 334 70mg every four weeks for up to 256 weeks. After week 52, C-SSRS, adverse event recording, and pregnancy testing continued monthly. After week 52, vital signs were recorded every 3 months (12 weeks) and ECGs, chemistry, hematology, and anti-AMG antibodies were recorded every 6 months (24 weeks). The final safety follow up visit was 12 weeks after the last dose of IP was given.

Concurrent Medications

Please see study 20120295 section 6.3.1 for a description of concurrent medications.

Treatment Compliance

Treatment compliance was not measured in this trial. All doses of IP were administered in the clinic by the investigator or other authorized personnel.

Study Endpoints

Please see section 6.1.1 for the definition of migraine day used for defining a qualifying migraine for the primary endpoint. For the secondary endpoint in this study, the sponsor utilized the following definition for migraine attack:

Migraine Attack: An episode of any qualified migraine headache. The following rules were used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:
a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours will be considered as one attack and not two.
b) An attack treated successfully with medication but with relapse within 48 hours will be considered as one attack.

Primary Endpoint

The primary endpoint for this study is the change from baseline in monthly migraine days to the last four weeks of the 12-week double-blind treatment phase.

Secondary Endpoints

•At least a 50% reduction from baseline in monthly migraine days in the last four weeks of the 12-week double-blind treatment phase
•Change in monthly migraine attacks from baseline to the last four weeks of the 12-week double-blind treatment phase

Statistical Analysis Plan

Analysis Population

The full analysis set includes all patients who were randomized into the study. The efficacy analysis set includes patients in the full analysis set who received at least one dose of IP in the double-blind treatment phase and had ≥4 migraine days during the baseline phase. The per protocol set is a subset of the efficacy analysis set that includes patients who completed the 12-week double-blind treatment phase with no major protocol violations in their double-blind treatment phase only. For safety endpoints, all randomized patients who received at least one dose of IP were to be analyzed based on actual treatment received.

Stratification Factor

The study will be stratified by region: North America versus all other locations.

Baseline Covariates

- Age, region, race, sex
- Baseline monthly migraine days
- Baseline monthly migraine attacks
- Baseline monthly headache days
- Acute migraine medications used during the baseline phase
- Treatment with migraine prophylactic medication prior to entry
- Duration of disease

Hypothesis Testing

The original SAP states that the primary endpoint of the study will be tested for each of the 7mg, 21mg, and 70mg doses with two sided-significance level of 0.05 without adjustment for multiple testing. A later protocol amendment states that a sequential testing procedure was added to maintain the family-wise type I error at 0.05. The 21mg dose would only be tested if the 70mg dose is significant and the 7mg dose would only be tested if the 21mg dose is signifcant.

Null Hypothesis

In patients with episodic migraine, none of the AMG 334 treatment groups reduced from baseline the monthly migraine days compared to placebo

Alternative Hypothesis

In patients with episodic migraine, at least one of the AMG 334 treatment groups reduced from baseline the monthly migraine days compared to placebo

Statistical Methodology for Adjusting for Multiplicity

To maintain a type-I error of 0.05 for the primary endpoint, pairwise comparisons were tested in a sequential testing procedure against placebo in the following order: 70mg, 21mg, 7mg. The lower dose group would be tested only when the higher dose showed a statistically significant difference versus placebo.

Protocol Amendments

Two protocol amendments were made to the original protocol which was released on February 22, 2013. From the time of the original protocol to the time of the release of the first amendment, 100 patients had been enrolled. The first amendment was released on November 15, 2013. Inclusion and exclusion criteria were modified, and a closed testing procedure was added to control the family-wise error rate at 0.05 for the primary endpoint. After the first amendment was released, 383 additional patients enrolled.

A second protocol amendment was released on July 9, 2013, at which time all patients had already been enrolled. The second amendment extended the open-label treatment phase from 40 weeks up to 256 weeks. This allowed for the collection of long-term safety data beyond one year. The testing procedure for the primary endpoint was further refined.

The SAP to study 20120178 was amended on September 15, 2014. This amendment added a sequential testing procedure to control family-wise type I error at 0.05 for the primary endpoint.

Data Quality and Integrity: Sponsor's Assurance

The sponsor has stated that study centers were visited at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol, compliance with good clinical practice (GCP), and for accuracy of the data. Investigator staff training was provided by Amgen during investigator meetings, and routine monitoring visits. An independent audit of the study was conducted by Amgen's Global R&D Compliance and Audit Organization.

6.4.2. Study Results

Compliance with Good Clinical Practices

The sponsor asserts that this study was conducted in accordance with International Conference on Harmonization (ICH) GCP regulations, the GCPs applicable to the regions where the study was conducted, and in accordance with the ethical principles in the Declaration of Helsinki.

The sponsor asserts that the study protocol, amendments, and informed consent were reviewed and approved by an independent ethics committee (IEC) or an institutional review board (IRB) as appropriate for the country in which the study was conducted.

Financial Disclosure

Please see Appendix 13.2.

Patient Disposition

Randomized: 483 (placebo: 7mg: 21mg: 70mg: 140mg 160: 108: 103: 107)
Received 1 or more doses of IP: 472
Efficacy analysis set: 466
Per protocol analysis set: 421

The efficacy analysis set consisted of patients who received at least one dose of IP and had ≥ 4 migraine days during the baseline period.

The per protocol set was a subset of the efficacy analysis set consisting of patients who received the IP and did not have any important protocol deviations.

Protocol Violations/Deviations

There were 20 out of 483 randomized patients who had what the sponsor considered to be important protocol deviations. The most common protocol deviation was baseline migraine frequency outside of the specified range (7 patients). Of these 7 patients, 1 was in the placebo arm, 3 were in the 7mg arm, 2 were in the 21mg arm, and 1 was in the 70mg arm.

Table of Demographic Characteristics

There was a slightly higher percentage of male patients in the 70mg treatment group than in the placebo group (Table 39). There was a higher percentage of Hispanic patients in the placebo group than in the 70mg treatment group.

Table 39 Demographic Characteristics of All Randomized Patients for Study 20120178

Demographic Parameters	Placebo	Treatment Group		
	N=160 n(%)	7mg N=108 n(%)	21mg N=108 n(%)	70mg N=107 n(%)
Sex				
Male	28 (17.5)	20 (18.5)	21 (19.4)	24 (23.4)
Female	132 (82.5)	88 (81.5)	87 (80.6)	82 (76.6)
Age				
Mean years (SD)	41.4 (10)	40.3 (10.9)	39.9 (12.3)	42.6 (9.9)
Median (years)	42	40	42	43
Min, max (years)	18, 62	18, 60	18, 59	22, 59
Age Group				
18-40	71 (44.4)	55 (50.9)	49 (45.4)	42 (39.3)
41-55	78 (48.8)	46 (42.6)	47 (43.5)	56 (52.3)
56-62	11 (6.9)	7 (6.5)	12 (11.1)	9 (8.4)
Race				
White	143 (88.8)	97 (89.8)	100 (92.6)	103 (96.3)
Black or African American	13 (8.1)	10 (9.3)	7 (6.5)	2 (1.9)
Asian	2 (1.3)	0	1 (0.9)	1 (0.9)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0	0	0
Other or multiple	2 (1.3)	1 (0.9)	0	0
Ethnicity				
Hispanic or Latino	11 (6.9)	9 (8.3)	9 (8.3)	1 (0.9)
Not Hispanic or Latino	149 (93.1)	99 (91.7)	99 (91.7)	106 (99.1)
BMI (kg/m^2)				
Mean (SD)	25.9 (4.9)	27.0 (5.1)	25.9 (5.1)	25.8 (4.9)
Median	25.0	26.2	24.4	24.9
Min, Max	16.1, 47.4	18.3, 40.0	17.5, 40.0	14.8, 39.2
Region				
North America (USA/CAN)	85 (53.1)	58 (53.7)	58 (53.7)	58 (54.2)
Rest of the World	75 (46.9)	50 (46.3)	50 (46.3)	49 (45.8)

This table was created by the reviewer in JMP using the DM and VS SDTM datasets for study 20120178.

No baseline differences in disease severity or use of migraine medications were noted (Table 40).

Table 40 Other Baseline Characteristics for All Randomized Patients from Study 20120178

Baseline Characteristics	Placebo	Treatment Group		
	N= 160	7mg N=108	21mg N=108	70mg N=107
Disease Duration				
Mean in years (SD)	20.69 (11.5)	19.01 (11.4)	20.07 (12.5)	21.46 (11.7)
Median	21	17.5	19	19
Min, Max	2, 44.6	1, 41.3	1.1, 50	1.2, 53
Monthly Migraine Days				
Mean (SD)	8.77 (2.7)	8.62 (2.8)	8.93 (2.9)	8.58 (2.5)
Median	8.4	8	8.57	8
Min, Max	4.1, 17.2	0, 16.6	3, 16.6	3.9, 16.2
Monthly Headache Days				
Mean (SD)	9.8 (2.8)	9.8 (2.8)	10.1 (3.0)	9.9 (2.6)
Median	9.7	9.5	9.9	9.8
Min, Max	4.1, 18.3	0, 16.6	4, 19.4	3.9, 16.2
Treatment with prior migraine prophylactic medication				
Yes	66 (41.2)	47 (43.5)	45 (41.7)	47 (43.9)
No	94 (58.8)	61 (56.5)	63 (58.3)	60 (56.1)

The figures in this table were adapted from the sponsor's materials from the CSR for study 20120178. Some baseline figures were verified in JMP by the reviewer using ADaM dataset ADBASE.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was not assessed because the IP was administered by the investigator or other study authorized personnel.

The most frequently used concomitant medications were acute headache medications, which were used during the baseline and DBTP (Table 41). The two most commonly used categories of these medications were non-opioid acute headache medications, and triptan-based migraine medications.

Table 41 Most Commonly Used Concomitant Medications in Study 20120178

Medication Category	Placebo	Treatment Group		
	N=153	7mg N=108	21mg N=105	70mg N=106
Triptan-based	106 (69.3)	80 (74.1)	71 (67.6)	75 (70.8)
Non-opioid	109 (71.2)	84 (77.8)	82 (78.1)	83 (78.3)
Ergotamine	1 (0.7)	1 (0.9)	2 (1.9)	0
Opioid-based	7 (4.6)	6 (5.6)	3 (2.9)	5 (4.7)
Non-opioid containing butalbital	2 (1.3)	2 (1.9)	1 (1)	1 (0.9)
Opioid containing butalbital	0	1(0.9)	0	1 (0.9)

*These figures were taken from the sponsor's materials from the CSR for study 20120178. This table was created by the sponsor using the safety analysis set.

Efficacy Results - Primary Endpoint

The primary endpoint for this study is the change from baseline in mean monthly migraine days as compared to placebo. The mean monthly migraine days were calculated using the monthly migraine days from the last month of the three month DBTP. There was a statistically significant mean reduction in the change from baseline in 70mg dose as compared to placebo. There was no statistically significant difference between the 21mg dose and placebo; therefore, the 7mg dose was not tested for significance. The 70mg dose showed a -1.12-day reduction in number of MMDs as compared to placebo (Table 42). The treatment effect seen in the dose finding study was consistent with the results found in the phase 3 pivotal EM studies.

Table 42 Results for the Primary Endpoint for Study 20120178

	Placebo	Treatment Group		
	N=153	7mg N=107	21mg N=102	70mg N=104
***Baseline**				
N	153	108	105	105
Mean MMD (SD)	8.7 (0.2)	8.6 (0.3)	8.9 (0.3)	8.6 (0.2)
Mean of MMDs over month 3				

N	153	108	105	105
Mean (SE)	6.5 (0.4)	6.5 (0.4)	6.5 (0.4)	5.3 (0.4)
Median	5.8	6.4	6.1	4.5
Min, max	0, 23	0, 18.7	0, 20.2	0, 19
Change from baseline in mean over month 3				
N	153	108	105	105
Mean MMD (SE)	-2.2 (0.4)	-2.1 (0.4)	-2.4 (0.5)	-3.3 (0.4)
Median	-2.3	-2.1	-2.9	-3.5
Min, Max	-14, 11.2	-13, 6.8	-12.3, 12	-14.5, 10
Unadjusted difference from placebo in MMDs		0.11	-0.23	-1.09
****Adjusted analysis**				
LSM estimates	-2.3 (0.3)	-2.2 (0.4)	-2.4 (0.4)	-3.4 (0.4)
95% CI of LSM	(-2.9, -1.7)	(-2.9, -1.5)	(-3.1, -1.6)	(-4.1, -2.7)
Difference in LSM		**0.1**	**-0.1**	**-1.1**
95% CI of the difference		(-0.8, 1.1)	(-1.1, 0.9)	(-2.1, -0.2)
p-value		0.8	0.8	0.021

*Baseline figures and unadjusted figures were calculated by the reviewer using the ADAM datasets ADBASE and ADMONPRI in JMP from study 20120178.
**The adjusted analysis taken from the sponsor's materials is essentially the same as the unadjusted analysis. The adjusted analysis utilizes a generalized linear mixed model which includes treatment, visit, treatment by visit interaction stratification factors, and baseline values as covariates.

Data Quality and Integrity - Reviewers' Assessment

No major data quality and integrity issues were identified during the review of study 20120178.

Efficacy Results - Secondary and other relevant endpoints

The secondary endpoint change from baseline in monthly migraine attacks did not reach statistical significance. There was a numerically higher reduction in the number of monthly migraine attacks for the 70mg dose group as compared to placebo (-1.8 attacks for 70mg vs -1.4 attacks for placebo). The 7mg and 21mg dose groups were numerically less than placebo (-1.1 for the 7mg group and -1.4 for the 21mg group). Please see section 6.4.1 for the definition of monthly migraine attacks which differs from the definition of monthly migraine day.

The ≥50% response rate was statistically significant for the 70mg dose, but not for the lower doses (Table 43).

Table 43 Study 20120178: Results from Key Secondary Endpoint
Achievement of ≥50% Reduction in Mean Monthly Migraine Days from Baseline

	Placebo	Treatment Group		
	N=153	7mg N=107	21mg N=102	70mg N=104
Month 3				
≥50% Response n (%)	43 (29.9)	30 (28.8)	32 (34.4)	46 (46.5)
Difference in responder (Treatment less placebo)		-1.1	4.5	16.6
*NNT		N/A	22.2	6.0
**Adjusted Odds Ratio		0.93	1.25	2.0
95% CI		(0.53, 1.63)	(0.71, 2.18)	(1.17, 3.42)
p-value		0.80	0.44	0.011

* NNT was calculated by the reviewer.
**These figures were taken from the sponsor's materials for study 20120178.

Dose/Dose Response

This will be addressed in section 7.1.4.

Additional Analyses Conducted on the Individual Trial

The sponsor conducted some sensitivity analyses on the primary endpoint including last observation carried forward (LOCF) and a generalized linear mixed effect model for the per protocol analysis. The results for the sensitivity analyses (treatment effect ranging from -1.1 to -1.2-days reduction in MMD) were consistent with the planned analysis of the primary endpoint. The 7mg and 21mg doses again did not show a statistically significant result.

7 Integrated Review of Effectiveness

Design issues common to all three trials

All three pivotal studies and the dose-ranging study utilized a four-week baseline period prior to randomization to establish baseline migraine frequency, and ability to comply with the eDiary. The IHS guideline for controlled studies in migraine prophylaxis recommends at least a four-week baseline. Since migraine frequency can fluctuate greatly, a longer baseline might have provided a more stable estimate of the true baseline migraine frequency. The sponsor did

conduct a prospective assessment of baseline which may reduce the possibility of recall bias that retrospective data might incur.

Definitions of migraine days included both definite migraines, and probable migraines to be included in the analysis of the primary endpoint. This seems appropriate because all patients enrolled in the trial had to have an a priori diagnosis of migraine. Likely the headaches that did not have all features of migraine are in fact truly migraines in patients who have that diagnosis.

Various methods of imputation were used in sensitivity analyses to evaluate the effect of missing data (i.e., last observation carried forward, multiple imputation assuming missing at random or missing not at random). A treatment effect was seen consistently across all the studies, and all the methods of imputation for missing data.

7.1. Assessment of Efficacy across Trials

7.1.1. Primary Endpoints

For all three studies (20120295, 20120296, and 20120297), the primary endpoint was reduction from baseline in the number of monthly migraine days compared to placebo. The studies differed primarily in the doses, length of treatment, stratification factors, and time point at which the primary endpoint was measured (Table 44). The treatment effect measured in each of the three efficacy studies was statistically significant (Table 45).

Table 44 Differences in the Analysis of the Primary Endpoint amongst the Three Studies

Study	Population/ Randomization	Length of DBTP	Measurement of Primary Endpoint	Doses Studied	Stratification Factors
20120295	CM; 18-65; 3:2:2	3 months	Measured over last 4 weeks of DBTP	70mg, 140mg	Region and medication overuse (Y/N)
20120296	EM; 18-65; 1:1:	6 months	Measured over last 3 months of DBTP	70mg, 140mg	Region and treatment with migraine prophylaxis*
20120297	EM; 18-65; 1:1	3 months	Measured over last 4 weeks of DBTP	70mg	Region and treatment with migraine prophylaxis*

*Treatment naïve vs current/prior use

Table 45 Summary of Findings for the Primary Endpoint amongst the Three Pivotal Efficacy Studies

Study	Baseline MMD in days	Change from Baseline (days)			Difference from PBO (days)	
		PBO	70mg	140mg	70mg	140mg
20120295	~18	-4.2	-6.6	-6.6	-2.5	-2.5
20120296	~8	-1.8	-3.2	-3.7	-1.4	-1.9
20120297	~8	-1.8	-2.9	N/A	-1.0	N/A

Sponsor's data summarized from the CSRs of all three studies.

For all three studies, there was a statistically significant difference in change from baseline of MMDs for the 70mg dose. In addition, studies 20120196 and 20102095 demonstrated a statistically significant difference in change from baseline in MMDs for the 140mg dose as well. The treatment effect in these four studies ranged from a -1.0 to -2.5-day reduction in MMDs as compared to the reduction seen in placebo. On average patients experienced a 1 to 2.5-day reduction in the number of migraine headaches per month when subtracting out the effect of placebo. This finding is in line with what has been seen and accepted for approval in other development programs for migraine prophylaxis. The treatment effect seen in divalproex, and topiramate ranged from a 1.0 to 2.2-day reduction in monthly migraine days. In the FDA approved label for onabotulinumtoxinA, (b) (4)

In my view, because 70mg is the lowest effective dose, it should be primarily considered for approval while 140mg should be considered as potentially approvable if there is adequate efficacy data showing additional benefit for the 140mg dose without additional safety concerns. Analyses on the primary endpoint of the two studies that included the 140mg dose show a very similar effect size for the 70mg dose and the 140mg dose. In fact, the measured treatment effect of each dose falls within the confidence interval of the other dose. The studies were designed to show superiority of each dose over placebo and not over each other; therefore, on a purely pre-specified statistical basis one cannot say that 140mg is superior to 70mg. However, in reviewing the data presented, I looked for situations where certain groups of patients could potentially have more benefit from the 140mg dose over the 70mg dose (with the caveat that these analyses were post hoc, and not in keeping with the statistical analysis plan of the study). I did analyses by BMI, and baseline frequency of migraine days to look for a group that might benefit from a higher dose.

I looked at patients who are obese (BMI≥30 kg/m²) and a subset of that group, the morbidly obese (BMI ≥40 kg/m²) from study 20120296. The change from baseline in MMDs was essentially the same for all three arms of the study indicating that there was no additional benefit of 140mg in the obese or morbidly obese. In fact, obesity was associated with a markedly reduced treatment effect for both dose groups. (See section 7.1.3 for further discussion on BMI). In the EM and CM studies that included a 140mg dose, I looked at patients with baseline more 'severe' disease. In study 20120295 (CM) I analyzed patients whose baseline number of MMDs were ≥18, ≥20, and ≥25 (Tables 46 through 48) and patients in study 20120296 (EM) who had ≥ 12 MMDs at baseline. Patients who had a baseline number of MMDs ≥25 had a much greater change from baseline, and difference from placebo than what was seen in the overall study. In study 20120296, the treatment effect for 70mg and 140mg were similar for patients with ≥12 MMDs at baseline. For study 20120295, these numbers should be looked at cautiously because the number of patients is small, and this is a post hoc subgroup analysis. Patients with ≥25 MMD at baseline have a smaller degree to which they can worsen (i.e., maximum number of MMDs per month is 28, so there is more room for improvement then for worsening).

Table 46 Study 20120295: Patients with ≥18 MMDs at Baseline (Primary Endpoint)

	Placebo N=149	70mg N=91	140mg N=91
Change from Baseline in Days	-4.9	-6.7	-7.7
Difference from PBO in Days	-	-1.9	-2.4

Table 47 Study 20120295: Patients with ≥20 MMDs at Baseline (Primary Endpoint)

	Placebo N=103	70mg N=57	140mg N=55
Change from Baseline in Days	-5.0	-6.4	-8.1
Difference from PBO in Days	-	-1.4	-3.1

Table 48 Study 20120295: Patients with ≥25 MMDs at Baseline (Primary Endpoint)

	Placebo N=27	70mg N=16	140mg N=17
Change from Baseline in Days	-3.7	-4.3	-9.4
Difference from PBO in Days		-0.6	-5.8

Tables 46, 47, and 48 are reviewer calculated using dataset ADMONPRI from study 20120295 where PARAMCD=MMD, and AVISIT=WEEK 12, and BASE≥18 or BASE≥20 or BASE≥25. Analysis done of CHG by TRT01AN

Reviewer Comment: In summary, both 70mg and 140mg are effective doses for migraine prophylaxis. They have similar, and I would argue almost identical efficacy. The post hoc subgroup analysis described above suggest that patients with more severe disease (i.e., those with almost daily migraine) may benefit from the use of the 140mg dose as compared to the 70mg dose. This analysis should be looked at very cautiously because patients with nearly daily migraines can stay the same or improve, but they have a ceiling on how much they can worsen.

7.1.2. Secondary and Other Endpoints

All three studies included the secondary endpoint ≥ 50% reduction from baseline in monthly migraine days. Studies 201201296 and 20120297 include secondary endpoints related to the MPFID (b) (4)

Table 49 Differences in the Secondary Endpoints amongst the Three Efficacy Studies

Study	Secondary Endpoints			
20120295	≥ 50% reduction from baseline in monthly migraine days	Change from baseline in acute migraine specific medication treatment days	Change from baseline in cumulative headache hours*	
20120296	≥ 50% reduction from baseline in monthly migraine days	Change from baseline in acute migraine specific medication treatment days	Change from baseline in mean monthly average physical impairment domain scores	Change from baseline in mean monthly average impact on everyday activities domain scores
20120297	≥ 50% reduction from baseline in monthly migraine days	Change from baseline in acute migraine specific medication treatment days	Achievement of at least a 5-point reduction from baseline on average physical impairment domain scores*	Achievement of at least a 5-point reduction from baseline on average impact on everyday activities domain scores*

*These endpoints did not reach statistical significance.

At least 50% reduction from baseline in MMDs

For all three studies, the secondary endpoint for the 50% responder rate was statistically significant (Table 50). The number needed to treat for one person to achieve a 50% reduction in the number of MMD ranged from 6 to 10 for the 70mg dose, and ranged from 4 to 6 for the 140mg dose. These calculations can be found in sections 6.1.2, 6.2.2, 6.3.2, and 6.4.2 (study results).

Table 50 Secondary Endpoint: At least 50% Reduction from Baseline in MMDs

Study	**% of patients achieving at least 50% reduction from baseline in MMD**			**Difference from PBO (%)**	
	PBO	**70mg**	**140mg**	**70mg**	**140mg**
20120295 Odds ratio 95% CI p-value	23.5	39.9 2.2 (1.5, 3.3) <0.001	41.2 2.3 (1.6, 3.5) <0.001	16.4	17.7
20120296 Odds ratio 95% CI p-value	26.6	43.3 2.1 (1.5, 3.0) <0.001	50.0 2.81 (2.0, 3.9) <0.001	16.7	23.4
20120297 Odds ratio 95% CI p-value	29.5	39.7 1.6 (1.1, 2.3) 0.010	N/A	10.2	N/A

*This data is summarized from the sponsor's materials from the corresponding CSR.

Change from baseline in acute migraine specific medication treatment days

Across the studies patients are reducing their use of migraine specific medication (triptan or ergotamine) by approximately 0.5 to 2.5 days per month compared to placebo which is consistent with the findings from the primary endpoint (Table 51).

Table 51 Secondary Endpoint: Acute Migraine Specific Medication Treatment Days

Study	Baseline use in days	Change from Baseline (days)			Difference from PBO (days)	
		PBO	70mg	140mg	70mg	140mg
20120295 95% CI p-value	~9-10	-1.6	-3.5	-4.1	-1.9 (-2.6, -1.1) <0.001	-2.6 (-3.3, -1.8) <0.001
20120296 95% CI p-value	~3	-0.2	-1.1	-1.6	-0.9 (-1.2, -0.6) <0.001	-1.4 (-1.7, -1.1) <0.001
20120297 95% CI p-value	~3-4	-0.6	-1.2	N/A	-0.6 (1.0, -0.2) 0.002	N/A

*This data is summarized from the sponsor's materials from the corresponding CSR.

Change from baseline in cumulative headache hours

This secondary endpoint was measured in the chronic migraine study 20120295 only. Patients in the 70mg and 140mg groups had a larger reduction in cumulative headache hours, but this finding was not statistically significant after adjustment for multiple comparisons (p-value 0.28 for the 70mg dose, and 0.030 for the 140mg dose). Patients on placebo had a reduction of about 55 hours, 70mg had about a 65-hour reduction, and 140mg had about a 75-hour reduction in cumulative headache hours.

Reviewer Comment: These findings are unexpected because 70mg and 140mg had about the same reduction in MMDs, but 140mg had a larger reduction in cumulative headache hours than 70mg. It is also interesting to note that while the difference from placebo in MMD is about 2.5 days, there is only a 10 to 20-hour reduction from placebo in total headache hours. I speculate this difference may be related to the way a migraine day was measured for the primary endpoint. Days with use of migraine specific medication would count as a migraine day. On those days, presumably the number of migraine hours would be short. It might be hard to detect a treatment difference in cumulative hours of migraine if there were many days where the migraine was shortened in length due to the use of acute migraine medication.

Secondary endpoints related to MPFID

The sponsor is seeking labeling claims in regards to the MPFID. I have reproduced a portion of the proposed Table 4 from the proposed label (Table 52). Although the results of the MPFID secondary endpoints in study 20120296 reached statistical significance (Table 52), I do not believe they are clinically meaningful (b) (4) During IND

development, (b) (4) During development, the Division in conjunction with the COA staff expressed concerns that the proposed point changes were not large enough to be considered clinically meaningful. As discussed in the study results (6.1.2 and 6.2.2), (b) (4) When study 20120297 was analyzed, the responder definition did not meet statistical significance. The between-group response did not meet the previously proposed (b) (4) which the Division felt was (b) (4) during prior IND discussions.

(b) (4)

(b) (4)

7.1.3. **Subpopulations**

The sponsor performed subpopulation analyses on pooled data from studies 20120296, 20120297, and 20120178. The CM study was not included in the pooled analysis. This data provides an efficacy overview of the 70mg dose for up to 3 months of treatment. The sponsor used only the first three months of data from study 20120296 in the pooled data.

Analyses Pooled by Age

The sponsor conducted the pooled analyses by age using subgroups ≥median age or <median age. The treatment effect was consistent in the two groups (-1.3 and-1.0). I did my own analyses by age group as well. I did not include study 20120178 in these analyses because this study only included patients up to age 60 where the other two studies both included patients up to age 65.

Table 54 Pooled Analyses of Studies 20120296 and 20120297 by Age on the Primary Analysis

	Placebo		70mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
18-40	275	-1.7	259	-2.9	-1.1
41-55	252	-1.7	270	-3.3	-1.5
56-65	82	-2.4	73	-2.0	+0.4

Reviewer calculated using ISE dataset ADMONPRI where PARAMCD=MMD, and AVISIT=WEEK 12, evaluating CHG by TRT01PN

Baseline number of migraine days in the age 56-65 group was 8.5 days which is the same as what is seen in the overall population. It appears that there is no treatment effect in patients who are 56 years of age and older for the 70mg dose. This is a post hoc analysis with a small sample size, but the findings are interesting. Because of this finding, I looked at the two studies separately by age group to see if one of the studies was driving this finding (Appendix Tables 123 and 124). Both studies showed the same trend, that those over age 56 had a +0.4 to 0.5-day treatment effect in favor of placebo. I also analyzed study 20120295 in the same manner and found a similar finding that the treatment effect was in favor of placebo for the patients in the over age 56 age band (Appendix Table 122).

I was unable to perform a pooled analysis of the 140mg dose because only one of the EM studies included this dose (i.e., study 20120296). However, analysis of the age bands in study 20120296 for the 140mg dose shows that the 140mg dose maintains a favorable treatment effect over placebo for all three age bands (Appendix Table 123).

I also looked at age group by quartiles (Appendix Tables 125 through 128). In this analysis, the age groups were 18-33, 34-42, 43-50, and 51-65. The pooled analyses of studies 20120296 and 20120297 continued to show a markedly reduced treatment effect for the 70mg dose in the oldest age group (51-65). The analysis of the three individual studies (20120295, 20120296, and 20120297) by quartile continued to show a markedly reduced treatment effect in the older age group for the 70mg dose. The reduction was not as dramatic as the original analysis I have presented (Table 54), presumably due to the inclusion of younger patients into the uppermost quartile as compared to my original analysis.

Analyses Pooled by Sex

I analyzed the pooled ISE dataset for the primary endpoint by sex and I analyzed each of the four studies separately as well by sex. The pooled dataset only includes the EM studies and is inclusive of 20120178. There is a reduced treatment effect in the male subpopulation seen in the pooled data (Table 55) and across all three individually analyzed EM studies. For the CM study, the treatment effect in males is reduced to -1.4 days (compared to -2.5 days for the planned primary analysis). For females, across studies and in the pooled analysis, the treatment effect is consistent with what is seen in the primary planned analysis.

Table 55 Analysis of the Primary Endpoint Pooled by Sex

	Placebo		70mg		
Sex	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
Female	652	-1.8	595	-3.0	-1.2
Male	117	-2.4	113	-2.7	-0.3

Reviewer calculated using ISE dataset ADMONPRI where PARAMCD=MMD, and AVISIT=WEEK 12, evaluating CHG by TRT01PN (includes studies 20120178, 20120296, 20120297)

Analyses Pooled by Race/Ethnicity

The treatment effect in the white and Asian populations is consistent with the treatment effect seen in the planned analysis of the primary endpoint. In the black population, the treatment effect is in favor of placebo in the pooled analysis (Table 56). Overall, however, there are likely too few patients in these subgroups to make an adequate assessment of efficacy.

Table 56 Analysis of Primary Endpoint Pooled by Race

	Placebo		70mg		
Ethnicity	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
White	677	-1.6	641	-2.9	-1.3
Black	64	-3.9	50	-3.2	+0.8

Asian	10	-2.6	8	-3.7	-1.2

Reviewer calculated using ISE dataset ADMONPRI where PARAMCD=MMD, and AVISIT=WEEK 12, evaluating CHG by TRT01PN (includes studies 20120178, 20120296, 20120297)

Analyses by Body Mass Index (BMI)

Patients with a BMI greater than 40 kg/m² were excluded from study 20120295, but were not excluded in study 20120296 or study 20120297. In study 20120296, the sponsor conducted an analysis of the primary endpoint by looking at patients less than the median BMI (25.9 kg/m²) compared to those who were ≥ 25.9 kg/m². For patients who were less than the median BMI, treatment effect was -2.2 days for 70mg (95% CI -2.9, -1.5) and -2.9 days for 140mg (95%CI -3.5, -2.2). For patients who were greater than the median BMI, treatment effect for 70mg was -0.6 days (95% CI -1.3, 0.1) and -0.8 days for 140mg (95% CI -1.5, -0.1). I conducted a separate analysis on patients who were obese (BMI≥ 30 kg/m²). Again, this showed a reduced (nearly absent) treatment effect in patients with higher BMI. Treatment effect for 70mg was 0.06 days and for 140mg it was 0.14 days in patients who were obese (BMI≥30 kg/m²). Overall, in the episodic migraine studies, the efficacy appears to be reduced in those with greater than the median BMI and absent for those who are obese. For those who are obese, the point estimates for both doses is quite low (0.1 days reduction in MMD). There is no clear advantage to the 140mg dose in those of higher than median BMI or those who are obese.

Similar findings occurred in study 20120297. Patients with BMI less than the median BMI (26.0 kg/m²) had a treatment effect of -1.8 days while those patients with a BMI ≥ the median BMI had almost no treatment effect (-0.3 days with 95%CI of -1.1, 0.5). I calculated the treatment effect in obese patients (BMI≥30 kg/m²) and difference from placebo was essentially zero in this study.

In study 20120295 (CM), the treatment effect in patients with greater than the median BMI (25.4 kg/m²) was not reduced as it was in studies 20120296 and 20120297. In patients with less than the median BMI, treatment effect was -2.3 days for 70mg (95% CI -3.8, -0.7) and -2.5 days for 140mg (95% CI -4.0, -0.9). In those with greater than the median BMI, the treatment effect was -2.8 days for 70mg (95% CI -4.4, -1.3) and -2.5 days for 140mg (95% CI -4.0, -1.0). I did a similar analysis on 20120295 as I did on study 20120296 on patients who had a BMI≥30 and did not find a diminished treatment effect related to obesity. The reason for this finding is unclear.

Pooled data for studies 20120296, 20120297, and 20120178 show a mean BMI of 27.0, and median 25.7 (reviewer calculated). For the 70mg dose the treatment effect for those with less

than the median BMI was -1.8 (-2.3, -1.2). For those patients with ≥ median BMI, the treatment effect was -0.5 (-1.0, -0.02). Again, showing a markedly reduced treatment effect for those with greater than the median BMI.

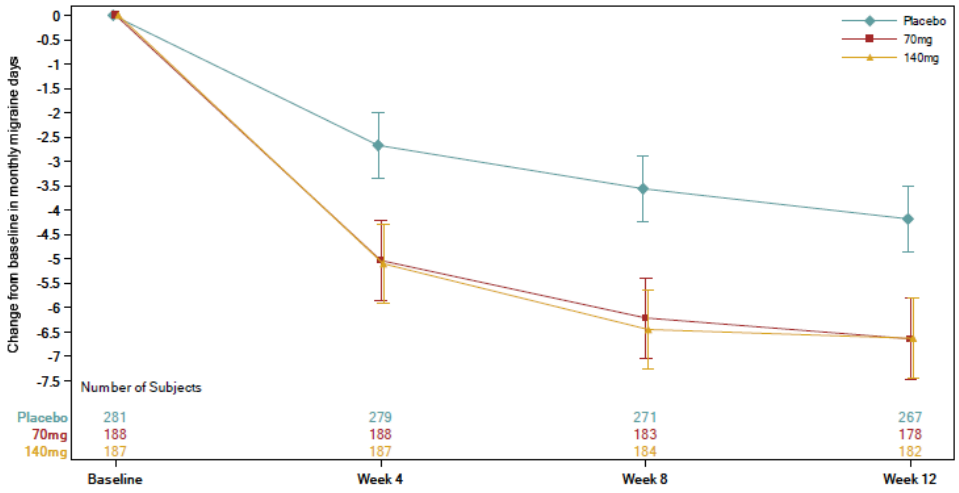
BMI analyses are also presented by quartile in the Appendix Tables 129 through 132. The quartiles roughly correspond to the clinical designations of overweight and obese. These tables are presented to show that the highest BMI has diminished to absent treatment effect compared to placebo even when there are roughly equal numbers of patients in treatment and placebo groups.

Reviewer Comment: According to the National Center for Health Statistics (November 2015), approximately 70% of the population is overweight (BMI≥25) and 36.5% of the U.S. population is obese (BMI≥30 kg/m²). Overweight and obesity is somewhat underrepresented in the sponsor's studies, and not reflective of the U.S. population. This is problematic because the treatment effect in the episodic migraine studies is markedly reduced in patients with BMI greater than the median and the treatment effect is nearly absent in patients who are obese. It is not clear why this trend does not hold true in the chronic migraine study (20120295).

7.1.4. Dose and Dose-Response

The sponsor has proposed marketing of the 140mg dose of erenumab to be given in two injections of 70mg SC monthly. There are two studies that include the 140mg dose are 20120295 and 20120296. Four studies include the 70mg dose. In study 20120295 (CM), both the 70mg and 140mg dose had a statistically significant reduction in monthly migraine days, but no dose-response was observed (Figure 10). For study 20120296, there was a numerical improvement in the 140mg dose group as compared to the 70mg dose group, but confidence intervals were overlapping (Figure 11) suggesting limited to no dose response.

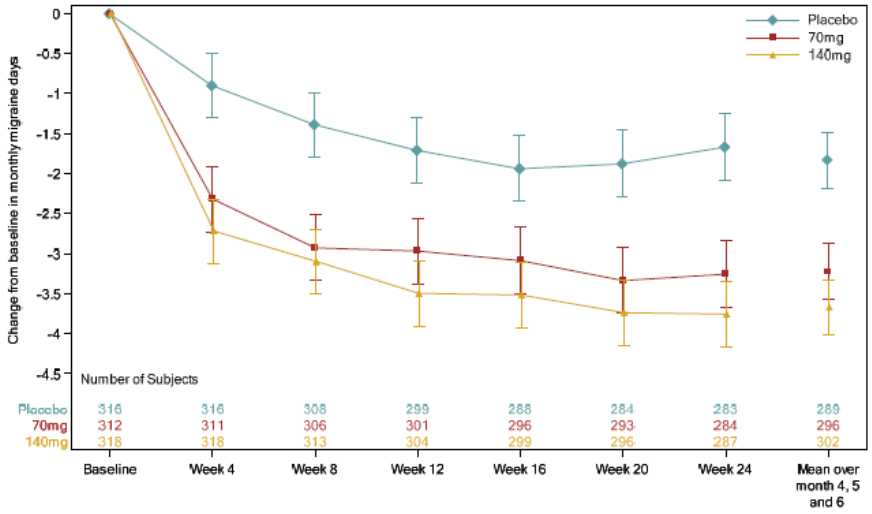
Figure 10 Least Squares Mean Changes from Baseline in MMDs for Study 20120295



Adjusted least square means and 95% confidence intervals from the primary analysis model are presented.

This figure is taken from the sponsor's materials in the ISE: 14-4.6.401

Figure 11 Least Squares Mean Changes from Baseline in MMDs for Study 20120296



Adjusted least squares means and 95% confidence intervals from the primary analysis model are presented. Week 24 data reflect the least squares mean change from baseline during the last 4 weeks of the double-blind treatment phase (ie, weeks 21 through 24).

This figure was taken from the sponsor's materials in the ISE: 14-4.6.404

7.1.5. Onset of Efficacy Effects

Onset of Effects: Study 20120296 and Study 20120295

Table 13 from section 6.1.2 and table 33 from section 6.3.2 show that the effect of erenumab seems to be apparent after the first dose in both study 20120296 (EM study) and 20120295 (CM study). The reduction in MMDs for both the 70mg and 140mg is evident at the end of month 1 (week 4) and is comparable to the findings from the primary analysis.

Other

Immunogenicity and efficacy: The overall rate of neutralizing antibodies in the ISS was 0.7% (17 patients). Generally, the neutralizing antibodies are the ones that may affect the efficacy of the product; however, there were too few patients who developed neutralizing antibodies to conduct an analysis or make any definitive conclusions about efficacy. During the review process, concerns arose about the lack of sensitivity of the cell-based assay of detecting neutralizing antibodies. To see if there was an effect of ADA development on efficacy, I analyzed all patients who developed any ADAs at any point during treatment with erenumab. I analyzed the double-blind period of all the studies that included a 70mg dose. I analyzed the CM study separately from the three EM studies (Table 58). In the DBTP for all four studies combined there were 94 patients who developed ADAs (Table 57) of which only 69 were on relevant doses (70mg or 140mg). I calculated the change from baseline in MMDs at week 12 for the CM study, and for the combined studies for patients who developed ADAs.

Table 57 Patients Developing ADAs in the DBTP

ADAs	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)	All doses N=1613 n(%)
Positive	25 (11.7)	56 (6.4)	13 (2.6)	94 (5.9)

Reviewer created table from dataset ADAB where APERIOD=1, BASETYPE=DOUBLE-BLIND, AVALC=POSITIVE analysis by TRT01AN

Table 58 Change from Baseline in MMD for Patients Developing ADAs

	Change from baseline in days			Difference from PBO (days)	
	PBO	70mg	140mg	70mg	140mg
20120295	-4.1 (N=282)	-7.6 (n=11)	-9.0 (n=3)	-3.1	-4.8
20120178, 20120296, 20120297	-1.9 (N=769)	-2.9 (N=45)	-4.5 (N=10)*	-1.0	-2.6

Reviewer created table from ISS dataset ADAB where APERIOD=1, BASETYPE=DOUBLE-BLIND, AVALC='positive' join by ADMONPRI (study 20120295) or ISE dataset ADMONPRI (where APERIOD=1, AVISIT=Week 12) analysis of CHG by TRT01PN
* 20120296 only

Reviewer Comment: With the limited data available, it appears that a treatment effect remains in patients who developed ADAs at some point during treatment with erenumab. However, this data should be interpreted very cautiously because there are very few patients to make any definitive comments on the efficacy of the drug in patients who have developed ADAs. With this limited data, I do not think the presence or absence of ADAs can guide clinical decision making. If a patient does not respond to treatment with erenumab, the drug should be discontinued regardless of the presence or absence of ADAs.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The sponsor attempted to capture the population that will most likely benefit from the use of erenumab. However, there are few issues that may arise in the postmarketing setting when the drug becomes more widely available that were not captured in the development program. The development plan only included patients up to age 65. There are no data available to inform on the efficacy and very little data to inform on the safety of the product in patients ages 65 to 75. There are also no data available to inform on the efficacy or safety of the product in the elderly population defined by the *Guidance for Industry: E7 Studies in Support of Special Populations: Geriatrics* as the population 75 and older. Some of the subgroup analyses I have presented by age suggest that there is reduced efficacy in the older age population (age 55-65) which in turn suggests that there may be reduced efficacy in patients older than age 65. This could potentially alter the risk-benefit profile in patients over age 65.

As discussed in the individual study results, approximately half of the data in this development

program was collected in foreign countries. As a result, the percentage of Hispanics and blacks in the studies does not reflect the percentages in the U.S. population. It is unknown at this point if differences in ethnicity or race affect the efficacy or safety of this product.

In the clinical studies, except for the clinical home use sub-study, all doses were administered in the clinic by a medical professional. This means that patients who came for their study visits were 100% compliant with their treatment as treatment did not need to be taken in between study visits. This type of compliance is unlikely to occur in a real-world setting and may potentially have a negative effect on efficacy. On the other hand, there is a reasonable expectation that compliance may be overall improved relative to other migraine prophylaxis medications as the patients only need to use this product once a month rather than daily.

Another area in which there is limited to no data is the use of this product in patients who are already taking a prophylactic medication. In the chronic migraine study, patients were excluded from the study if they were taking prophylactic medication. The sponsor added a protocol amendment during development to allow patients taking prophylactic medication to enter the episodic migraine studies (20120296 and 20120297); however, the amendment was added very late so in reality very few patients on prophylaxis entered the studies. In the postmarketing setting, it is reasonable to expect that many people who will be prescribed erenumab will already be taking a prophylactic medication for migraine. There is no data at this point to show that adding this agent will or will not provide additional efficacy in patients who are already taking a prophylactic medication.

Finally, as detailed in section 7.1.3, patients who are overweight (BMI≥25 kg/m^2) have reduced treatment effect, and patients who are obese (BMI≥30 kg/m^2) show nearly no evidence of a treatment effect from erenumab in the episodic migraine studies. This will be problematic in the U.S. population where according to the National Center for Health Statistics, 70.7% of adults age 20 and over have a BMI ≥25 kg/m^2.

7.2.2. Other Relevant Benefits

Erenumab is given by injection once monthly. This type of dosing regimen may be desirable to some patients who have difficulty remembering to take medication daily or twice daily. It is possible that this type of regimen may increase compliance.

7.3. Integrated Assessment of Effectiveness

The sponsor has submitted enough evidence to meet the statutory evidentiary standard. Studies 20120295, 20120296, and 20120297 all provide evidence that 70mg is an effective dose for the preventive treatment of migraine. All three pivotal studies and the dose-ranging study show that 70mg reduces the number of monthly migraine days as compared to placebo in

patients who have a diagnosis of migraine. The primary endpoint and several key secondary endpoints all consistently show that 70mg is an effective dose. Studies 20120295 and study 20120296 additionally show that 140mg is an effective dose.

In aggregate, the studies show that erenumab reduces the number of monthly migraine days by 1 to 2.5 days when the placebo effect is subtracted out. This degree of treatment effect has been established and accepted in prior development programs (i.e., topiramate, valproic acid, propranolol). Those patients with episodic migraine may be able to appreciate a one to two-day per month reduction in monthly migraine days. That potentially translates to fewer days of disability, and reduced need for acute medications which have their own short and long-term side effects. For those patients with chronic migraine, the clinical meaningfulness is less clear. A two to three-day reduction per month in migraines may be harder for patients to appreciate when they are experiencing near daily migraines. However, in prior development programs (i.e., onabotulinumtoxinA) a 1.5 to 2.5-day reduction compared to placebo has been accepted for chronic migraine.

8 Review of Safety

8.1. Safety Review Approach

The safety review includes studies 20120178, 20120295, 20120296, 20120297, and 20130255 (open label extension study for 20120295). There is also discussion of study 20140254 (treadmill study). This study is not included in the sponsor's pooled data. The sponsor has defined the safety population as any patient who received one or more doses of investigational product from studies 20120178, 20120295, 20120296, 20120297, and 20130255.

Table 59 Clinical Studies Contributing to the Integrated Analysis of Safety

Study/ Data Lock	Dose	Patients in double-blind safety set	Patients in open-label safety set
20120178/ Sept 1, 2016	Placebo, 7mg, 21mg, 70mg	Total: 472 7mg: 108 21mg: 105 70mg: 106 Placebo: 153	Total: 383 70mg: 383 Switch to 140mg: 225

20120295/ complete 20130255/ Jan 23, 2017	Placebo, 70mg, 140mg	Total: 660 70mg: 190 140mg: 188 Placebo: 282	Total: 609 70mg: 549 140mg: 259 70mg only: 350 Switch to 140mg: 199 140mg only: 60
20120296/ Jan 19, 2017	Placebo, 70mg, 140mg	Total: 952 70mg: 314 140mg: 319 Placebo:319	Total: 845 (70mg or 140mg)
20120297/ July 11, 2016	Placebo, 70mg	Total: 572 70mg: 283 Placebo: 289	70mg: 538

The safety analyses from the phase 2 and 3 studies in this BLA are presented by the sponsor in four pools. DNP and Amgen discussed and agreed upon the safety data pools during the pre-BLA meeting. These four pools are as follows:

Pool A: 12-week, placebo-controlled pool consisting of data collected in the first 3 months of the double-blind, placebo-controlled phases from studies 20120178, 20120295, 20120296, and 20120297 with 1613 patients exposed to erenumab.

Pool B: 24-week, placebo-controlled pool from the double-blind phase of study 20120296 with 633 patients exposed to erenumab.

Pool C: 70mg or 140mg from first dose through to the data cut-off (including double-blind and open label extension phases) with 2499 patients exposed to erenumab.

Pool D: patients with continuous exposure to 70mg or 140mg for a minimum of 1 year through the data cut-off with 1198 patients exposed to erenumab.
In this review, I summarize information from the sponsor's materials, and supplement them with analyses that I conducted using data provided in the Summary of Clinical Safety (SCS), Integrated Summary of Safety (ISS), 120-Day Safety Update, and sponsor provided datasets. The sponsors datasets were initially analyzed by the Office of Computational Science (OCS) JumpStart team. The analyses that I performed were carried out using the sponsor provided datasets in the JMP software program. For the adverse event section in this review, I focus on events reported from all the migraine studies to identify commonly reported events and infrequent events of potential concern. I present data from controlled phases of migraine studies to identify relative differences in risk by treatment for drug relatedness.

Certain analyses that I conducted used the sponsor's identified pools described above. At other times, I utilized a reviewer defined pool such as the entire double-blind treatment period, or the open-label treatment period. I utilized all the data obtained in studies 20120178, 20120295, 20120296, and 20120297 during the blinded portion of the treatment. This includes the full 6 months of safety data obtained in study 20120296. The sponsor's Pool A only included three months of data from study 20120296 which is a 6-month study. To conduct an analysis on the entire DBTP, I identified the DBTP by utilizing the variable APERIOD where period 1 was the DBTP for all the studies in the ISS, and periods 2 and 3 were the open-label treatment periods. I have noted throughout the safety review when I am using a sponsor created pool or the entire DBTP.

All four of the studies had a 70mg arm, but only two of the studies had a 140mg arm. For most the tables, I report on the combined data of all four studies in the ISS including a combined placebo group. At times, I conducted an evaluation of study 20120295 combined with study 20120296 which each have a 140mg arm to ensure that the comparison to placebo is consistent.

Anticipated areas of interest for the safety review

The safety concerns that are theoretically associated with CGRP inhibition are cardiovascular, cerebrovascular, peripheral vascular, and gastrointestinal. CGRP is a potent vasodilator. The theoretical concern is that CGRP receptor antagonism during times of ischemia may prevent compensatory vasodilatation from occurring. Another potential safety concern is hepatic injury. This concern has arisen with small molecule CGRP receptor inhibitors. Drugs from the 'gepant' class of CGRP receptor antagonists have been reported to cause elevated liver enzymes in the setting of daily use (Yao et al). There are general safety concerns associated with injectable products and with monoclonal antibodies such as immunogenicity, hypersensitivity, and injection site reactions.

8.2. Review of the Safety Database

At the time of the data cut-offs to support the filing, 3150 subjects have received at least one dose of erenumab. Patients in the phase 2 and 3 studies were exposed to 7mg, 21mg, 70mg, and 140mg with the majority of the exposures being to the 70mg dose. Amgen is seeking approval of the 140mg dose given as two 70mg SC injections. Overall a total of 2537 patients have been exposed to at least one dose of erenumab exclusive of healthy volunteers. Of these 2537 patients, 2128 have been exposed to 70mg at any time and 1198 have been exposed to 140mg at any time.

8.2.1. Overall Exposure

Table 60 Safety Population, Size, and Denominators for Erenumab Across Studies

Safety Database for Erenumab		
Clinical Trial Groups	Erenumab (n=3150)	Placebo (n=1085)
Healthy Volunteers	613	42
Controlled trials for migraine*	1613	1043
Uncontrolled trials for migraine**	924	0
Pool A	1613	1043
Pool B	633	319
Pool C	2499	0
Pool D	1198	0

The data in this table is taken from the sponsor's material: ISS table 14-5.4.1
*Studies 20120178, 20120295, 20120296, and 20120297
**These patients are the placebo patients from the controlled studies who switched to erenumab in the open label phases of studies 20120178, 20120295, 20120296, and 20120297.

Table 61 Overall Extent of Continuous Exposure to Erenumab

	Number of patients exposed to erenumab:			
	≥3 months	≥6 months	≥12 months	≥18 months
Dose	N=	N=	N=	N=
Any dose	2392	2066	1213	291
70mg	1969	1598	682	287
140mg	1067	768	134	0

Note: Patients who have received more than one dose of erenumab may be counted more than once according to the extent of exposure they have received of the dose. For example, if a patient received 6 months of 70mg and 6 months of 140mg, that patient will be counted in both the 70mg and 140mg under the >=6 months column. The data in this table is taken from the sponsor's materials in the Summary of Clinical Safety (SCS).

According to the sponsor, the mean duration of exposure to any dose of erenumab was 47.5 weeks. There has been significantly more exposure to the 70mg dose than the 140mg dose. There has been 1673.1 subject-years (SY) of exposure for the 70mg dose group and 589.4 SY of exposure for the 140mg dose.
At the time of the 120-day safety update, an overall of 2537 patients had been exposed to at

least one dose of erenumab (exclusive of healthy volunteers). Of these 2128 had been exposed to at least one dose of 70mg and 1223 had been exposed to at least one dose of 140mg. Since the time of the BLA submission, the sponsor reports an additional 281 SY of exposure. There has been a mean cumulative duration of exposure to erenumab of 53.3 weeks. No additional patients had been treated for 18 months or more at the time of 120-day safety update (Table 62).

Table 62 Overall Extent of Continuous Exposure (120-day Safety Update)

	Number of patients exposed to erenumab:			
	≥3 months	≥6 months	≥12 months	≥18 months
Dose	N=	N=	N=	N=
Any dose	2451	2280	1320	291
70mg	2028	1811	707	287
140mg	1171	1041	176	0

Note: Patients who have received more than one dose of erenumab may be counted more than once according to the extent of exposure they have received of the dose. For example, if a patient received 6 months of 70mg and 6 months of 140mg, that patient will be counted in both the 70mg and 140mg under the ≥6 months column. The data in this table is taken from the sponsor's materials in the 120-day safety update.

The ISS represents 7856 AEs that occurred in 1944 patients inclusive of those who received any form of IP. At the 120-day safety update, the ISS included 8864 AEs reported by 2010 patients.

8.2.2 Relevant characteristics of the safety population:

Migraine occurs more commonly in women than in men. The prevalence of the disease peaks in the fourth decade of life. The demographic characteristics in the erenumab development program are not entirely representative of the intended treatment population. Migraine is more prevalent in women than men (3:1), but the ratio in these studies of women to men is on the order of 5:1 or 6:1. The racial distribution of the study population also is not entirely representative of the U.S. racial distribution. The age of patients in the studies was very restricted. Patients over age 65 are not represented at all in the pivotal studies. In general, the selection criteria for the migraine studies resulted in a relatively young, healthy population. The migraine studies excluded patients with the following disorders: chronic pain syndromes, major psychiatric disorders, seizure disorders, major neurological disorders, HIV, or hepatic disease. Patients with myocardial infarction, TIA, stroke, unstable angina, or CABG within 12 months of the study were excluded also. This may limit the generalizability of the safety data to the larger population when considering that postmarketing use will be much less restrictive.

In the double-blind treatment period, 2682 patients were randomized. Of these 2656 received at least one dose of investigational product. The demographic characteristics of the patients

who received at least one dose of IP are presented below (Table 62a).

Table 62a Summary of Demographic Characteristics for the Safety Analysis Set

Demographic Parameters	Placebo	Treatment Group			Total
	N=1043 n (%)	7mg or 21mg N=213 n (%)	70mg N=893 n (%)	140mg N=507 n (%)	N=2656 n (%)
Sex					
Male	174 (16.7)	41 (19.2)	138 (15.5)	76 (15.0)	429 (16.2)
Female	869 (83.3)	172 (80.8)	755(84.5)	431 (85.0)	2227 (83.8)
Age					
Mean years (SD)	41.8 (11.1)	40.0 (11.6)	41.7 (11.2)	41.3 (11.2)	41.5 (11.2)
Median (years)	42	41	43	43	42
Min, max (years)	18, 66	18, 60	18, 65	18, 65	18, 66
Age Group					
18-40	468 (44.9)	104 (48.8)	379 (42.5)	217 (42.8)	1168 (44.0)
41-55	443 (42.5)	91 (42.7)	413 (46.2)	239 (47.1)	1186 (44.7)
56-66	132 (12.6)	18 (8.5)	101 (11.3)	51 (10.1)	302 (11.3)
Race					
White	934 (89.5)	195 (91.5)	813 (91.0)	475 (93.7)	2417 (91.0)
Black or African American	74 (7.1)	16 (7.5)	59 (6.6)	24 (4.7)	173 (6.5)
Asian	14 (1.3)	1 (0.5)	11 (1.2)	4 (0.8)	30 (1.1)
American Indian or Alaska Native	2 (0.2)	0	0	1 (0.2)	3 (0.1)
Native Hawaiian or Other Pacific Islander	2 (0.2)	0	0	1 (0.2)	3 (0.1)
Other or multiple	17 (1.6)	1 (0.5)	10	2 (0.4)	30 (1.1)
Ethnicity					
Hispanic or Latino	86 (8.2)	18 (8.5)	55 (6.2)	32 (6.3)	191 (7.2)
Not Hispanic or Latino	957 (91.8)	195 (91.5)	838 (93.8)	475 (93.7)	2465 (92.8)
BMI (kg/m^2)					
Mean (SD)	26.8 (5.8)	26.4 (5.1)	26.9 (5.8)	26.7 (5.9)	26.8 (5.7)
Median	25.6	25.3	25.9	25.5	25.6
Min, Max	15.8, 53.0	17.5, 40.0	14.8, 54.7	17.1, 54.7	14.8, 54.7
Region					
North America (USA/CAN)	544 (52.2)	115 (54.0)	471 (52.7)	248 (48.9)	1378 (51.9)
Rest of the World	499 (47.8)	98 (46.0)	422 (47.3)	259 (51.1)	1278 (48.1)

This table was created by the reviewer using the ISS dataset ADSL using JMP where the safety flag was set to 'Y' and ISS dataset ADVS where PARAMCD=BMI and BASETYPE=DOUBLE-BLIND.

8.2.3 Adequacy of the safety database:

The overall exposure to erenumab fulfills the minimum ICH guidelines for chronically administered medications (i.e., 1500 exposed overall, 300 to 600 exposed for 6 months, and 100 exposed for one year). There were some patients treated with the 70mg dose for 18 months or more, but none for the 140mg dose. The safety greater than one year of chronic antagonism of the CGRP receptor cannot be determined from these studies for the 140mg dose, and the information is limited for the 70mg dose. The demographics of this database are somewhat inconsistent with the migraine population. The database does not accurately reflect the ratio of females to males who suffer from migraines. The median BMI is not reflective of the U.S. population. Major cardiovascular disease, which will be discussed in detail in section 8.5.1, is not represented. The limited information on age older than 65 and race does not allow for conclusions on safety of erenumab by older age or race. The sponsor followed the patients for three to four months after discontinuation of erenumab. This is approximately 4 to 5 half-lives since the drug has about a 21-day half-life. This should adequately capture AEs while the drug is present in the body.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Amgen's datasets were assessed by the Office of Computational Science using the JumpStart program. Several issues with the datasets were identified by the JumpStart team and the sponsor was asked to correct these issues.

8.3.2. Categorization of Adverse Events

Sponsor's Definitions of AEs, SAEs, and TEAEs

The sponsor used standard definitions of adverse events (AEs), serious adverse events (SAEs), and treatment emergent adverse events (TEAEs). The sponsor defined adverse events as any untoward medical occurrence in a clinical trial subject whether or not it is related to study treatment. The definition of adverse event included worsening of a pre-existing medical condition including migraine with regards to increase in severity, frequency, duration, or worse than expected outcome.

SAEs were defined as AEs that meet of the following criteria: fatal, life threatening, requires hospitalization, results in disability, results in a congenital anomaly, or any other medically important serious events. The event could also be categorized as an SAE if the investigator deemed it clinically important.

TEAEs were defined as AEs that occur upon or after the administration of the first dose of IP.

Process of Recording, Coding, and Categorizing AEs

The investigator was responsible for reporting all AEs from the time of the first dose of IP through the end of the safety follow-up visit. The investigator was responsible for reporting all SAEs from the time of signing the informed consent through to the end of the safety follow-up visit. The Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE) was used to grade adverse events. Severity of AEs was graded as Grade 1=mild; Grade 2=moderate; Grade 3= severe; Grade 4=life threatening; Grade 5=fatal. The investigator was expected to follow adverse events until stabilization or reversibility occurred. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.

Reviewer Comment: I was unable to determine from the protocols how the AEs were elicited (i.e., by open-ended questions or targeted questions). The method of collecting AEs could potentially affect how many AEs were elicited.

Adverse Event Analyses

For Pools A and B, adverse events were summarized by the sponsor by subject incidence, with some summaries presented using exposure-adjusted subject incidence rates per 100 subject-years to allow for comparison of short-term to long-term safety.

For Pools C and D, data are summarized by the sponsor by exposure adjusted subject incidence rates per 100 subject-years. This was defined as the number of subjects with at least one reported occurrence of an event in each time-period divided by the total subject-years at risk during that phase.

For the summary tables, the sponsor notes that the denominator within each dose group represents the number of subjects who had received at least one dose at that dose level. Patients who received more than one dose level would be counted in the denominator for both dose levels.

Assessment of the Sponsor's Verbatim Terms and Coding

The sponsor provided verbatim terms and coded them to preferred terms. I reviewed all AEs in the ADAE dataset to see if recoding or adding terms was needed. Overall the coding appeared acceptable. I added a term 'cardiac failure' to the database for the patient who died of heart failure.

The sponsor tabulated incidence of TEAEs by system organ class and preferred term by treatment group for the DBTP. For the open-label period, exposure-adjusted incidence rates of TEAEs were tabulated by the sponsor.

AEs of interest

The sponsor performed standardized MedDRA Queries (SMQs) for AEs topics of interest including cardiovascular, cerebrovascular, immune system, gastrointestinal, administration site, hepatobiliary, nervous system, and psychiatric disorders.

8.3.3. **Routine Clinical Tests**

According to the sponsor, the investigator was responsible for determining whether an abnormal value in an individual patient represents a clinically significant change from baseline. In general, abnormal lab values, ECG findings, or vital signs without clinical significance based on the investigator's judgement were not recorded as adverse events. However, any clinical sequelae were to be recorded as the adverse event. The adverse event was to be followed until stabilization or reversibility.

Methodology and Frequency of Routine Clinical Testing

Pregnancy testing was completed for all four studies at screening, baseline, and then at least every 4 weeks for the duration of the studies. ECGs were done at screening, at the first dosing visit prior to dosing, and then every 4 weeks for the first 12 weeks of the double-blind treatment period. For the 6-month study 20120296, an additional ECG was done at week 24. Chemistry and hematology were done at screening, at the first dosing visit prior to dosing, and then every 4 weeks for the studies 20120178 and 20120295. For study 20120296, chemistry and hematology were done at screening, first dosing visit prior to dosing, then at weeks 4, 12, and 24. For study 20120297, chemistry and hematology was done at screening, first dosing visit prior to dosing, and then at weeks 4 and 12. Anti-AMG antibodies were measured at the first dosing visit prior to dosing and then at weeks 4, and 12 for all studies with additional antibody testing at weeks 2 and 8 for studies 20120178 and 20120295 and week 24 for study 20120296.

Table 63 Quintiles Reference Ranges for Laboratory Tests

Lab Test	SI Unit	Reference Range
Hematocrit	g/dl	F 35-47; M 40-52
Hemoglobin	g/dl	F 11.6-16.2; M 13.0-17.5
Leukocytes (WBC)	x10E3/ul	4.1-12.3
Platelets	x10E3/ul	140-450
Erythrocytes (RBC)	x10E6/ul	F 3.8-5.5; M 4.1-5.9
Lymphocytes	%	15.5-46.6
Monocytes	%	3.1-12.5
Neutrophils	%	40.9-77.0
Eosinophils	%	0-6.0
Basophils	%	0-2.4
AST/SGOT	U/L	F ≤31; M ≤37
ALT/SGPT	U/L	F ≤33; M ≤41
Total Bilirubin	mg/dl	≤1.2
Direct Bilirubin	mg/dl	0-0.3
CK total	IU/L	F 26-192; M 39-308
Alkaline Phosphatase	IU/L	F 35-104; M 40-129
BUN	mg/dl	6-20
Creatinine	mg/dl	F 0.5-0.9; M 0.7-1.2
TSH	mIU/L	0.55-4.78
Albumin	g/dl	3.5-5.2
Total Protein	g/dl	6.0-8.0
Triglycerides	mg/dl	<150
Cholesterol (total)	mg/dl	<200
Potassium	mmol/L	3.3-5.1
Sodium	mmol/L	135-147
Calcium	mg/dl	8.4-10.3
Bicarbonate	mEq/L	19-29
Glucose	mg/dl	74-106

Sponsor provided in a clinical information request.

Vital Signs

Vital signs were measured and recorded at screening, baseline, just prior to randomization, and every 4 weeks during the double-blind treatment periods. Vital signs included systolic and diastolic blood pressure, heart rate, and body temperature. Blood pressure was measured in a semi-recumbent or supine position. At least two measurements were taken separated by at

least 5 minutes, and the average was recorded.

8.4. Safety Results

8.4.1. Deaths

In total, there were two deaths in the erenumab database. There were too few deaths to make any conclusions about the relative mortality risks by treatment. One death was in study 20120178 and one death was in study 20120296. Both occurred during open-label treatment with erenumab. The CRFs and patient profiles provided by the sponsor were reviewed and summarized below. The patient profiles included autopsy reports for both patients and a cardiology consultation for the patient in study 20120296.

Case 1: Patient (b) (6) Sudden Death

This 54-year-old white male was participating in the open-label portion of study 20120178 when he died. He received his first dose of investigational product in the double-blind treatment period on (b) (6), and his first dose in the open-label treatment period on (b) (6) During the double-blind treatment period, he received 7mg of erenumab and during the open-label treatment period he received 70mg of erenumab. In total, he received three doses of 7mg of erenumab, and 21 doses of 70mg of erenumab. The patient's last study visit occurred on (b) (6) at which time no new medical problems were recorded. On (b) (6) the patient was found dead in his apartment in a state of decomposition. He underwent autopsy on (b) (6) which demonstrated advanced decomposition, and severe coronary atherosclerosis. There was 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.

The patient had a past medical history hypertension diagnosed in (b) (6) for which he took lisinopril and hydrochlorothiazide, but was not on an anti-hypertensive medication during the study. Blood pressures were normotensive during the study ranging from 88-125/61-85. He was obese with a BMI of 33 kg/m². During the study, he had several ECGs that were reported as showing left anterior hemiblock. The patient's father died at age 39 and had a medical history of alcohol abuse, hypertension, and heart attack.

Reviewer Comment: The patient had severe atherosclerotic disease on his autopsy. In addition, his toxicology screen showed the presence of norpseudoephedrine and phenylpropanolamine which are alpha and beta-adrenergic receptor antagonists with sympathomimetic activity. They cause the release of norepinephrine which results in a positive inotropic effect on the heart. The presence of these drugs confounds the cause of death.

Case 2: Patient (b) (6) Sudden Death

This 43-year-old male died while participating in the open-label portion of study 20120296. He received the first dose of investigational product on (b) (6) He began treatment in the open-label phase on (b) (6). In the double-blind treatment phase, he received 70mg of erenumab, and during the open-label treatment period he received 140mg of erenumab. In total, he received six doses of 70mg and four doses of 140mg. He was found dead on (b) (6) and underwent autopsy on (b) (6) The autopsy showed right ventricular dysplasia and arteriosclerosis. The autopsy report noted generalized grade 1 atherosclerosis, fatty infiltration of the myocardium of the right ventricle, and left ventricular hypertrophy. The patient had genetic testing that showed that the patient was heterozygous for a frameshift mutation in the SCN5A gene. On autopsy, he was given a diagnosis of heart failure due to an arrhythmogenic cardiomyopathy.

This patient had a past medical history of high cholesterol and high triglycerides and a history of mitral valve insufficiency. He also had a history of an abnormal ECG for which he had initially undergone a cardiology consultation in (b) (6) At that time the cardiologist found his ECG to be in sinus rhythm with an atypical repolarization in V2. In (b) (6) he underwent another cardiology consultation and was referred for evaluation of Brugada syndrome, but was otherwise asymptomatic at the time. He underwent Ajmaline testing to evaluate for Brugada syndrome. His baseline ECG was sinus rhythm with left anterior hemiblock, and atypical repolarization in V2. Ajmaline 100mg was administered intravenously and the study was reported as negative. No treatment or follow up was recommended at that time by the cardiologist.

Reviewer Comment: In summary, there were two unexpected deaths in patients treated with erenumab. Both deaths were unexpected deaths in relatively young males (ages 43 and 54) and had a cardiovascular cause of death.

In Case 1, it appears that the patient died from complications of ingesting cardiac stimulants in the setting of severe atherosclerosis. In Case 2, it seems plausible that the patient died from an arrhythmia. This arrhythmia may have developed either secondary to his underlying genetic disease (SCN5A mutation) or from his underlying cardiomyopathy which is presumably secondary to his genetic mutation as well.

Although both deaths are confounded and have plausible causes of death not related to the investigational product, I believe it is still possible to consider a theoretical mechanism by which chronic CGRP antagonism may have played a role especially in Case 1. Theoretically antagonism of the CGRP receptor may have prevented compensatory vasodilatation in the

setting of cardiac ischemia. Please see the consult from the Division of Cardiovascular and Renal Products (DCRP) that evaluated the nonclinical literature that assesses the theoretical risk of CGRP antagonism.

I obtained a cardiology consult from the Division of Cardiovascular and Renal Products (DCRP) to review these two cases. Our cardiologist felt that both cases had a plausible cause of death other than use of erenumab and did not feel that the cases impacted approvability or labeling decisions. Please see the consultation from Dr. Preston Dunnmon, DCRP.

8.4.2. **Serious Adverse Events**

There were 2499 patients who were treated with at least one dose of 70mg or 140mg of erenumab in the integrated safety database which was pooled data from the phase 2 and phase 3 studies (20120178, 20120295, 20120296, and 20120297). Of these, there were 125 patients who reported a nonfatal serious adverse event with a total of 161 serious adverse events reported. There were six additional SAEs in studies that were not included in the ISS and an additional case of acute liver injury that was reported to the IND. Of patients exposed to erenumab, approximately 5% reported a serious adverse event. I searched the database for designated medical events (DMEs) that occurred while patients were on active treatment with erenumab. These events were not necessarily coded as SAEs. Their narratives are included in this section under a separate heading. For patients who had received erenumab, the following DMEs were not found in the ISS database: acute pancreatitis, acute respiratory failure, agranulocytosis, amyotrophic lateral sclerosis, aplastic anemia, congenital anomalies, disseminated intravascular coagulation, endotoxic shock, hemolysis, hemolytic anemia, liver failure, liver necrosis, liver transplant, neuroleptic malignant syndrome, pancytopenia, progressive multifocal leukoencephalopathy, pulmonary fibrosis, pulmonary hypertension, rhabdomyolysis, serotonin syndrome, Stevens-Johnson syndrome, sudden death, suicide, Torsade de Pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. Those DMEs that were found that are reviewed in this section include acute liver injury, ischemic colitis, seizure, hearing loss, neutropenia, anaphylaxis, transient blindness. The case of acute liver injury reviewed here occurred in a study that is not included in the BLA and ISS.

The double-blind placebo-controlled data was examined for imbalances between placebo treated patients and patients treated with erenumab. There were 56 SAEs in the pooled double-blind treatment period. One SAE (ovarian cyst rupture) occurred in the 7mg dose group and was not included in the table below. The most commonly reported SAEs were infections, musculoskeletal disorders, and nervous system disorders. I summarized by MedDRA system organ class (SOC) and subdivided the SAEs by PT that occurred in the DBTP. Because there

were so few SAEs, I did not present them by individual study, but instead presented the pooled data for all four studies (Table 64).

The only imbalance noted in MedDRA SOC between drug and placebo is in the infections and infestations SOC for the 140mg dose. In this SOC for the 140mg dose, four of the infections are attributed to one patient. This patient's case is reviewed under narratives of selected SAEs below: 20120196- (b) (6)

Table 64 SAEs: Pooled Data from DBTP

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	Placebo N=1043 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
Ear and Labyrinth Disorders	**0 (0)**	**1 (0.1)**	**0 (0)**
Vertigo	0	1 (0.1)	0
Gastrointestinal Disorders	**2 (0.2)**	**0 (0)**	**2 (0.4)**
Abdominal adhesions	0	0	1 (0.2)
Abdominal pain	0	0	1 (0.2)
Pancreatitis	1 (0.1)	0	0
Vomiting	1 (0.1)	0	0
General/Administration Site	**1 (0.1)**	**2 (0.2)**	**1 (0.2)**
Non-cardiac chest pain	1 (0.1)	2 (0.2)	1 (0.2)
Hepatobiliary Disorders	**2 (0.2)**	**2 (0.2)**	**0 (0)**
Cholecystitis	2 (0.2)	0	0
Cholelithiasis	0	2 (0.2)	0
Immune System Disorders	**2 (0.2)**	**0 (0)**	**0 (0)**
Hypersensitivity	2 (0.2)	0	0
Infections and Infestations	**2 (0.2)**	**3 (0.3)**	**6 (1.2)**
Appendicitis	0	1 (0.1)	0
Clostridium difficile colitis	0	0	1 (0.2)
Gastroenteritis	0	0	1 (0.2)
Kidney infection/pyelonephritis	0	1 (0.1)	2 (0.4)
Parotitis	1 (0.1)	0	0
Sepsis	0	0	1 (0.2)
Urinary tract infection	1 (0.1)	1 (0.1)	0
Vestibular neuronitis	0	0	1 (0.2)
Injury, Poisoning, Procedural Complications	**2 (0.2)**	**3 (0.3)**	**2 (0.4)**
Fractures	0	2 (0.2)	1 (0.2)
Cartilage injury	0	0	1 (0.2)
Fall	1 (0.1)	0	0
Intentional overdose	1 (0.1)	0	0

Post-traumatic neck syndrome	0	1 (0.1)	0
Metabolism and Nutrition	**1 (0.1)**	**0 (0)**	**0 (0)**
Hyponatremia	1 (0.1)	0	0
Musculoskeletal and Connective Tissue	**4 (0.4)**	**5 (0.6)**	**1 (0.2)**
Arthralgia	1 (0.1)	0	0
Back/spine pain	0	1 (0.1)	1 (0.2)
Costochondritis	0	1 (0.1)	0
Flank pain	1 (0.1)	0	0
Intervertebral disc protrusion	1 (0.1)	3 (0.3)	0
Osteoarthritis	1 (0.1)	0	0
Neoplasms Benign, Malignant, and Unspecified	**1 (0.1)**	**1 (0.1)**	**0 (0)**
Fibroma	0	1 (0.1)	0
Uterine leiomyoma	1 (0.1)	0	0
Nervous System Disorders	**2 (0.2)**	**5 (0.6)**	**1 (0.2)**
Cerebral venous thrombosis	0	0	1 (0.2)
Migraine	2 (0.1)	5 (0.6)	0
Reproductive System and Breast Disorders	**1 (0.1)**	**1 (0.1)**	**0 (0)**
Endometriosis	1 (0.1)	0	0
Ovarian cyst	0	1 (0.1)	0
Total # SAEs	**20 (1.9)**	**23 (2.6)**	**13 (2.6)**
Total # patients reporting an SAE in DBTP	**19 (1.8)**	**18 (2.0)**	**8 (1.6)**

Reviewer created table from ISS dataset ADAE (numerator) where APERIOD=1 and ADSL (denominator) and AESER flag=Y. This table includes data from studies 20120178, 2012095, 20120296, and 20120297.

Reviewer Comment: This analysis was also done by pooling the two studies with a 140mg arm i.e., 20120295 and 20120296, and there was no change in the conclusion.

The open-label exposure was examined for SAEs as well. I examined the rates the SAEs occurred in the OLE to see if they were consistent with what was seen in the DBTP. I also examined the open-label period to see if any new information that was not apparent in the DBTP became apparent with longer treatment. In total, there were 101 SAEs reported by 83 patients in the open-label period (Table 65). Again, the overall rate of SAEs was low, no SOC contained ≥1% of the SAEs.

Table 65 SAEs: Open Label Experience

MedDRA System Organ Class Serious Adverse Event (Preferred Term**)**	70mg only N=1221 n(%)	140mg only N=327 n(%)	70mg and 140mg** N=827 n(%)	Total N=2375 n(%)
Cardiac Disorders	**4 (0.3)**	**1 (0.3)**	**1 (0.1)**	**6 (0.3)**
Atrial fibrillation	1 (0.1)	0	0	1(<0.1)
Cardiac failure	0	0	1 (0.1)	1(<0.1)
Hypertensive heart disease	1 (0.1)	0	0	1(<0.1)
Myocardial ischemia	2 (0.2)	0	0	2 (0.1)
Pericarditis	0	1 (0.3)	0	1(<0.1)
Congenital, Familial, and Genetic Disorders	**1 (0.1)**	**0**	**1 (0.1)**	**2 (0.1)**
Arrhythmogenic right ventricular dysplasia	0	0	1 (0.1)	1(<0.1)
Myocardial bridging	1 (0.1)	0	0	1(<0.1)
Eye Disorders	1 (0.1)	0	1 (0.1)	2 (0.1)
Idiopathic orbital inflammation	1 (0.1)	0	0	1(<0.1)
Visual Impairment	0	0	1 (0.1)	1(<0.1)
Gastrointestinal Disorders	**6 (0.5)**	**0**	**7 (0.8)**	**13 (0.5)**
Abdominal adhesions	0	0	1 (0.1)	1(<0.1)
Abdominal hernia	0	0	1 (0.1)	1(<0.1)
Abdominal pain	0	0	1 (0.1)	1(<0.1)
Colitis ischemic	0	0	1 (0.1)	1(<0.1)
Diverticulum	0	0	1 (0.1)	1(<0.1)
Dyspepsia	1 (0.1)	0	0	1(<0.1)
Fecaloma	1 (0.1)	0	0	1(<0.1)
Gastritis	1 (0.1)	0	0	1(<0.1)
Gastrointestinal/peritoneal hemorrhage	2 (0.2)	0	0	2 (0.1)
Hiatal Hernia	0	0	1 (0.1)	1(<0.1)
Pancreatic cyst	1 (0.1)	0	0	1(<0.1)
Volvulus	0	0	1 (0.1)	1(<0.1)
General and Administration Site	**0**	**0**	**1 (0.1)**	**1(<0.1)**
Non-cardiac chest pain	0	0	1 (0.1)	1(<0.1)
Hepatobiliary Disorders	**0**	**0**	**3 (0.4)**	**3 (0.1)**
Alcoholic liver disease	0	0	1 (0.1)	1(<0.1)
Cholecystitis	0	0	1 (0.1)	1(<0.1)
Hepatic cyst	0	0	1 (0.1)	1(<0.1)
Infections and Infestations	**3 (0.2)**	**2 (0.6)**	**7 (0.8)**	**12 (0.5)**
Appendicitis	0	0	2 (0.1)	2(0.1)
Cellulitis	0	0	1 (0.1)	1(<0.1)

Diverticulitis	0	1 (0.3)	1 (0.1)	2 (0.1)
Erysipelas	0	1 (0.3)	0	1(<0.1)
Gastroenteritis	0	0	2 (0.2)	2 (0.1)
Pneumococcal bacteremia	1 (0.1)	0	0	1(<0.1)
Pneumonia	0	0	1 (0.1)	1(<0.1)
Post-procedural infection	1 (0.1)	0	0	1(<0.1)
Postoperative abscess	1 (0.1)	0	0	1(<0.1)
Injury, Poisoning, Procedural Complications	**1 (0.1)**	**2 (0.6)**	**3 (0.4)**	**6 (0.3)**
Fracture (radius, femur)	0	0	2 (0.2)	2 (0.1)
Ligament rupture	0	0	1 (0.1)	1(<0.1)
Post-procedural edema	0	1 (0.3)	0	1(<0.1)
Subdural hematoma	0	1 (0.3)	0	1(<0.1)
Wound	1 (0.1)	0	0	1(<0.1)
Metabolism and Nutrition	**0**	**1 (0.3)**	**0**	**1(<0.1)**
Dehydration	0	1 (0.3)	0	1(<0.1)
Musculoskeletal and Connective Tissue	**4 (0.3)**	**0**	**5 (0.6)**	**9 (0.4)**
Costochondritis/musculoskeletal chest pain	1 (0.1)	0	1 (0.1)	2 (0.1)
Intervertebral disc protrusion	2 (0.2)	0	2 (0.2)	4 (0.2)
Metatarsalgia	1 (0.1)	0	0	1(<0.1)
Osteoarthritis	0	0	1 (0.1)	1(<0.1)
Rotator cuff syndrome	0	0	1 (0.1)	1(<0.1)
Neoplasms Benign, Malignant, and Unspecified	**7 (0.6)**	**1 (0.3)**	**0**	**8 (0.3)**
Breast/invasive lobular breast cancer	3 (0.2)	0	0	3 (0.1)
Breast fibroma/uterine leiomyoma	2 (0.2)	1 (0.3)	0	3 (0.1)
Lung adenocarcinoma stage III	1 (0.1)	0	0	1(<0.1)
Papillary thyroid cancer	1 (0.1)	0	0	1(<0.1)
Nervous System Disorders	**7 (0.6)**	**0**	**9 (1.1)**	**16 (0.7)**
Radiculopathy	0	0	2 (0.2)	2 (0.1)
Medication overuse headache/migraine	4 (0.3)	0	2 (0.2)	6 (0.3)
Optic neuritis	0	0	1 (0.1)	1(<0.1)
Pre-syncope/syncope	2 (0.2)	0	3 (0.4)	5 (0.2)
Toxic encephalopathy	1 (0.1)	0	0	1(<0.1)
Transient ischemic attack	0	0	1 (0.1)	1(<0.1)
Psychiatric Disorders	**4 (0.3)**	**0**	**2 (0.2)**	**6 (0.2)**
Adjustment disorder	1 (0.1)	0	0	1(<0.1)
Alcoholism	0	0	1 (0.1)	1(<0.1)
Depression	3 (0.2)	0	1 (0.1)	4 (0.2)
Renal and Urinary Disorders	**0**	**0**	**1 (0.1)**	**1(<0.1)**
Pelvic-ureteric obstruction	0	0	1 (0.1)	1(<0.1)

Reproductive System and Breast Disorders	**1 (0.1)**	**0**	**3 (0.4)**	**4 (0.2)**
Endometriosis	1 (0.1)	0	0	1(<0.1)
Fallopian tube/ovarian cyst	0	0	2 (0.2)	2 (0.1)
Menorrhagia	0	0	1 (0.1)	1(<0.1)
Respiratory, Thoracic, Mediastinal Disorders	**4 (0.3)**	**0**	**0**	**4 (0.2)**
Acute respiratory distress syndrome	1 (0.1)	0	0	1(<0.1)
Dyspnea	1 (0.1)	0	0	1(<0.1)
Laryngeal hematoma	1 (0.1)	0	0	1(<0.1)
Pulmonary embolism	1 (0.1)	0	0	1(<0.1)
Skin and Subcutaneous Tissue Disorders	**1 (0.1)**	**0**	**0**	**1(<0.1)**
Urticaria	1 (0.1)	0	0	1(<0.1)
Surgical and Medical Procedures	**2 (0.2)**	**0**	**0**	**2 (0.1)**
Anoplasty	1 (0.1)	0	0	1(<0.1)
Rectocele repair	1 (0.1)	0	0	1(<0.1)
Vascular Disorders	**3 (0.2)**	**0**	**1 (0.1)**	**3 (0.1)**
Arteriosclerosis	1 (0.1)	0	0	1(<0.1)
Deep vein thrombosis/thrombosis	2 (0.2)	0	1 (0.1)	3 (0.1)
Total # of SAEs	**49 (4.0)**	**7 (2.1)**	**45 (5.5)**	**101 (4.3)**
Total # of patients	**37 (3.0)**	**7 (2.1)**	**39 (4.7)**	**83 (3.5)**

Reviewer created table from ISS dataset ADAE (numerator) where APERIOD=2 or APERIOD=3 and ADSL (denominator). Analysis of AEDECOD by AEBODSYS and TRTI2AN
*The open-label experience is a subset of Pool C. I did not include the SAEs experienced during the double-blind treatment period in this table.
**The doses in this column refer to patients who received both 70mg and 140mg in the open-label portion of the studies.

I also summarized all the SAEs experienced by patients who were exposed to at least 1 dose of erenumab, but I did not include those SAEs experienced by patients who were on placebo at the time of the SAE. There were 136 SAEs experienced by 106 patients who received erenumab 70mg or 140mg (Table 66). The overall rate of SAEs remained low, no SOC contained ≥1% of the SAEs.

Table 66 SAEs: All Exposed in ISS to 70mg or 140mg (Pool C)

MedDRA System Organ Class Serious Adverse Event (Preferred Term**)**	Any dose (70mg or 140mg) N=2499 n(%)
Cardiac Disorders	**6 (0.2)**
Atrial fibrillation	1 (<0.1)
Cardiac failure	1 (<0.1)
Hypertensive heart disease	1 (<0.1)
Myocardial ischemia	2 (0.1)
Pericarditis	1 (<0.1)
Congenital, Familial, and Genetic Disorders	**2 (0.1)**
Arrhythmogenic right ventricular dysplasia	1 (<0.1)
Myocardial bridging	1 (<0.1)
Ear and Labyrinth Disorders	1 (<0.1)
Vertigo	1 (<0.1)
Eye Disorders	**2 (0.1)**
Idiopathic orbital inflammation	1 (<0.1)
Visual Impairment	1 (<0.1)
Gastrointestinal Disorders	**15 (0.6)**
Abdominal adhesions	2 (0.1)
Abdominal hernia	1 (<0.1)
Abdominal pain	2 (0.1)
Colitis ischemic	1 (<0.1)
Diverticulum	1 (<0.1)
Dyspepsia	1 (<0.1)
Fecaloma	1 (<0.1)
Gastritis	1 (<0.1)
Gastrointestinal/peritoneal hemorrhage	2 (0.1)
Hiatal Hernia	1 (<0.1)
Pancreatic cyst	1 (<0.1)
Volvulus	1 (<0.1)
General and Administration Site	**4 (0.2)**
Non-cardiac chest pain/chest discomfort	4 (0.2)
Hepatobiliary Disorders	**5 (0.2)**
Alcoholic liver disease	1 (<0.1)
Cholecystitis	3 (0.1)
Cholelithiasis	2 (0.1)
Hepatic cyst	1 (<0.1)
Infections and Infestations	**21 (0.8)**

Appendicitis	3 (0.1)
Cellulitis	1 (<0.1)
Clostridium difficile colitis	1 (<0.1)
Diverticulitis	2 (0.1)
Erysipelas	1 (<0.1)
Gastroenteritis	3 (0.1)
Kidney infection/pyelonephritis	3 (0.1)
Pneumococcal bacteremia	1 (<0.1)
Pneumonia	1 (<0.1)
Post-procedural infection	1 (<0.1)
Postoperative abscess	1 (<0.1)
Sepsis	1 (<0.1)
Urinary tract infection	1 (<0.1)
Vestibular neuronitis	1 (<0.1)
Injury, Poisoning, Procedural Complications	**11 (0.4)**
Cartilage injury	1 (<0.1)
Fracture (ankle, femur, radius)	5 (0.2)
Ligament rupture	1 (<0.1)
Post-procedural edema	1 (<0.1)
Post-traumatic neck syndrome	1 (<0.1)
Subdural hematoma	1 (<0.1)
Wound	1 (<0.1)
Metabolism and Nutrition	1 (<0.1)
Dehydration	1 (<0.1)
Musculoskeletal and Connective Tissue	**15 (0.6)**
Back pain	1 (<0.1)
Costochondritis/musculoskeletal chest pain	3 (0.1)
Intervertebral disc protrusion	7 (0.3)
Metatarsalgia	1 (<0.1)
Osteoarthritis	1 (<0.1)
Rotator cuff syndrome	1 (<0.1)
Spinal pain	1 (<0.1)
Neoplasms Benign, Malignant, and Unspecified	**9 (0.4)**
Breast/invasive lobular breast cancer	3 (0.1)
Breast fibroma/uterine leiomyoma	4 (0.2)
Lung adenocarcinoma stage III	1 (<0.1)
Papillary thyroid cancer	1 (<0.1)
Nervous System Disorders	**22 (0.9)**
Cerebral venous thrombosis	1 (<0.1)

Radiculopathy	2 (0.1)
Medication overuse headache/migraine/vestibular migraine	11 (0.4)
Optic neuritis	1 (<0.1)
Pre-syncope/syncope	5 (0.2)
Toxic encephalopathy	1 (<0.1)
Transient ischemic attack	1 (<0.1)
Psychiatric Disorders	**6 (0.2)**
Adjustment disorder	1 (<0.1)
Alcoholism	1 (<0.1)
Depression	4 (0.2)
Renal and Urinary Disorders	1 (<0.1)
Pelvic-ureteric obstruction	1 (<0.1)
Reproductive System and Breast Disorders	**5 (0.2)**
Endometriosis	1 (<0.1)
Fallopian tube/ovarian cyst	3 (0.1)
Menorrhagia	1 (<0.1)
Respiratory, Thoracic, Mediastinal Disorders	**4 (0.2)**
Acute respiratory distress syndrome	1 (<0.1)
Dyspnea	1 (<0.1)
Laryngeal hematoma	1 (<0.1)
Pulmonary embolism	1 (<0.1)
Skin and Subcutaneous Tissue Disorders	1 (<0.1)
Urticaria	1 (<0.1)
Surgical and Medical Procedures	**2 (0.1)**
Anoplasty	1 (<0.1)
Rectocele repair	1 (<0.1)
Vascular Disorders	**4 (0.2)**
Arteriosclerosis	1 (<0.1)
Deep vein thrombosis/thrombosis	3 (0.1)
Total # of SAEs	**136**
Total # of patients	**106 (4.2)**

Reviewer created table from ADAE where POOL2RFL=Y, and AESER=Y

At the time of the 120-day safety update there were 162 SAEs experienced by 126 patients (5.0%) who had received erenumab 70mg or 140mg. No new safety concern in regards to SAEs is apparent with the addition of the 120-day safety update data (Table 67 and 68).

Table 67 Additional SAEs included in the 120-day Safety Update

MedDRA System Organ Class Serious Adverse Event (Preferred Term)	Any dose N=2499 n(%)
Blood and Lymphatic Disorders	**1 (<0.1)**
Anemia	1 (<0.1)
Eye Disorders	**2 (0.1)**
Iridocyclitis	1 (<0.1)
Visual acuity reduced	1 (<0.1)
Gastrointestinal Disorder	**3 (0.1)**
Esophagitis	1 (<0.1)
Gastrointestinal reflux	1 (<0.1)
Rectal prolapse	1 (<0.1)
Infections and Infestations	**6 (0.2)**
Appendicitis	2 (0.1)
Diverticulitis	1 (<0.1)
Pneumonia	1 (<0.1)
Tooth abscess	1 (<0.1)
Tubo-ovarian abscess	1 (<0.1)
Injury, Poisoning, Procedural Complications	**2 (0.1)**
Ligament rupture	1 (<0.1)
Post-procedural pulmonary embolism	1 (<0.1)
Investigations	**1 (<0.1)**
Blood potassium decreased	1 (<0.1)
Metabolism and Nutrition Disorders	**1 (<0.1)**
Hypoglycemia	1 (<0.1)
Musculoskeletal and Connective Tissue Disorders	**1 (<0.1)**
Lumbar spinal stenosis	1 (<0.1)
Neoplasms, Benign, Malignant, and Unspecified	**6 (0.2)**
Breast cancer	1 (<0.1)
Papillary thyroid cancer	1 (<0.1)
Prolactin-producing pituitary tumor	1 (<0.1)
Uterine leiomyoma/fibroma	3 (0.1)
Nervous System Disorders	**4 (0.2)**
Cauda equina syndrome	1 (<0.1)
Headache/migraine	2 (0.1)
Idiopathic intracranial hypertension	1 (<0.1)

Reviewer created table using 120-day update ISS dataset ADAE where AESER=Y, and TRTA ≠ placebo

Table 68 Total SAEs by SOC inclusive of the 120-day Update

MedDRA System Organ Class	Any dose N=2499 n(%)
Blood and Lymphatic Disorders	1 (<0.1)
Cardiac Disorders	6 (0.2)
Congenital, Familial, and Genetic Disorders	2 (0.1)
Ear and Labyrinth Disorders	1 (<0.1)
Eye Disorders	4 (0.2)
Gastrointestinal Disorder	18 (0.7)
General and Administration Site	4 (0.2)
Hepatobiliary Disorders	5 (0.2)
Infections and Infestations	26 (1.0)
Injury, Poisoning, Procedural Complications	14 (0.6)
Investigations	1 (<0.1)
Metabolism and Nutrition Disorders	2 (0.1)
Musculoskeletal and Connective Tissue Disorders	16 (0.6)
Neoplasms, Benign, Malignant, and Unspecified	15 (0.6)
Nervous System Disorders	26 (1.0)
Psychiatric Disorders	6 (0.2)
Renal and Urinary Disorders	1 (<0.1)
Reproductive System and Breast Disorders	5 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders	3 (0.1)
Skin and Subcutaneous Tissue Disorders	1 (<0.1)
Surgical and Medical Procedures	2 (0.1)
Vascular Disorders	4 (0.2)
Total # of AEs	**162**
Total # of patients	**126 (5.0)**

Reviewer created table from 120-day safety update ADAE where POOL2RFL=Y, and AESER=Y, analysis by AEBODSYS

Narratives of Selected SAEs

Chest pain (non-cardiac)

1. Patient 20120178-(b) (6) (non-cardiac chest pain)

This 54-year-old white female who was participating in the open-label treatment phase of study 20120178 experienced chest pain requiring hospitalization. Her work up during her admission included chest x-ray, ECG, carotid ultrasound, transthoracic echocardiogram, and serial cardiac enzymes. Work-up was unremarkable and she was diagnosed with non-cardiac chest pain related to stress and anxiety. She had been receiving erenumab 70mg, and had received 34

doses of 70mg. Subsequently, she was increased to 140mg without further incident and went on to receive four additional doses of 140mg.

2. Patient 20120295 (b) (6) (non-cardiac chest pain)

This 54-year-old female was participating in the DBTP of study 20120295 when she experienced chest pain requiring hospitalization. The patient felt pressure in her chest that was worse with exertion. She also had shortness of breath, and nausea. The patient additionally had an episode of chest pain prior to receiving any investigation product as well. The patient had received three doses of 70mg in the double-blind treatment period at the time of her SAE. Her relevant medications were Adderall, levothyroxine, and losartan/HCTZ. Her work up included chest x-ray, treadmill stress test, and cardiac enzymes. Work-up was unremarkable. The patient continued into the open-label portion of the study.

3. Patient 20120296- (b) (6) (non-cardiac chest pain)

This 39-year-old white female was participating in the DBTP of study 20120296 when she experienced chest pain requiring hospitalization. The patient had a migraine with nausea the night preceding her chest pain. Relevant concomitant medications included sumatriptan. On the morning of admission (b) (6) she had substernal, mid-chest pain with radiation to the left shoulder while at rest especially when lying down and worse with deep breathing. The patient underwent work up including ECG which initially showed sinus tachycardia with T-wave inversions in V1 to V3 with mild ST segment elevation in lead III. Follow up ECG showed mild transient ST elevation in lead III, and non-specific T-wave inversion in leads II, III, and aVF. She also underwent CT angiography of the chest that ruled out pulmonary embolism. On her examination, she was noted to have tenderness to palpation along the left chest wall and along the ribs. She had serial cardiac enzymes which were negative. Her discharge papers indicate that she was diagnosed with non-cardiac chest pain, possibly pleuritic or costochondritis and recommended to follow up with cardiology. At the time of her SAE, she had received 6 doses of erenumab 140mg in the DBTP. She continued into the open-label treatment period and received 7 doses of 70mg of erenumab.

Reviewer Comment: I requested the patient's ECGs from the sponsor which they provided. This patient's ECGs were reviewed by our cardiologist, Dr. Preston Dunnmon. He felt that the patient's ECGs showed no changes compared to her screening ECG that may be suggestive of ischemia.

4. Patient 20120296- (b) (6) (non-cardiac chest pain)

This 60-year-old white female was participating in the DBTP of study 20120296 when she experienced chest pain requiring hospitalization on (b) (6) The patient had left arm tingling and numbness radiating to the left should blade with left chest discomfort. The patient's pain was reported to be reproducible and worsened with movement. The patient

underwent serial cardiac enzymes, and exercise stress test which were reported to be normal. She was diagnosed with radiculopathy. Several days prior to this, the patient also had an upper respiratory tract infection. The patient received her first dose of erenumab on (b) (6) At the time of her SAE, she had received 4 doses of 70mg of erenumab. Following her SAE, she received 2 additional doses of 70mg, and then went on to receive 7 doses of 70mg in the open label treatment period.

5. Patient 20120178- (b) (6) (musculoskeletal chest pain)

This case is reviewed under thromboses. The patient had a pulmonary embolism which is likely the cause of the chest pain. This occurred in the open-label period.

6. Patient 20120295- (b) (6): (Grade 4) (costochondritis)

This 42-year-old female experienced 5 SAEs. The patient received erenumab 70mg in (b) (6) and had received three doses at the time of her first SAE. She experienced right sided chest pain and pressure with shortness of breath and diaphoresis requiring hospitalization in (b) (6) during the DBTP. She underwent chest x-ray, ECG, and lab testing. Her ECG showed a sinus rhythm with an incomplete right bundle branch block (also noted at screening). Her troponins were negative, and echocardiogram was normal. She was diagnosed with costochondritis. The patient continued into the open-label portion of the study on 70mg. She then experienced an episode of depression, anxiety, and possible suicidal ideation. She was hospitalized for 3 days due to the suspected suicidal ideation. The patient also underwent surgery to repair a rectocele that was the result of a prior perineal laceration. The initial injury occurred many years prior to entry into the study.

7. Patient 20120295- (b) (6) (costochondritis)

This 41-year-old female was participating in the open-label treatment phase of study 20120295. She completed three doses of 70mg in the DBTP, and started treatment with 140mg in the open label phase on (b) (6). On (b) (6), she experienced left sided chest pain with some radiation to the left shoulder. She had an ECG and troponins which were normal. She underwent CT coronary arteriography which was reported as normal. She continued to receive erenumab 140mg after the first episode of chest pain. On (b) (6), she experienced a second episode of chest pain again radiating to the left shoulder and this time was hospitalized. She again had an ECG and troponins which were negative. She underwent myocardial scintigraphy which was normal. She also underwent a stress test that was normal. Her (b) (6) dose of erenumab was not given due to her hospitalization. She resumed treatment with erenumab 140mg in (b) (6) and received 4 doses without further adverse events.

Reviewer Comment: The cases classified by the sponsor as non-cardiac chest pain seem reasonably ascribed by the sponsor. The patients who experienced non-cardiac chest pain went on to continue treatment after the SAE without further difficulties. Case 3 seems less certain given that the patient was given a non-cardiac chest pain diagnosis, but still asked to follow up with cardiology for her ECG findings. However, even in Case 3 the patient's treating physicians felt comfortable that her symptoms were not cardiac, and she did continue erenumab without further complication (albeit on a lower dose). The ECGs in Case 3 were reviewed by our cardiologist who felt that the ECG findings were not indicative of ischemia.

For Cases 6 and 7, the sponsor did not provide enough evidence to conclusively make a diagnosis of costochondritis. However, I think the cardiac workup was sufficient to classify the symptoms as non-cardiac. Case 5 is probably more likely to be pleuritic chest pain then musculoskeletal given the presence of the pulmonary embolism. However, I agree that the chest pain is likely non-cardiac.

Syncope/pre-syncope

1. Patient 20120178-(b) (6)

This 31-year-old female was participating in the open-label treatment phase of study 20120178 when she experienced what is reported as syncope. The event was unwitnessed, but was self-reported as lasting 'seconds'. The patient underwent CT and MRI which were reported as normal. The patient also underwent a tilt test and cardiac echo. Tilt test was reported as normal, and echo was reported as 'small concentric hypertrophy of myocardium'. The patient had an implantable device recorder placed which recorded no abnormalities. The patient initially received erenumab three doses of 7mg in the DBTP, 30 doses of erenumab 70mg in the open-label period and one dose of 140mg. She received 18 of these doses of erenumab after experiencing the SAE.

Reviewer Comment: I cannot completely exclude the role of erenumab. An alternative cause of syncope was not presented. However, she did continue on erenumab without further incident.

2. Patient 20120178-(b) (6)

This 33-year-old female was participating in the open-label treatment phase of study 20120178 when she experienced an episode of loss of consciousness. The patient received her first dose of erenumab 70mg on (b) (6), and received a total of 19 doses prior to the onset of her SAE. On (b) (6), the patient was reported to be unconscious very briefly at home. The patient had new onset of recurrent episodes of loss of consciousness that were increasing in frequency and severity. The patient underwent EEG monitoring that showed several episodes of 'near syncope' with no concurrent EEG abnormalities. She underwent carotid ultrasound, and an echocardiogram. She had a CT and an MRI that showed a non-specific area

of cystic encephalomalacia in the left cerebellar hemisphere. She had a neurology and cardiology consultation and was eventually placed on midodrine for her recurrent episodes of presumed syncope. She did not receive further doses of erenumab after her reported SAE.

Reviewer Comment: My general impression of this case is that this is most likely pseudosyncope. However, the patient's physicians started her on midodrine, and she did not receive further doses of erenumab so I cannot completely exclude the role of erenumab in this SAE.

3. Patient 20120295 (b) (6)

This 37-year-old white female was participating in the open-label treatment phase of study 20120295 when she collapsed on (b) (6). It is unknown per the narrative whether the patient lost consciousness. The patient reported headache, dizziness, nausea, and imbalance for several weeks prior to the collapse. She received three doses of 140mg of erenumab in the DBTP. She received her first open-label treatment on (b) (6) (70mg). On (b) (6) after two doses of 70mg, she was increased back to 140mg. The patient was hospitalized on (b) (6) for the event and underwent CT of the head, chest x-ray, EEG, carotid ultrasound, and 24-Holter monitoring. CT of the head was reported to be normal. EEG was reported to have 'paroxysmal changes in connection with background activity.' Carotid ultrasound showed 1.1mm of mixed echogenicity in the carotid artery bulbs. Holter monitoring was normal. The patient was reported to have had a prior 'syncope' event in (b) (6) prior to starting treatment with erenumab. After the event the patient continued in the trial, and received 4 additional doses of 140mg of erenumab.

Reviewer Comment: I cannot completely exclude the role of erenumab. An alternative cause of syncope was not presented. However, she did continue on erenumab without further incident.

4. Patient 20120296 (b) (6)

This 29-year-old white female was participating in the open-label treatment phase of study 20120296 when she experienced a syncopal event. The patient had a prior history of syncope as well. The patient had worked a night shift, and was observed to 'collapse'. The patient indicated that she had an 'intensive migraine headache' just prior to the loss of consciousness. EEG and ECG were reported normal. MRI showed a developmental venous anomaly in the right frontal lobe which had been present on prior MRIs. The patient received 6 doses of erenumab 140mg and 3 doses of 70mg of erenumab prior to the episode. She continued to receive 70mg in the study for 4 additional doses.

Reviewer Comment: Syncope may have been vasovagal from the pain of her migraine. She was able to continue on erenumab without further incident. The role of erenumab in this case appears unlikely.

5. Patient 20120297-[redacted]

This 54-year-old white female who was participating in the open-label portion of study 20120297 when she experienced an episode of loss of consciousness for which she was hospitalized. Prior to the loss of consciousness, she was being treated for a urinary tract infection, and had nausea, vomiting, and diarrhea. The patient was found to be hypotensive with a systolic blood pressure of 80. She had a CT of the head which was reported normal. She received 70mg of erenumab in the DBTP and 70mg in the OLE. The narrative indicates that she was diagnosed with volume depletion. The patient received 3 doses of 70mg in the DBTP and two doses in the OLE prior to her SAE. She continued erenumab after the SAE for 3 additional doses.

Reviewer Comment: The cases of syncope are difficult to adjudicate since they are mostly unwitnessed. Four of the five cases seem reasonable to ascribe to syncope. However, I do not think the cases of syncope are drug-related. In four out of five cases, the patients were able to continue on erenumab after the SAE without further incident. When looking at all cases of reported syncope, and not just those reported as SAEs, there was no imbalance between placebo and treatment in the rate of pre-syncope/syncope in the double-blind treatment period. In the placebo group, the rate was 0.5%, for 70mg it was 0.4%, and for 140mg it was 0.6%.

Thromboses

1. Patient 20120296-[redacted] (Grade 4)

This 37-year-old white male with a history of hyperthyroidism was participating in the open-label phase of Study 20120296 when he was found unconscious while hiking alone on [redacted] He was found to have suffered a closed head injury which was unwitnessed. He was also found to have a cerebral venous sinus thrombosis of the sigmoid sinus and a traumatic cerebellar contusion for which he underwent right suboccipital craniectomy and C1 laminectomy. The patient was also found to have facial bone fractures. The patient received the first dose of erenumab 140mg in the DBTP on [redacted]. He continued into the open-label phase on 140mg on [redacted] He received his last dose on [redacted] He received nine doses of erenumab 140mg, but none after his SAE. He presented for follow up in [redacted] and had no neurological sequelae.

An IR was sent to the sponsor for more information in this case. The sponsor reported that the cerebral injuries were on the right side. A CT venogram reported that "the left sigmoid sinus is dominant and the right internal jugular vein appears to be predominantly supplied by the inferior petrosal sinus. The limits the evaluation of the diminutive transverse and sigmoid sinuses. The transverse sigmoid sinus is again noted to be displaced anteriorly by epidural fluid and then taper near the transverse/sigmoid junction. There is probably occlusive thrombus in

this region although congenital absence of the sigmoid sinus is a known anatomic variant." Patient had been using ecstasy.

Reviewer Comment: Unfortunately, this patient was hiking alone so there is not enough information to determine the sequence of events leading to the closed head injury. It is possible he experienced a seizure, or syncopal episode that led to the fall. It is unknown whether he experienced the venous sinus thrombosis first which then led him to fall, hit is head, and lose consciousness. The cause of the cerebral venous sinus thrombosis is also not clear. He was hiking at the time so dehydration is a possible cause, but is speculative. It is also possible that the cerebral venous sinus thrombosis (CVST) was secondary to the closed head injury. The patient hit his head hard enough to fracture several facial bones and cause a cerebellar subdural hematoma that required evacuation. The patient had a possible right sigmoid sinus thrombosis in association with a right cerebellar hematoma that required craniectomy for evacuation. CVST has been associated with closed head injury and especially head injury associated with skull fractures (Wiggins et al. 2013, Kinal 1967, Taha et al. 1993, Delgado et al. 2010). Overall I cannot rule out the role of erenumab in the patient's closed head injury. The thrombosis is likely to be secondary to the closed head injury.

2. Patient 20120196 (b) (6)

This 46-year-old white female who was participating in the double-blind phase of study 20120296 developed a urinary tract infection and high fever. She received her first dose of erenumab 140mg on (b) (6), and a second (and last) dose on (b) (6) She experienced a urinary tract infection associated with a fever on (b) (6) She was admitted to the hospital and diagnosed with pyelonephritis, *Clostridium difficile* colitis, and sepsis. Her urine culture was positive for *E. coli*, and blood culture was positive for gram negative rods. Stool culture was positive for *C. difficile*. She developed a DVT associated with a peripherally inserted central catheter (PICC) line during this time. She was treated with antibiotics, and these SAEs were reported as resolved on (b) (6)

In (b) (6), the patient had three days of headache associated with left lower extremity weakness. On (b) (6), the patient experienced a cerebral venous thrombosis of the left transverse and sigmoid sinuses diagnosed by a CT venogram performed on (b) (6) She also underwent MRI of the brain. The MRI report stated the following: "Typical signal abnormality is consistent with acute/subacute thrombosis involving the left transverse and sigmoid dural venous sinuses and visualized left internal jugular vein segments. No associated venous infarction." She was treated with warfarin. Her coagulopathy work up was negative including Factor V Leiden, protein C and S, beta 2 glycoprotein, prothrombin gene mutation and cardiolipin antibodies. This SAE occurred 107 days after the first dose of

erenumab and 79 days after the last dose. At her follow-up visit in (b) (6) she was noted to have some ataxia on physical exam.

She had a prior history of deep vein thrombosis (DVT) and pulmonary embolism (PE) in (b) (6) She also has a history of recurrent heparin-induced thrombocytopenia. In (b) (6) she was prescribed warfarin for her DVT and PE. She was prescribed rivaroxaban in (b) (6) but it was discontinued to (b) (6) due to menorrhagia.

Reviewer Comment: The presence of the PICC line is a risk factor for clotting. She had additional risk factors for the development of the CVT: recent hospitalization (within previous 90 days) (Spencer et al. 2006), past medical history of thromboembolism, history of heparin-induced thrombocytopenia, and infection in the prior three months (Spencer et al. 2006). Prior history of VTE confers a relative risk of 7.9 for recurrence per one community based epidemiological study (Samama et al 2000). In an outpatient, prospective cohort study, the risk of recurrence after an acute episode of venous thrombosis was 18, 25, and 30% at two, five, and eight years (Prandoni et al. 1996). This patient's thromboses are unlikely to be secondary to treatment with erenumab.

3. Patient 20120196 (b) (6)

This 52-year-old white female who was participating in the open-label phase of study 20120296 when she developed a DVT. She received 6 doses of 140mg and her first dose was given (b) (6) She then went on to receive 6 additional doses of 70mg in the OLE. She experienced a lower extremity DVT on (b) (6) but continued erenumab treatment. Her last dose was (b) (6). This patient had a prior history of pulmonary embolism (b) (6) DVT (b) (6) and inferior vena cava (IVC) filter placement (b) (6) In (b) (6) the patient had been on OCPs. She was treated in (b) (6) with 6 months of anticoagulation after the IVC filter was placed. In (b) (6) she underwent a workup for coagulopathy. She was found to be heterozygous for prothrombin G20210A gene mutation, and she was reported to have a slightly increased homocysteine level. Antithrombin level, protein C and S activity level were all normal. Factor V Leiden gene mutation and phospholipid antibodies including lupus anticoagulant, cardiolipin antibodies and beta-2 glycoprotein 1 antibodies were all absent.

Reviewer Comment: This patient has a genetic mutation that predisposes her to clotting. The role of erenumab in this case is unlikely.

4. Patient 20120178- (b) (6)

This 56-year-old white female was participating in the open-label phase of study 20120178 when she experienced a DVT. The patient's mother had a 'history of clots' for which she received warfarin. The patient received 3 doses of 21mg of erenumab in the DBTP and an

additional 27 doses of 70mg of erenumab in the OLE. Her first dose was given (b) (6) On (b) (6) the patient experienced a deep vein thrombosis of the left peroneal vein, along with chest pain found to be caused by a pulmonary embolism to the right middle lobe. The patient was treated with warfarin for the DVT. She had been taking aspirin 81mg since (b) (6) but this was discontinued when the anticoagulation for the DVT was started. No coagulopathy workup was performed. Her risk factor for the DVT and pulmonary embolism was a prolonged immobilization (6 weeks) due to a fracture of her left foot. Foot fracture occurred on (b) (6) and immobilization continued through (b) (6) The DVT and PE occurred on (b) (6) Erenumab was continued and the patient's last dose was (b) (6)

Reviewer Comment: This is likely a provoked DVT/PE secondary to immobilization.

5. Patient 20120297- (b) (6)

This 49-year-old white male was participating in the open-label phase of study 20120297 when he experienced a rupture of his cruciate ligament in the left knee. He had a prior history of a left knee meniscus injury in (b) (6) He underwent surgery (b) (6) for the injury, and developed a pulmonary embolism (b) (6) during the hospitalization for the repair of the ligament. He was treated with heparin and rivaroxaban after developing the PE. After surgery, he was partially immobilized for 6 weeks. He remained hospitalized until (b) (6) In total, he received 11 doses of erenumab 70mg.

Reviewer Comment: This is likely a provoked DVT/PE secondary to immobilization.

Reviewer Comment: A more detailed look at thromboses is presented in section 8.5.1. Overall I was unable to find a clear link between treatment with drug and thromboses/emboli. Many of the cases were provoked, or had confounding factors leading to the thrombosis.

Other selected SAEs

1. Urticaria: Patient 20120297- (b) (6)

This 64-year-old white female who was participating in the open-label treatment phase of study 20120297 when she experienced urticaria. She first received erenumab 70mg in the open label period on (b) (6). On (b) (6) she experienced urticaria on the left arm which progressed to the entire body and included the eyelids. She reported significant sun exposure around the same time. She was given lansoprazole on (b) (6). Her last dose of erenumab was given in the abdomen on (b) (6) She was treated with prednisone, diphenhydramine, prednisolone, and fexofenadine. The rash resolved on (b) (6) She received an additional dose of erenumab on (b) (6) without incident. The investigator

attributed the event to the lansoprazole and discontinued it on (b) (6) The investigator switched the patient to an alternative proton pump inhibitor.

2. Myocardial Ischemia: Patient 20120178-(b) (6)

This 51-year-old white female was participating in the open-label treatment phase of study 20120178 when she experienced shortness of breath, hypertension, and tachycardia on (b) (6) She received her first open-label dose of erenumab 70 mg on (b) (6). She was reported to have a normal ECG, normal lab testing for myocardial ischemia, and normal 24-hour blood pressure measurements. These AEs were reported to resolve on (b) (6) She received a second dose of open-label treatment on (b) (6) and experienced shortness of breath again on (b) (6) At this point, IP was discontinued. She underwent an exercise ECG which showed myocardial ischemia, but took sumatriptan four hours prior to the exercise ECG which showed ST segment depressions in II, III, aVF, and V4 through V6. On (b) (6) the patient underwent coronary angiography which showed normal main stem, normal anterior interventricular branch, normal circumflex branch, and normal right coronary artery. TTE was essentially normal with slight mitral valve insufficiency.

Reviewer Comment: The role of erenumab is unlikely in this case since the patient had normal coronary vasculature.

SAEs occurring after discontinuation:

1. Multiple SAEs: Patient 20120178(b) (6)

This 33-year-old female experienced 4 SAE while participating in study 20120178. Two SAEs occurred while she was taking erenumab 70mg, and two SAEs occurred after discontinuation of the drug. The patient experienced status migrainosus requiring hospitalization about 8 days after receiving her first dose of erenumab 70mg. One month later she experienced an episode of vertigo requiring hospitalization. The patient became pregnant sometime in (b) (6) She received her last dose of erenumab on (b) (6) She developed HELLP syndrome, a life-threatening complication of pregnancy often related to hypertension or pre-eclampsia, in (b) (6) Due to the HELLP syndrome, she had a Caesarean section and delivered a pre-mature baby at 31 weeks.

2. Alcoholic liver disease/elevated transaminases: Patient 20120295-(b) (6)

This 40-year-old female was participating in the OLE of study 20120295. The patient received her first dose of erenumab 70mg in the OLE on (b) (6). Her last dose of erenumab was (b) (6) In (b) (6) the patient was diagnosed with alcoholism and alcoholic liver disease. She was reported to be drinking 200ml of alcohol and 1 beer daily prior to hospitalization in psychiatry for alcohol addiction. In (b) (6) her AST was 167 U/L, and ALT 112 U/L. While hospitalized, her AST was 26 U/L, and ALT was 28 U/L. After discharge from the

hospital, the patient resumed drinking alcohol and her AST rose to 301 U/L, and ALT to 1534 U/L. She was then re-hospitalized from (b) (6) During this time AST and ALT returned to normal (16 U/L and 10 U/L).

Grade 4 SAEs (not already discussed above)

1. Intestinal obstruction/fecaloma: Patient 20120178-(b) (6)

This 44-year-old-white female with a history of a congenital perineal atresia/fistula and intestinal surgery in childhood was participating in the open-label treatment phase of study 20120178. The patient was hospitalized for a non-invasive treatment of massive fecal impaction. She had received three doses of 70mg of erenumab in the DBTP, and 28 doses of 70mg in the open-label phase. The AE occurred in (b) (6), and the patient continued treatment until at least (b) (6)

Reviewer Comment: This AE is likely related to drug. Constipation is one of the common AEs seen in the studies. The patient's medical history may have predisposed her to this more serious outcome.

2. Uterine fibroids: Patient 20120296-(b) (6)

This 43-year-old female was participating in the open label phase of study when she was diagnosed with uterine leiomyoma. This was characterized as an SAE because the patient was hospitalized and underwent removal of the uterus. The patient received her first dose of 70mg on (b) (6). She received 6 doses of 70mg, and then switched to 140mg in the OLE. She received 7 doses of 140mg in the open-label period. She was diagnosed with the uterine leiomyoma two months after her last dose of erenumab.

3. Papillary thyroid cancer: Patient 20120297-(b) (6)

This 48-year-old female was participating in the open-label treatment phase of study 20120297 when she was diagnosed with papillary thyroid cancer. She received three doses of 70mg of erenumab in the DTBP and one additional dose in the open-label treatment period.

4. Multiple Grade 4 AEs: Patient20120297(b) (6)

This 55-year-old white female was participating in the open-label treatment phase of study 20120297. She had received placebo in the DBTP. In the open-label phase she had received two doses of erenumab 70mg by the time of her AE. In (b) (6), the patient was hospitalized due to multifocal pneumococcal bacteremia. She was further diagnosed with adult respiratory distress syndrome (ARDS), and subsequently developed atrial fibrillation. Laboratory results showed elevated troponins (peak of 0.51) and she was diagnosed with myocardial demand ischemia from the ARDS/multifocal pneumonia. After the event resolved she continued treatment with erenumab and received three additional doses of 70mg.

Narratives for SAEs that are not captured in the ISS

1. Tendon Rupture: Patient (b) (6)

This 29-year-old female received a single dose of erenumab 70mg on (b) (6). On (b) (6) the patient experienced a left ruptured Achilles tendon while playing basketball which required hospitalization and surgery to repair the tendon rupture.

2. Polyarthritis: Patient 20101268- (b) (6)

This 49-year-old male was participating in Study 20101268 when he started to develop joint pain in his shoulders, hips, and knees. He received the first dose of erenumab 70mg on (b) (6) and developed the joint symptoms on (b) (6). Last dose of erenumab was (b) (6) Symptoms continued to worsen through (b) (6) when he developed a skin rash. In (b) (6) he underwent lab testing, and PET scan which confirmed inflammation and ruled out vasculitis. He had skin and muscle biopsies that were reported as normal. One year after he had last dose of erenumab, the patient experienced a deep vein thrombosis (DVT) and pulmonary embolism (PE). He had a prior history of hepatitis B, PE and DVT in (b) (6) as well, prior to receiving erenumab.

3. Depression: Patient (b) (6)

This 32-year-old female with a history of alcohol abuse, bipolar disorder, and eating disorder received a single dose of erenumab 70mg. One month after the single dose, she was hospitalized for depression. She denied suicidal ideation. The investigator reported that non-compliance with her medication may have been a triggering factor for the event.

4. Fatigue: Patient (b) (6)

This 24-year-old female received a single dose of erenumab 70mg. One month later she experienced fatigue. This was reported as an SAE because the patient required hospitalization.

5. Suicidal thoughts/depression: Patient 20101268 (b) (6)

This 45-year-old female was participating in study 20101268. She had received 3 doses of 140mg SC of erenumab. The last dose was given on (b) (6) The patient was hospitalized for suicidal thoughts and depression on (b) (6) She continued to be followed through (b) (6)

6. Spontaneous abortion: Patient (b) (6)

This 30-year-old female experienced a spontaneous abortion two months after a single dose of erenumab 140mg.

The narratives included below are not necessarily of SAEs. I noted where applicable if an event was an SAE.

Review of Designated Medical Events

1. Drug-induced liver injury (DILI): Patient 20160349-[redacted] (SAE)

This 51-year-old female received a single dose of erenumab 140mg on [redacted] She was participating in a single-dose PK study. One week later, on [redacted] during a routine visit, she was found to have elevated transaminases and total bilirubin (ALT 1626 U/L, AST 1713 U/L, total bilirubin 1.3mg/dl) with prior baseline labs of AST 17 U/L, ALT 15 U/L, and tbili 0.3mg/dl. Laboratory testing was repeated on [redacted] which showed ALT 6025 U/L, AST 2065 U/L, and total bilirubin 4.9mg/dl. She experienced some clinical symptoms including nausea, vomiting, abdominal pain, decreased appetite, and jaundice. She was not encephalopathic. Ultrasound of the right upper quadrant showed no acute findings, and no evidence of biliary dilatation. Follow up testing showed decreasing AST, and ALT (1528 U/L/ 152 U/L) with increasing Tbili (3.3mg/dl) and INR of 1.41.

The patient had a medical history of cholecystectomy, hysterectomy, abdominoplasty, depression, fibromyalgia, and right bundle branch block. She admitted to ingesting an unknown quantity of chlordiazepoxide in response to the recent death of her boyfriend. She had taken a ten-day course of amoxicillin-clavulanic acid and metronidazole starting [redacted] She took two doses of fluconazole 200mg (one tablet per week for two weeks) starting [redacted] She was on atenolol, folic acid, and gabapentin at the time of the initial liver injury.

Reviewer Comment: This case of drug-induced liver injury is significantly confounded by the patient's concomitant medications. According to LiverTox, Clinical and Research Information on Drug-Induced Liver Injury provided by the NIH, use of amoxicillin-clavulanate is the most common cause of clinically apparent DILI. The injury can occur within a few days up to as long as eight weeks after receiving therapy with an average delay of three weeks. The patient also took an unknown quantity of chlordiazepoxide, which is extensively liver metabolized. According to LiverTox, there are rare cases of clinically apparent liver injury from the use of chlordiazepoxide likely related to the production of a metabolic intermediate.

I obtained a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding this case. Dr. Mehta's conclusion is that an unidentified cause is the most likely explanation of the acute liver injury. She feels that a bile duct stone is the second most likely explanation. Her conclusion is that erenumab and amoxicillin-clavulanic acid are the least likely causes. Please see the consult from Dr. Ruby Mehta and section 8.5.2 for further discussion of this case.

2. Ischemic colitis: Patient 20120178[redacted] (SAE)

This 58-year-old white male with a history of deafness, pulmonary embolism, hypercholesterolemia, and irritable bowel syndrome was participating in the open-label portion

of study 20120178 when he experienced rectal bleeding for which he underwent colonoscopy. The colonoscopy showed diverticula, and ischemic colitis. The patient received his first dose of investigational product in the DBTP on (b) (6) He entered the OLE on (b) (6) During the DBTP, he received three doses of 70mg of erenumab, and during the OLE he received 23 doses of 70mg, and four doses of 140mg. After the diagnosis of ischemic colitis, the patient continued in the study and his dose was increased from 70mg to 140mg of erenumab. His concomitant medications were naproxen, sumatriptan, lovastatin, and diclofenac.

Reviewer Comment: Erenumab may have had a role in the case of ischemic colitis although it is unlikely since the patient continued on erenumab on a higher dose without complication.

3. Seizure: Patient 20120178 (b) (6) (SAE)

This 34-year-old female who experienced a generalized tonic-clonic seizure had been taking erenumab 70mg in the DBTP. She received her first dose of erenumab 70mg on (b) (6) The seizure occurred on (b) (6) which was three months after her last dose of erenumab. The erenumab had been discontinued due to hypertension with blood pressure reading of 180/100.

4. Seizure: Patient 20120178- (b) (6)

This 26-year-old female with a medical history of bulimia experienced a seizure while participating in the open-label treatment phase of study 20120178. The seizure was reported as a 'febrile convulsion' by the sponsor. She was diagnosed with influenza B at the time of her 'febrile convulsion.' She received her first dose of investigational product in DBTP on (b) (6) and her first dose in the OLE on (b) (6). The seizure occurred on (b) (6) She had received three doses of 7mg of erenumab in the DBTP, and 25 doses of 70mg in the open-label period. After the seizure, erenumab was discontinued.

5. Seizure: Patient 20120178- (b) (6)

This 32-year-old female with a medical history of seizures (b) (6) who was participating in the open-label treatment phase of study 20120178 experienced a seizure. The patient received three doses of erenumab 21mg during the DBTP, and subsequently received 70mg of erenumab in the OLE. The patient's participation in the study was ended due to a determination of previously undisclosed medical history of seizures.

Reviewer Comment: It is unlikely that the three SAEs of seizure are related to erenumab. One of the seizures occurred three months after discontinuation of the drug, and one occurred in a patient with a history of seizures. There was not enough information to determine if the third case was in fact a 'febrile convulsion'. However, a febrile convulsion would be unusual in the adult population.

6. Deafness/hearing loss: Patient 20120295-(b) (6)

This 51-year-old female was participating in the open-label extension of study 20120295 when she experienced deafness/hearing loss. She received three doses of 140mg of erenumab in the DBTP, and 70mg in the open-label period. Her first dose of erenumab was September (b) (6) She experienced the hearing loss on (b) (6). She was reported to have a concomitant upper respiratory tract infection. This hearing loss resolved by (b) (6) during which time she continued erenumab.

7. Neutropenia/thrombocytopenia: Patient 20120297 (b) (6)

This 54-year-old female was participating in the open-label treatment phase receiving erenumab 70mg when she experienced neutropenia. Her laboratory assessments in (b) (6) showed a decreased white blood cell count (1.8 with normal range 4.1-12.3) and platelets 122 (normal range 140-540). She was asymptomatic. Her follow up labs in (b) (6) showed resolution of these abnormalities. She continued erenumab with no change in the dosage.

8. Blindness transient: Patient 20120178-(b) (6)

This 28-year-old female was participating in the open-label treatment phase of study 20120178 when she experienced blurry vision in the left eye on (b) (6) The patient received her first dose of erenumab 21 mg in the DBTP on (b) (6) She received her first open-label dose of erenumab 70mg on (b) (6) The patient developed worsening vision in the left eye, and pain with eye movement. She underwent an MRI of the brain and a fluorescein angiogram as well as an evaluation by ophthalmology, and a retinal specialist. The patient was admitted to the hospital on (b) (6) for treatment of optic neuritis. She was given methylprednisolone, and her vision improved. On (b) (6), her vision loss worsened, and she was started on prednisone and subsequently diagnosed with multiple sclerosis. Her vision loss resolved by (b) (6) Her treatment with erenumab was interrupted briefly during (b) (6) but she resumed erenumab in (b) (6) Her dose was increased to 140mg. In total, she received three doses of 21mg, 31 doses of 70mg, and two doses of 140mg.

Some of the events that are designated medical events were not coded as SAEs in the ISS database: two cases of hearing loss, one case of transient blindness, one case of neutropenia, and three cases of anaphylaxis. There were 3 cases of anaphylaxis in the ISS database. They were attributed to a stinging insect, food allergy, and a penicillin allergy. None appeared to be related to erenumab.

Grade 4 CK Elevations

CK elevations were not SAEs, but narratives of interest were included.

1. Patient 20120296 (b) (6)

This 62-year-old white male who was participating in the DBTP of study 20120296 experienced markedly elevated blood creatine phosphokinase (CK) to 9619. This elevation occurred 4 weeks after a single dose of erenumab 140mg. Follow-up labs showed resolution. He received 12 additional doses of erenumab without further incident. The narrative provided no information as to possible cause.

2. Patient 20120296- (b) (6)

This 26-year-old white female who was participating in the DBTP of study 20120296 experienced markedly elevated CK to 3899. The patient's finally accepted screening value was 80, but she had a previous screening value of 2633. The elevated CK occurred after she had received 5 doses of erenumab 140mg. The elevated CK resolved by the time of the next lab check four weeks later. She received three more doses of erenumab without further incident. The narrative provided no information to possible cause.

3. Patient 20120297- (b) (6)

This 22-year-old white female who was participating in the open-label treatment phase of study 20120297 when she experienced markedly elevated CK to 2374. Follow up labs taken four days later showed resolution. She had received two doses of erenumab 70mg prior to the elevated CK. She subsequently received six more doses of erenumab without incident. The narrative provided no information to possible cause.

Reviewer Comment: For these grades 4 CK elevations, I found no evidence of associated muscle pain/cramps or cardiac/chest pain. All grade 4 CK elevations were transient. However, the sponsor did not identify a cause for these elevations. The role of erenumab seems unlikely though as the half-life is long, and the patients had quick resolution of the CK elevation. All three cases the patients continued to receive erenumab without further CK elevations.

Reviewer Comment: The rate of serious adverse events is overall quite low. In the double-blind portions of the combined studies, there are no significant differences in the rates of SAEs in placebo compared to treatment. Initially there appeared to be an imbalance in SAEs in the Infections/Infestations SOC. When evaluating the SAEs in that SOC, the majority of the infections can be attributed to a single patient who had a complicated hospital course.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

For the studies included in the ISS, the protocols recommended permanent discontinuation of

the investigational product for the following reasons:

a. Possible drug induced liver injury if all the criteria are met: total bilirubin >2x the upper limit of normal (ULN) or INR> 1.5 AND increased AST or ALT from >3x ULN AND no other cause for laboratory abnormalities is found
b. A patient experiences a severe or life-threatening adverse event reported by the investigator to be related to the investigational product.

In the overall ISS database, there were 101 patients where the investigational product was withdrawn due to an adverse event, of which 88 were taking erenumab at the time of withdrawal.

In the double-blind portion of the studies, I calculated a total of 13 patients (1.2%) in the placebo group, 15 patients (1.7%) in 70mg group, and 12 patients (2.4%) in 140mg group who experienced AEs that led to discontinuation of IP (Table 69). While the rate of discontinuation due to AEs was twice that in the 140mg group as compared to placebo, the actual numbers and percentages of patients who discontinued due to AEs is quite low.

Table 69 Discontinuations Due to Adverse Events in the DBTP

MedDRA System Organ Class Adverse Event (Preferred Term)	Placebo N=1043 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
Cardiac Disorders	**0**	**1 (0.1)**	**2 (0.4)**
Palpitations	0	1 (0.1)	1 (0.2)
Ventricular extrasystoles	0	0	1 (0.2)
Ear and Labyrinth Disorders	0	**1 (0.1)**	**2 (0.4)**
Tinnitus	0	0	1 (0.2)
Vertigo	0	1 (0.1)	1 (0.2)
Gastrointestinal Disorders	**1 (0.1)**	**4 (0.4)**	**3 (0.6)**
Abdominal pain	0	1 (0.1)	0
Constipation	0	0	1 (0.2)
Dyspepsia/GERD	1 (0.1)	0	1 (0.2)
Irritable bowel syndrome	0	1 (0.1)	0
Nausea	0	1 (0.1)	0
Oral pain	0	0	1 (0.2)
Vomiting	0	1 (0.1)	0
General/Administration Site	**1 (0.1)**	**3 (0.3)**	**1 (0.2)**
Fatigue	1 (0.1)	1 (0.1)	1 (0.2)
Injection site rash	0	1 (0.1)	0

Temperature intolerance	0	1 (0.1)	0
Immune System Disorders	**1 (0.1)**	1 (0.1)	**0**
Allergy to arthropod sting	0	1 (0.1)	0
Hypersensitivity	1 (0.1)	0	0
Infections and Infestations	**0**	**0**	**1 (0.2)**
Vestibular neuronitis	0	0	1 (0.2)
Injury, Poisoning, Procedural Complications	**1 (0.1)**	**0**	**0**
Intentional overdose	1 (0.1)	0	0
Investigations	**1 (0.1)**	**0**	**0**
Electrocardiogram T wave inversion	1 (0.1)	0	0
Musculoskeletal and Connective Tissue	**0**	**3 (0.3)**	**1 (0.2)**
Arthralgia	0	2 (0.2)	0
Pain in extremity	0	1 (0.1)	0
Rheumatic disorder	0	0	1 (0.2)
Nervous System Disorders	**2 (0.2)**	**3 (0.3)**	**0**
Dizziness	0	1 (0.1)	0
Migraine/headache	2 (0.2)	2 (0.2)	0
Pregnancy, Puerperium, and Perinatal	**0**	1 (0.1)	**0**
Pregnancy	0	1 (0.1)	0
Psychiatric Disorders	**1 (0.1)**	**3 (0.3)**	**2 (0.4)**
Affect lability/mood swings	0	1 (0.1)	1 (0.2)
Attention deficit/hyperactivity disorder	0	0	1 (0.2)
Insomnia	0	1 (0.1)	0
Nervousness	0	1 (0.1)	0
Panic attack	1 (0.1)	0	0
Reproductive System and Breast Disorders	**0**	1 (0.1)	**1 (0.2)**
Metrorrhagia	0	1 (0.1)	1 (0.2)
Respiratory, Thoracic, and Mediastinal	**2 (0.2)**	**0**	**0**
Cough	1 (0.1)	0	0
Dyspnea	1 (0.1)	0	0
Skin and Subcutaneous Tissue Disorders	**4 (0.4)**	**1 (0.1)**	**1 (0.2)**
Alopecia	2 (0.2)	0	0
Erythema	1 (0.1)	0	0
Urticaria	0	1 (0.1)	0
Rash	1 (0.1)	0	1 (0.2)
Vascular Disorders	**0**	**1 (0.1)**	**0**
Hypertension	1 (0.1)	1 (0.1)	0
Total # of Events*	15 (1.4%)	23 (2.5%)	14 (2.8%)
Total # of Patients	13 (1.2%)	15 (1.7%)	12 (2.4%)

Reviewer created table from ISS dataset ADAE (numerator) where APERIOD=1 and ADSL (denominator).
*Some patients reported more than one adverse event.

The open-label exposure was examined for discontinuations due to adverse events as well. In total, there were 61 adverse events reported by 57 patients in the open-label period leading to withdrawal of erenumab (Table 70).

Table 70: Open-Label Experience: Discontinuations Due to AEs by Events

MedDRA System Organ Class Adverse Event (Preferred Term)	70mg only N=1301 n(%)	140mg only N=371 n(%)	70mg and 140mg** N=827 n(%)	Total N=2499 n(%)
Blood and Lymphatic System Disorders	**1 (0.1)**	**1 (0.3)**	**0**	**2 (0.1)**
Monocytopenia	1 (0.1)	1 (0.3)	0	2 (0.1)
Cardiac Disorders	**1 (0.1)**	**0**	**3 (0.4)**	**4 (0.2)**
Arteriosclerosis coronary artery	0	0	1 (0.1)	1 (<0.1)
Cardiac failure	0	0	1 (0.1)	1 (<0.1)
Myocardial ischemia	1 (0.1)	0	0	1 (<0.1)
Tachycardia	0	0	1 (0.1)	1 (<0.1)
Congenital, Familial, and Genetic Disorders	**0**	**0**	**1 (0.1)**	**1 (<0.1)**
Arrhythmogenic right ventricular dysplasia	0	0	1 (0.1)	1 (<0.1)
Ear and Labyrinth Disorders	0	**0**	**1 (0.1)**	**1 (<0.1)**
Vertigo	0	0	1 (0.1)	1 (<0.1)
Eye Disorder	**1 (0.1)**	**0**	**0**	1 (<0.1)
Idiopathic orbital inflammation	1 (0.1)	0	0	1 (<0.1)
Gastrointestinal Disorders	**4 (0.3)**	**0**	**1 (0.1)**	**5 (0.2)**
Gastritis	1 (0.1)	0	0	1 (<0.1)
Nausea	1 (0.1)	0	1 (0.1)	2 (0.1)
Pancreatic cyst	1 (0.1)	0	0	1 (<0.1)
Swollen tongue	1 (0.1)	0	0	1 (<0.1)
General/Administration Site	**5 (0.4)**	**0**	**1 (0.1)**	**6 (0.2)**
Fatigue	0	0	1 (0.1)	1 (<0.1)
Generalized edema	1 (0.1)	0	0	1 (<0.1)
Influenza like illness	1 (0.1)	0	0	1 (<0.1)
Injection site pain	1 (0.1)	0	0	1 (<0.1)
Injection site urticaria	1 (0.1)	0	0	1 (<0.1)
Peripheral edema	1 (0.1)	0	0	1 (<0.1)
Hepatobiliary Disorders	**1 (0.1)**	**0**	**1 (0.1)**	**2 (0.1)**
Alcoholic liver disease	0	0	1 (0.1)	1 (<0.1)
Biliary cirrhosis primary	1 (0.1)	0	0	1 (<0.1)
Immune System Disorders	**1 (0.1)**	**0**	**0**	**1 (<0.1)**

Hypersensitivity	1 (0.1)	0	0	1 (<0.1)
Injury, Poisoning, Procedural Complications	**0**	**1 (0.3)**	**0**	**1 (<0.1)**
Subdural hematoma	0	1 (0.3)	0	1 (<0.1)
Investigations	**1 (0.1)**	**1 (0.3)**	**0**	**2 (0.1)**
Alanine aminotransferase increased	1 (0.1)	1 (0.3)	0	2 (0.1)
Musculoskeletal and Connective Tissue	**2 (0.2)**	**0**	**1 (0.1)**	**3 (0.1)**
Arthralgia	1 (0.1)	0	0	1 (<0.1)
Arthritis	0	0	1 (0.1)	1 (<0.1)
Intervertebral disc protrusion	1 (0.1)	0	0	1 (<0.1)
Neoplasms Benign, Malignant, Unspecified	**5 (0.4)**	**1 (0.3)**	**0**	**6 (0.2)**
Breast/invasive lobular breast cancer	2 (0.2)	0	0	2 (0.1)
Breast fibroma	0	1 (0.3)	0	1 (<0.1)
Lung adenocarcinoma stage III	1 (0.1)	0	0	1 (<0.1)
Papillary thyroid cancer	2 (0.2)	0	0	2 (0.1)
Nervous System Disorders	**6 (0.5)**	**1 (0.3)**	**4 (0.5)**	**11 (0.4)**
Seizure	1 (0.1)	0	0	1 (<0.1)
Migraine/headache	3 (0.2)	1 (0.3)	4 (0.5)	8 (0.3)
Somnolence	1 (0.1)	0	0	1 (<0.1)
Syncope	1 (0.1)	0	0	1 (<0.1)
Psychiatric Disorders	**3 (0.2)**	**0**	**3 (0.4)**	**6 (0.2)**
Anxiety	1 (0.1)	0	1 (0.1)	2 (0.1)
Depression	2 (0.2)	0	1 (0.1)	3 (0.1)
Irritability	0	0	1 (0.1)	1 (<0.1)
Respiratory, Thoracic, and Mediastinal	**1 (0.1)**	**0**	**1 (0.1)**	**2 (0.1)**
Dyspnea	1 (0.1)	0	1 (0.1)	2 (0.1)
Skin and Subcutaneous Tissue Disorders	**2 (0.2)**	**1 (0.3)**	**2 (0.2)**	**5 (0.2)**
Alopecia	0	0	1 (0.1)	1 (<0.1)
Rash	2 (0.2)	1 (0.3)	0	3 (0.1)
Urticaria	0	0	1 (0.1)	1 (<0.1)
Vascular Disorders	**2 (0.2)**	**0**	**0**	**2 (0.1)**
Hypertension	1 (0.1)	0	0	1 (<0.1)
Raynaud's phenomenon	1 (0.1)	0	0	1 (<0.1)
Total # AEs	**36 (2.8)**	**6 (1.6)**	**19 (2.3)**	**61 (2.4)**
Total # Patients				**57 (2.3)**

Reviewer created table from ISS dataset ADAE (numerator) where APERIOD=2 or APERIOD=3
*The open-label experience is a subset of Pool C. I did not include the AEs experienced during the double-blind treatment period in this table. **The doses in this column refer to patients who received both 70mg and 140mg in the open-label portion of the studies.

120-day Safety Update

There were only 3 more cases of withdrawal due to AEs at the time of the 120-day update (palpitations, worsening visual acuity secondary to prior suprasellar epidermoid tumor, and hypertension). The patient who discontinued due to hypertension was hypertensive at baseline (135/86 and 157/92). She remained hypertensive during treatment with placebo, and during the first few months of treatment with erenumab in the OLE. She was put on benazepril, and diltiazem with improvement of her hypertension. Her AE of hypertension does not appear to be related to erenumab.

Review of Notable Discontinuations

In the DBTP, there were two patients who dropped out due to constipation: one in the 140mg arm, and one in the 70mg arm. The patient receiving 140mg had constipation severe enough to require treatment, and led to discontinuation. There was an additional patient in the 70mg group who dropped out due to worsening constipation. This patient was coded as worsening irritable bowel syndrome, but it appears that the constipation aspect of her IBS is what worsened. This patient received two doses of erenumab 70mg. She was taking linaclotide for constipation, and required an increased dose of medication.

In the DBTP, there was a patient who was normotensive at baseline and had several hypertensive readings after starting on erenumab 70mg. Blood pressure was 160/110 at 27 days after the first dose, and 180/100 30 days after the second dose. The patient was started on ramipril, but no follow up blood pressures were recorded. The role of erenumab in this case cannot be excluded.

In the OLE, there was one case of discontinuation due to worsening Raynaud's phenomenon. This is discussed in more detail in section 8.5.1 Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease. There was one case of a patient who discontinued due to 'flu-like illness'. This patient tolerated three doses of placebo in the DBTP. He received two doses of 70mg in the OLE, and reported flu-like illness three days after receiving the second dose of erenumab.

Reviewer Comment: There was nearly double the rate of discontinuation due to AEs in the treatment groups as compared to placebo during the DBTP, but the actual numbers of patients who discontinued due to AEs and the rates of discontinuation due to AEs were overall low. The rate of discontinuation due to AEs remained consistent in the open-label treatment period.

8.4.4. **Significant Adverse Events**

AEs Leading to Dose Interruption

In the integrated database of all randomized patients, there were 49 patients (1.9%) on erenumab who reported adverse events resulting in dose interruption. The most common AEs resulting in dose interruption were arthralgia, joint swelling, asthma, and migraine/headache. Abnormal ECG resulting in dose interruption was experienced by two patients (left bundle branch block, and QT prolongation).

AEs by Intensity

The Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE) was used to grade adverse events. Severity of AEs was graded as Grade 1=mild; Grade 2=moderate; Grade 3= severe; Grade 4=life threatening; Grade 5=fatal.

There were 7866 AEs reported in the ISS database. The majority of the AEs (95.7%) reported were either Grade 1 or Grade 2 in intensity (Table 71). There were no imbalances noted in toxicity grade between placebo and treatment during the DBTP (Table 72).

Table 71 AEs in the ISS Database by Grade

	# of AEs	% of AEs*	# of patients	% of patients**
Grade 1	4331	55.1	1469	55.3
Grade 2	3190	40.6	1331	50.1
Grade 3	329	4.2	241	9.1
Grade 4	10	0.1	7	0.3
Grade 5	3	<0.1	2	0.1

Reviewer created table using ISS ADAE database, analysis of AETOXGR and AETOXGR by USUBJID
*The denominator is the total number of AEs reported (7866).
**The denominator is the total number of randomized patients in the database (2656). This column does not sum to 100 because some patients reported more than one adverse event.

Table 72 AE Toxicity Grade Summary by Dose in the DBTP

	Placebo		70mg		140mg	
	AEs N=1224 n(%)	Pts N=1043 n(%)	AEs N=1028 n(%)	Pts N=893 n(%)	AEs N=691 n(%)	Pts N=507 n(%)
Grade 1	702 (57.4)	375 (36.0)	614 (59.7)	315 (35.3)	408 (59.0)	184 (36.3)
Grade 2	478 (39.1)	309 (29.6)	370 (36.0)	236 (26.4)	249 (36.0)	142 (28.0)
Grade 3	43 (3.5)	38 (3.6)	43 (4.2)	34 (3.8)	33 (4.8)	20 (3.9)
Grade 4	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.2)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Reviewer created table from ISS ADAE where APERIOD=1, analysis of AETOXGR by TRT01AN

120-day Update

At the 120-day update there were no additional cases of Grade 5 AEs reported. There were three additional Grade 4 AEs reported.

Reviewer Comment: The majority of AEs reported were of either Grade 1 or Grade 2 severity. The Grade 4 and Grade 5 AEs are discussed under sections 8.4.1 Deaths, and 8.4.2 SAEs. There were no imbalances noted between placebo and treatment groups in toxicity grade of AEs.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs in the ISS database occurring in more than 1% of treated patients were various types of infections (URI, colds, rhinitis, flu-like illnesses, bronchitis, urinary tract infections), injection site reactions, gastrointestinal symptoms (nausea, vomiting, dyspepsia, diarrhea, abdominal pain, constipation), headache/migraine, dizziness, cough, somnolence, arthralgia, pruritus, and insomnia (Table 73). Many of these AEs occurred at rates similar to placebo. I reviewed TEAEs in the DBTP occurring in greater than 2% of treated patients and evaluated their frequency compared to placebo. I summarized the TEAEs that occurred in 2% or greater of the treatment population, and which also had an imbalance from placebo with a risk difference of 1% or 2% (Tables 74, 75, 77, and 78). (b) (4) my analysis of the individual studies' TEAEs for comparison to the pooled data. (b) (4), and my tables do not. I also included a table that shows relative risk of common AEs in 140mg dose versus placebo in studies 20120295 and 20120296 as those are the only two studies with a 140mg arm. I created the tables in TEAE section utilizing FDA-

created queries. For the tables utilizing 3-month data, the DBTP was identified utilizing the sponsor's flag POOL1RFL. To identify the entire DBTP inclusive of 6-month data, I utilized APERIOD=1 to identify all AEs that occurred in the DBTP.

Table 73 Common TEAEs in the DBTP occurring in ≥1% of Erenumab Treated Patients

	Placebo N=1043 n(%)	**70mg** N=893 n(%)	**140mg** N=507 n(%)	**All doses: 70mg or 140mg**
Infection, all	251 (24.1)	217 (24.3)	139 (27.4)	356 (25.4)
URI, cold, rhinitis, flu-like illness	163 (15.6)	144 (16.1)	89 (17.6)	233 (16.6)
Injection site reaction (all)	34 (3.3)	53 (5.9)	25 (4.9)	78 (5.6)
Headache/migraine	59 (5.7)	45 (5.0)	18 (3.6)	63 (4.5)
Urinary tract infection	24 (2.3)	16 (1.8)	16 (3.2)	32 (2.3)
Dyspepsia, nausea, vomiting, indigestion, epigastric pain, gastritis	45 (4.3)	33 (3.7)	20 (3.9)	53 (3.8)
Asthenia, fatigue, malaise	29 (2.8)	27 (3.0)	13 (2.6)	40 (2.9)
Constipation	12 (1.2)	13 (1.5)	20 (3.9)	33 (2.4)
Arthralgia, arthritis	22 (2.1)	18 (2.0)	13 (2.6)	31 (2.2)
Dizziness, lightheadedness	14 (1.3)	12 (1.3)	8 (1.6)	20 (1.4)
Cramps, muscle spasms	4 (0.4)	1 (0.1)	10 (2.0)	11 (0.8)
Cough	12 (1.2)	8 (0.9)	9 (1.8)	17 (1.2)
Insomnia	8 (0.8)	7 (0.8)	8 (1.6)	15 (1.1)
Pruritus (including injection site)	12 (1.2)	12 (1.3)	13 (2.6)	25 (1.8)
Vertigo	13 (1.3)	9 (1.0)	6 (1.2)	15 (1.1)
Chest pain (non-cardiac or unknown)	9 (0.9)	4 (0.5)	6 (1.2)	10 (0.7)
Fracture	3 (0.3)	5 (0.6)	5 (1.0)	10 (0.7)
Allergic reaction, hypersensitivity	10 (1.0)	9 (1.0)	3 (0.6)	12 (0.9)
Hypertension, blood pressure increased	14 (1.3)	9 (1.0)	1 (0.2)	10 (0.7)

Reviewer created table from ISS dataset ADAE. *'All doses' only includes patients who received 70mg, or 140mg in the DBTP of studies 20120178, 20120295, 20120296, 20120297

I selected the TEAEs based on the frequency of the event (at least 2%) with imbalance relative to placebo in the DBTP. An AE was included in Table 74 if the risk difference in either dose was 1% or greater. Table 75 uses a risk difference of 2% or greater. Tables 74 and 75 utilize 3-month data. Tables 77 and 78 utilize all the data in the DBTP inclusive of 6-month data from study 20120296.

Table 74 TEAEs in the DBTP with Risk Difference of ≥1% (3-month data)

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=890	n=787	n=507		
Cramps, muscle spasms	4 (0%)	1 (0%)	10 (2%)	0	2
Constipation	10 (1%)	9 (1%)	16 (3%)	0	2
Injection site reaction	27 (3%)	45 (6%)	23 (5%)	3	2
infection, viral	23 (3%)	33 (4%)	17 (3%)	1	0
Cough	8 (1%)	6 (1%)	8 (2%)	0	1
Pruritus	6 (1%)	6 (1%)	9 (2%)	0	1

*Studies 20120295, 20120296, 20120297 inclusive of 3-month data

Table 75 TEAEs in the DBTP with Risk Difference of ≥2% (3-month data)

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=890	n=787	n=507		
Cramps, muscle spasms	4 (0%)	1 (0%)	10 (2%)	0	2
Constipation	10 (1%)	9 (1%)	16 (3%)	0	2
Injection site reaction	27 (3%)	45 (6%)	23 (5%)	3	2

*Studies 20120295, 20120296, 20120297 inclusive of 3-month data

Table 77 TEAEs in the DBTP with Risk Difference of ≥1% (inclusive of 6-month data)

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=890	n=787	n=507		
infection, all	221 (25%)	196 (25%)	138 (27%)	0	2
URI, cold, flu	143 (16%)	130 (17%)	88 (17%)	1	1
injection site reaction	27 (3%)	48 (6%)	25 (5%)	3	2
infection, viral	30 (3%)	36 (5%)	24 (5%)	2	2
constipation	11 (1%)	10 (1%)	20 (4%)	0	3
arthralgia, arthritis, arthrosis	16 (2%)	16 (2%)	13 (3%)	0	1
cramps, muscle spasms	4 (0%)	1 (0%)	10 (2%)	0	2
insomnia	10 (1%)	8 (1%)	8 (2%)	0	1

*Studies 20120295, 20120296, 20120297 inclusive of 6-month data

Table 78 TEAEs in the DBTP with Risk Difference of ≥2% (inclusive of 6-month data)

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=890	n=787	n=507		
Cramps, muscle spasms	4 (0%)	1 (0%)	10 (2%)	0	2
Constipation	11 (1%)	10 (1%)	20 (4%)	0	3
Injection site reaction	27 (3%)	48 (6%)	25 (5%)	3	2
Infection, all	221 (25%)	196 (25%)	138 (27%)	0	2

*Studies 20120295, 20120296, 20120297 inclusive of 6-month data

Reviewer Comment: The common adverse event table I have created (Table 75) is similar to the sponsor's table (b) (4) *Constipation should be considered for the list of warnings and precautions. There was one SAE related to constipation that resulted in hospitalization (fecaloma described in SAEs). There was one case of drug withdrawal and one case of drug interruption, both in 140mg arm due to the AE constipation. At the time of the 120-day update, there were 10 additional cases of constipation reported, none resulting in drug withdrawal or interruption.*

I have included the results of the individual studies as well (Tables 79 through 81). These tables are 3-month data except for 20120296 which is a 6-month study. These tables were created

using a risk difference of 2% or greater in either dose group (when rounding). For the same tables utilizing a risk difference of 1% or greater individual studies, please see Appendix Tables 144 through 146.

Table 79 TEAEs from Study 20120295 with a Risk Difference of 2% or Greater

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=282	n=190	n=188		
Cramps, muscle spasms	4 (1%)	2 (1%)	7 (4%)	0	3
Constipation	1 (0%)	0 (0%)	8 (4%)	0	4
Injection site reaction	6 (2%)	9 (5%)	14 (7%)	3	5
Infection, viral	3 (1%)	7 (4%)	5 (3%)	3	2
Pruritus	1 (0%)	1 (1%)	4 (2%)	1	2
Abdominal pain, distention, bloating	3 (1%)	5 (3%)	4 (2%)	2	1
Epistaxis	0 (0%)	3 (2%)	0 (0%)	2	0
Influenza	0 (0%)	5 (3%)	1 (1%)	3	1
Cough	3 (1%)	1 (1%)	6 (3%)	0	2

Reviewer created table from study 20120295, 3-month data

Table 80 TEAEs from Study 20120296 with a Risk Difference of 2% or Greater

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=319	n=314	n=319		
Infection, all	92 (29%)	89 (28%)	102 (32%)	0	3
Infection, viral	11 (3%)	13 (4%)	19 (6%)	1	3
Injection site reaction	6 (2%)	19 (6%)	11 (3%)	4	1
Constipation	4 (1%)	5 (2%)	11 (3%)	1	2
URI, cold, flu	60 (19%)	63 (20%)	69 (22%)	1	3

Reviewer created table from study 20120296, 6-month data

Table 81 TEAEs from Study 20120297 with a Risk Difference of 2% or Greater

	Placebo	Erenumab 70 mg	Risk Difference 70mg/placebo
	n=283	n=289	
Injection site reaction	15 (5%)	20 (7%)	2
URI, cold, flu	42 (15%)	49 (17%)	2

Reviewer created table from study 20120297, 3-month data

In Table 82, I present the TEAEs from pooled data from studies 20120295 and 20120296 that occurred in 1% or more of treated patients, and had a relative risk of about 2 (with rounding) compared to placebo. This table includes 6-month data from study 20120296.

Table 82 TEAEs Occurring in ≥1% of Treated patients with Relative Risk of 2 (6-month data)

	Placebo	Erenumab 140 mg	140mg/placebo
	n=601	n=507	
Cramps, muscle spasms	4 (0.7%)	10 (2%)	3.0
Constipation	5 (0.8%)	20 (3.9%)	4.7
Injection site reaction	12 (2%)	25 (4.9%)	2.5
Pruritus	5 (0.8%)	9 (1.8%)	2.1
Fracture	2 (0.3%)	5 (1%)	3.0
Infection, viral	15 (2.5%)	24 (4.7%)	1.9
Rash/dermatitis	4 (0.7%)	6 (1.2%)	1.8

*Studies 20120295 and 20120296

8.4.6. Laboratory Findings

Overview of Laboratory Testing in the Development Program

Laboratory data was analyzed from the ISS dataset ADLB. The sponsor used the CTCAE scale for the grading of laboratory data. I conducted my own analyses on the DBTP, OLE, or on the entire ISS as noted.

Mean Change from Baseline Analyses (DBTP)

I performed my own analyses for AST (SGOT), ALT (SGPT), TBili, Alk Phos, and CK (CPK). For these analyses, I looked at mean change over time. These were pooled analyses from the ISS database ADAE. Three of the four studies had 3-month data, and one had 6-month data (i.e., 20120296); therefore, analyses of Week 4 and Week 12 were of all four studies, and of Week 24 was of only study 20120296. I did not detect any clinically meaningful differences in mean changes for AST, ALT, TBili, and Alk Phos (Tables 83 through 86). I was concerned that there was an increase over time in mean CK (Table 87 and 88), so I conducted additional analyses on the studies individually. This finding only occurred in study 20120296, and did not occur in the other studies (20120295, and 20120297 data not shown).

I reviewed the sponsor's analyses for mean changes from baseline over time for sodium, potassium, glucose, creatinine, BUN, hemoglobin, hematocrit, neutrophils, red blood cells, MCV, and platelets. I did not detect any clinically meaningful mean changes from baseline in the sponsor's analyses.

Table 83 Mean Change from Baseline AST/SGOT in the DBTP

AST	Placebo	7mg or 21mg	70mg	140mg
Week 4	-0.4	-0.3	0.1	-0.1
Week 12	-0.2	0.5	0.2	-0.2
*Week 24	0.2	N/A	0.8	1.1

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=SGOT
*Study 20120296 only

Table 84 Mean Change from Baseline ALT/SGPT in the DBTP

ALT	Placebo	7mg or 21mg	70mg	140mg
Week 4	-0.7	-0.8	-0.1	-0.4
Week 12	-0.7	-0.2	0.1	-0.4
*Week 24	-1.0	N/A	-0.8	-0.3

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=SGPT
*Study 20120296 only

Table 85 Mean Change from Baseline TBili in the DBTP

TBili (mg/dl)	Placebo	7mg or 21mg	70mg	140mg
Week 4	0.005	0.003	0.001	-0.008
Week 12	0.001	0.000	-0.002	-0.001
Week 24*	-0.004	N/A	-0.008	-0.001

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=BILI_TLC
*Study 20120296 only

Table 86 Mean Change from Baseline Alk Phos in the DBTP

Alk Phos	Placebo	7mg or 21mg	70mg	140mg
Week 4	-0.31	-0.83	-0.35	-0.93
Week 12	0.09	0.14	-0.27	-0.76
Week 24*	-0.13	N/A	-0.43	-0.76

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=ALP
*Study 20120296 only

Table 87 Mean Change from Baseline CK (CPK) in the DBTP

CK (U/L)	Placebo	70mg	140mg
Week 4	-4.25	0.5	10.5
Week 12	1.0	6.7	-0.1
*Week 24	3.8	22.5	21.4

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=CK2. This includes only studies 20120295, 20120296, and 20120297.
*20120296 only

Table 88 Mean Change from Baseline CK in Study 20120296 in OLE

CK (U/L)	All Treated (70mg or 140mg)
Week 28	8.1
Week 36	22.7
Week 52	25.4

Reviewer created table from subset of ISS ADLB where PARAMCD=CK2 and AVISIT=Week 28, 36, or 52 and BASETYPE=AMG334 Treatment

Table 89 Toxicity Grade for CK in the DBTP

	Placebo N=1043 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
Grade 1	104 (10.0)	77 (8.6)	55 (10.8)
Grade 2	12 (1.2)	14 (1.6)	7 (1.4)
Grade 3	3 (0.3)	4 (0.4)	2 (0.4)
Grade 4	1 (0.1)	5 (0.6)	3 (0.6)

Reviewer created table using a subset of ADLB where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=CK2.
*Patients may have had more than one abnormal CK. They were counted only once for each abnormal grade.

CK tox grading:
Grade 1: >ULN up to 2.5xULN
Grade 2: ≥2.5xULN up to 5xULN
Grade 3: >5xULN up to 10x ULN
Grade 4: >10xULN

Table 90 Grade 4 Elevations in CK in the Entire ISS

Subject ID	Dose	Baseline	Maximum
(b) (6)	70mg	756	5687
	70mg	102	3845
	140mg	132	9619
	140mg	80	3899
	140mg	234	2337
	70mg	65	2195
	70mg	89	6170
	70mg	92	2374

Reviewer Comment: In study 20120296 there seemed to a be a trend for increasing CK over time. I did a similar type of analysis on studies 20120295 and 20120297 to see if there is a trend for increasing CK as time on drug increases. There was no pattern in either of these two studies and no general increase in CK with increasing time on drug. There appeared to be an imbalance between placebo and erenumab treatment in Grade 4 CK elevations in the DBTP, so I investigated this finding more carefully. I examined all the cases where a patient had a Grade 4 CK elevation. These elevations were transient, and did not recur. One patient even had a prior history of an elevated CK. There were too few cases to draw a conclusion about grade 4 CK elevations. None of the cases of Grade 3 or Grade 4 were reported to have clinical symptoms consistent with rhabdomyolysis.

Analyses Focused on Outliers

I summarized post-baseline transaminase elevations in patients participating in the DBTP (Table 91). This table does not account for the patient's baseline AST or ALT. This table summarizes any elevation in AST or ALT after the patients have received at least one dose of erenumab. At the suggestion of our DGIEP consultant, a cut-off of 30 U/L was used for the ULN to create this table which is summarized by patient. Some patients had more than one elevation in their transaminases. I conducted the same analysis for Tbili using a cutoff of 1.2 mg/dl for the ULN suggested by our DGIEP consultant (Table 92). I also looked at the transaminase elevations and Tbili for all patients exposed to erenumab (Tables 93 and 94). Overall I do not detect any imbalances between placebo and treatment groups for elevations in transaminases or Tbili.

Table 91 Post Baseline Transaminase Elevations in the DBTP

	Placebo N=1043 n(%)	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
AST				
≥3x ULN	2 (0.2)	1 (0.5)	2 (0.2)	2 (0.4)
≥5x ULN	0	1 (0.5)	0	0
≥10x ULN	0	0	0	0
ALT				
≥3x ULN	10 (1.0)	0	4 (0.4)	5 (1.0)
≥5x ULN	1 (0.1)	0	3 (0.3)	1 (0.2)
≥10x ULN	0	0	0	0

*Reviewer created table using ISS dataset ADLB where PARAMCD=SGOT or SGPT and BASETYPE=DOUBLE-BLIND and APERIOD=1.

Table 92 Post Baseline TBili Elevations in the DBTP

	Placebo N=1043 n(%)	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
TBili				
> 1xULN	34 (3.3)	1 (0.5)	17 (1.9)	16 (3.2)
≥1.5xULN	6 (0.6)	0	5 (0.6)	7 (1.4)
≥ 2xULN	0	0	1 (0.1)	0

*Reviewer created table using ISS dataset ADLB where PARAMCD=BILI_TLC and BASETYPE=DOUBLE-BLIND and APERIOD=1.

Table 93 Post Baseline Transaminase Elevations in the Entire ISS (all exposed)

	All doses (70mg or 140mg) N=2499 n(%)
AST	
≥3x ULN	23 (0.9)
≥5x ULN	4 (0.2)
≥10x ULN	1 (<0.1)
ALT	
≥3x ULN	33 (1.3)
≥5x ULN	12 (0.5)
≥10x ULN	1 (<0.1)

*Reviewer created table using ISS dataset ADLB where PARAMCD=SGOT or SGPT and BASETYPE=DOUBLE-BLIND

Table 94 Post Baseline TBili Elevations in the Entire ISS (all exposed)

	All doses N=2499 n(%)
TBili (mg/dl)	
≥ 1xULN	127 (5.0)
≥1.5xULN	23 (0.9)
≥ 2xULN	3 (0.1)

*Reviewer created table using ISS dataset ADLB where PARAMCD=BILI_TLC and ABFL ≠Y

Reviewer comment: The one case of AST/ALT ≥10x ULN with a normal TBili and initially elevated alk phos happened three months after discontinuation of erenumab. This case was also confounded by alcohol abuse. Please see the narrative for case 20120295- (b) (6) *in section 8.4.2 Serious Adverse Events under events occurring after discontinuation. None of the cases of AST or ALT≥3x ULN were associated with Tbili ≥2x ULN*.

There were no cases of Hy's Law in the ISS database. There is no evidence of an excess of transaminase elevations ≥3xULN as compared to placebo. Overall, there were very few marked elevations of either transaminase. The one case of acute liver injury that was discussed in section 8.4.2 appears to be confounded by the use of hepatotoxic drugs and is discussed further in section 8.5.2.

Please see the review from Dr. Ruby Mehta, DGIEP for more details on the single case of acute liver injury, and analysis of liver enzymes in the entire database.

Investigation Related Adverse Events

In the integrated database, there were 178 AEs in the Investigations SOC of which 55 were in the in DBTP. In general, investigation related AEs were low in the DBTP with no notable imbalances compared to placebo (Table 95).

Table 95 Investigation AEs in the DBTP

Preferred Term	Placebo N=1043 n(%)	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
ALT or AST or liver function or hepatic enzyme increased	1 (0.1)	0	2 (0.2)	3 (0.6)
Blood calcium increased	0	0	1 (0.1)	0
Blood creatine phosphokinase increased	4 (0.4)	0	2 (0.2)	2 (0.4)
Blood glucose decreased	3 (0.3)	0	0	0
Blood glucose increased	1 (0.1)	1 (0.5)	1 (0.1)	0
Blood iron decreased	0	0	1 (0.1)	0
Blood TSH decreased	2 (0.2)	0	0	0
Blood triglycerides increased	0	0	0	1 (0.2)
ECG change/P wave abnormal/T wave inversion	2 (0.2)	1 (0.5)	0	2 (0.4)
Gastric PH decreased	1 (0.1)	0	0	0
Glomerular filtration rate abnormal	2 (0.2)	0	0	0
Urine output increased	0	1 (0.5)	0	0
Weight decreased	0	0	0	3 (0.6)
Weight increased	9 (0.9)	1 (0.5)	6 (0.7)	2 (0.4)

*Reviewer created table from ISS dataset ADAE where APERIOD=1 and AEBODSYS=Investigations

8.4.7. **Vital Signs**

Overview of Vital Sign Testing in the Development Program

Vital signs including blood pressure, heart rate, respiratory rate, and temperature were measured according to the schedule of assessments (see Section 6 under Study Design for a summary of the schedules of assessments for individual studies). The sponsor conducted an additional study to assess whether there was an additive effect of erenumab on blood pressure when given with sumatriptan (study 20140255). The sponsor also conducted a 24-hour ambulatory blood pressure monitoring and exposure response analysis of blood pressure versus serum concentration of erenumab (study 20101268).

The sumatriptan/erenumab interaction study did not show any evidence of increased resting blood pressure when the two drugs were given concomitantly. The 24-hour ambulatory

monitoring showed no increases in SBP or DBP associated with erenumab.

I reviewed the sponsor's tables and conducted my own analyses of vital signs. The sponsor analyzed Pool A and Pool B for mean changes in vital signs as well as outliers. No imbalances from placebo were noted in the analyses of Pool A and Pool B in mean changes. I conducted analyses on the entire DBTP, and followed the mean changes over time to see if there were any trends (Tables 96 through 98).

Vital Sign Mean Changes from Baseline

Table 96 Mean Change from Baseline SBP in the DBTP

SBP (mmHg)	Placebo	7mg or 21mg	70mg	140mg
Week 4	-0.41	-1.28	-0.49	-0.02
Week 12	-0.41	-1.57	-0.48	-0.99
Week 24*	-1.95	N/A	-1.88	-1.39

Reviewer created table using a subset of ADVS where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=SYSBP

Table 97 Mean Change from Baseline DBP in the DBTP

DBP	Placebo	7mg or 21mg	70mg	140mg
Week 4	-0.54	-1.50	0.01	0.10
Week 12	-0.60	-1.35	-0.29	-0.35
Week 24*	-1.15	N/A	-0.62	-0.40

Reviewer created table using a subset of ADVS where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=DIABP

Table 98 Mean Change from Baseline HR in the DBTP

HR (bpm)	Placebo	7mg or 21mg	70mg	140mg
Week 4	0.28	1.19	-0.46	-0.23
Week 12	-0.11	1.02	-0.29	-0.53
Week 24*	-0.73	N/A	-0.21	-1.25

Reviewer created table using a subset of ADVS where APERIOD=1 and BASETYPE=DOUBLE-BLIND and PARAMCD=HR

*Study 20120296 only

Reviewer Comment: There were no clinically relevant changes in mean values from baseline for systolic blood pressure, diastolic blood pressure, or heart rate. No consistent trends were seen with increasing duration of treatment.

Potentially Clinically Significant Changes in Vital Signs

The sponsor was asked to provide a table the number and percentage of patients with at least one post-treatment vital sign measurement meeting any of these criteria:

- Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg

The sponsor provided this table in the SCS for the DBTP on the integrated data (Table 47 from the SCS). I reviewed this table and did not detect any imbalance between erenumab, and placebo.

I calculated how many patients with normal baseline vital signs who then developed vital signs outside of normal range during post-treatment. I found no differences between the placebo arm and the treatment arms (Table 99).

Table 99 Post Baseline Changes in Vital Signs in DBTP

	Placebo N=1043 n(%)	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
HR				
<60 and base HR ≥60	134 (12.8%)	33 (15.5%)	117 (13.1)	70 (13.8%)
≥100 and base HR <100	18 (1.7%)	2 (0.9%)	19 (2.1%)	8 (1.6%)
SBP				
<90 and base SBP≥90	14 (1.3%)	3 (1.4%)	10 (1.1%)	10 (2.0%)
≥140 and base SBP <140	100 (9.6%)	10 (4.7%)	86 (9.6%)	45 (8.9%)
DBP				
<50 and base DBP ≥50	2 (0.2%)	1 (0.5%)	3 (0.3%)	1 (0.2%)
>100 and base DBP ≤100	14 (1.3%)	2 (0.9%)	20 (2.2%)	8 (1.6%)

Reviewer created table using a subset of ISS ADVS where APERIOD=1 and BASETYPE=DOUBLE-BLIND.

I summarized the number of patients over time who had an increase or decrease from baseline in the SBP by 10mmHg or more during the DBTP (Table 100). For the week 12 measurement,

this was pooled data from all four studies (20120178, 20120295, 20120296, and 20120297). I did not detect any notable differences between placebo and treatment groups.

Table 100 Change by 10mmHg or more from Baseline SBP over time in the DBTP

	Placebo N (week 12)=988 N (week 24)=284 n(%)	70mg N (week 12)=861 N (week 24)=286 n(%)	140mg N (week 12)=484 N (week 24)=289 n(%)
Increase in SBP			
Week 12	134 (13.6)	125 (14.5)	57(11.8)
Week 24*	34 (12.0)	30 (10.5)	40 (13.8)
Decrease in SBP			
Week 12	161 (16.3)	151 (17.5)	90 (18.6)
Week 24*	58 (20.4)	54 (18.9)	54 (18.7)

Reviewer created table using ISS ADVS where PARAMCD=SYSBP and APERIOD=1 and BASETYPE=DOUBLE-BLIND
*Study 20120296 only

The sponsor provided a table in the SCS where it appears that there is an imbalance between placebo and 140mg of erenumab in patients who have an increase from baseline ≥10mmHg in DBP with normal baseline DBP. To examine this finding more thoroughly, I looked at all patients in the DBTP who had increases by 10mmHg or more (Table 101). I used the integrated dataset which combines all four studies (20120178, 20120295, 20120296, and 20120297). I also tried combining just studies 20120295 and 20120296 which have the 140mg arms to get a more accurate comparison to placebo (Table 102). I also did this analysis by the individual studies (20120295, 20120296, 20120297, and 20120178) (see Tables 103 and 104 and Appendix Tables 148 and 149). There appears to be a consistent trend that a greater percentage of patients treated with erenumab have a ≥10mmHg increase in DBP.

Table 101 Increase by ≥10mmHg from Baseline DBP over time in the DBTP

	Placebo n/N (%)	70mg n/N (%)	140mg n/N(%)
Week 4	67/1024 (6.5)	80/881 (9.1)	48/502 (9.6)
Week 8	73/999 (7.3)	77/873 (8.8)	49/498 (9.8)
Week 12	82/988 (8.3)	79/861 (9.2)	51/484 (10.5)
Week 24*	22/284 (7.7)	21/286 (7.3)	29/289 (10.0)

Reviewer created table using ISS ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN where CHG≥10
*Study 20120296 only

Table 102 Increase by ≥10mmHg from Baseline DBP over time in DBTP of Studies 20120295 and 20120296 Combined

	Placebo n/N (%)	70mg n/N (%)	140mg n/N(%)
Week 4	36/584 (6.2)	45/497 (9.1)	48/502 (9.6)
Week 8	35/575 (6.1)	42/494 (8.5)	49/498 (9.8)
Week 12	46/569 (8.1)	41/489 (8.4)	51/484 (10.5)
Week 24*	22/284 (7.7)	21/286 (7.3)	29/289 (10.0)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN where CHG≥10
*Study 20120296 only

Table 103 Increase by ≥10mmHg from Baseline DBP over time in DBTP of Study 20120295

	Placebo n/N (%)	70mg n/N (%)	140mg n/N(%)
Week 4	20/273 (7.3)	19/183 (10.4)	19/186 (10.2)
Week 8	15/270 (5.6)	14/185 (7.6)	16/185 (8.6)
Week 12	26/274 (9.4)	13/185 (7.0)	18/183 (9.8)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, or Week 12; analysis of CHG by TRT01AN where CHG≥10

Table 104 Increase by ≥10mmHg from Baseline DBP over time in DBTP of Study 20120296

	Placebo n/N (%)	70mg n/N (%)	140mg n/N(%)
Week 4	16/311 (5.1)	26/308 (8.4)	29/314 (9.2)
Week 8	20/298 (6.7)	28/306 (9.2)	33/305 (10.8)
Week 12	20/295 (6.8)	27/304 (8.9)	33/301 (10.9)
Week 24	22/284 (7.7)	21/286 (7.3)	29/289 (10.0)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN where CHG≥10

Reviewer Comment: There appears to be a consistent trend that patients receiving erenumab are more likely than placebo patients to have a ≥10mmHg increase in their diastolic blood pressure. The clinical significance of this is not clear at this point.

Vital Sign Outliers: Entire ISS Database

There were three patients with heart rates reported greater than 120bpm. These three patients were in the open-label phase and were taking erenumab. The highest reported was 124bpm. There were seven patients in study 20120297 who were reported to have heart rates between 15-18 bpm and one patient with a heart rate of 810 during the open-label period. This appears to be a data quality problem with that study.

There were two patients on treatment with erenumab with systolic blood pressures below 80mmHg. There was one patient with a SBP reported to be 195mmHg. There were no diastolic blood pressures reported higher than 120mmHg. There were eight patients with DBP greater than 110 and the highest reported was 118mmHg in one patient.

Reviewer Comment: There were very few patients who had vital signs that were outliers.

8.4.8. **Electrocardiograms (ECGs)**

In all of the studies included in the ISS, ECGs were read at a central facility external to the sponsor. The sponsor then analyzed ECG abnormalities overall, and by ECG abnormalities at baseline. The sponsor presented these abnormalities by the four pools described in section 8.1.

In Pool A, the only ECG abnormality that showed an imbalance between placebo and treatment groups was ectopic supraventricular rhythms. Ectopic supraventricular rhythms occurred in 0.3% of placebo patients, 0.7% of patients in the 70mg group, and 1.8% of patients in the 140mg group. In Pool B, the rates of ectopic supraventricular rhythms were 0.3% for placebo, 1.3% for 70mg and 2.2% for 140mg. The sponsor defined ectopic supraventricular rhythms as premature atrial complexes, premature junctional complexes, ectopic atrial tachycardia, multifocal atrial tachycardia, paroxysmal supraventricular tachycardia, and junctional escapes.

To further evaluate this finding, an information request (IR) was sent to the sponsor. The sponsor was asked to provide vital sign data at the time of the abnormal ECG, the duration of the arrhythmia, the tracing of the arrhythmia, duration of treatment with erenumab at the time of the abnormality, any AEs such as dizziness or syncope during the study, and any cardiac biomarker data if available around the time of the event.

The IR was reviewed by our cardiology consultant Dr. Preston Dunnmon from DCRP including the tracings, narratives, and explanation of the supraventricular rhythm findings. Dr. Dunnmon agreed with the sponsor's assessment that most of the tracings were sinus rhythm, or the finding occurred at baseline. Dr. Dunnmon felt that there was no evidence of excessive tachycardia or bradycardia in erenumab-treated patients.

Other ECG findings

There were no imbalances in Pool A between placebo and treatment with erenumab for the following post-baseline ECG findings: first degree AV block, incomplete right bundle branch block, intraventricular conduction defect, left anterior hemiblock, right bundle branch block, atrial premature complexes, frequent ventricular premature complexes, ventricular premature complexes, sinus bradycardia, sinus tachycardia, ST segment depression, biphasic T-waves, flat T-waves, or inverted T-waves.

ECG Intervals

The sponsor provided summary statistics for the PR interval, QRS complex, and QTc. This included change from baseline. QT will be discussed in section 8.4.9.

PR interval: According to the sponsor's calculations, there appears to be a dose dependent imbalance between placebo and erenumab treatment in the increase in PR interval from baseline. The sponsor calculated in Pool A, that 1% of patients in the placebo group, 1.2% in the 70mg group, and 2.0% in the 140mg group had a normal baseline PR interval with a maximum of >210msec during the study included. The sponsor's calculations of Pool B also showed a dose dependent change from baseline in maximum PR (Table 105)

I attempted to reproduce the sponsor's findings in Pool A and Pool B, but was unable to do so. I was unable to reproduce the numbers they provided in the ISS tables 14-8.4.9.5 and 14-8.4.9.6. I did not find a dose-dependent change from baseline to maximum PR interval >210msec (Table 105).

In addition, there seems to be no dose-dependent difference in mean change from baseline PR (Table 106).

Table 105 Patients with Normal Baseline PR Interval with Max >210msec

	PBO n(%)	70mg n(%)	140mg n(%)
*Pool A	10 (1.0)	11 (1.2)	10 (2.0)
**Pool A	15 (1.4)	11 (1.2)	7 (1.4)
*Pool B	2 (0.6)	2 (0.6)	5 (1.6)
**Pool B	4 (1.3)	5 (1.6)	3 (0.9)

*Sponsor calculated from ISS tables 14-8.4.9.5 and 14-8.4.9.6
**My calculation for Pool A: (ISS ADEG where PARAMCD=PR, and BASETYPE=DOUBLE-BLIND, APERIOD=1, POOL1RFL=Y, BASECAT1= '≥120 to 210', and AVALCAT1='>210')
For Pool B: (ISS ADEG where PARAMCD=PR, and BASETYPE=DOUBLE-BLIND, APERIOD=1, POOL4RFL=Y, BASECAT1= '≥120 to 210', and AVALCAT1='>210')

Table 106 Mean Change PR Interval in the DBTP

	PBO	7mg or 21mg	70mg	140mg
Mean baseline PR	158.31	158.63	157.25	157.76
Mean PR at week 12	158.42	157.62	157.59	157.95
Mean change	0.11	-1.01	0.34	0.19

Reviewer created table using ISS ADEG where PARAMCD=PR, and BASETYPE=DOUBLE-BLIND; and APERIOD=1

Reviewer Comment: An IR was sent to the sponsor to clarify the apparent dose dependent change in the PR interval. The sponsor found an error in tables 14-8.4.9.5 and 14-8.4.9.6 which they corrected and sent in the response to our IR (SN0036, dated 12/5/2017). The new tables are in agreement with my findings in Table 105 and no dose-dependent change in the PR interval was found.

QRS interval: There were no differences noted between placebo and treatment with erenumab on the QRS interval.

ECG Related AEs

ECG abnormalities were reported as AEs. I evaluated the Cardiac and Investigations SOC for ECG related AEs. There were 53 reported AEs in the entire ISS database related to potential ECG abnormalities. I analyzed these AEs by the DBTP and then the open-label period (Tables 107 and 108). Three ECG AEs resulted in drug withdrawal and three resulted in drug interruption.

Table 107 AEs related to ECG abnormalities in the DBTP

Preferred Term	Placebo N=1043 n(%)	7mg or 21mg N=213 n (%)	70mg N=893 n(%)	140mg N=507 n(%)
Arrhythmia	1 (0.1)	0	1 (0.1)	0
Atrial Fibrillation	0	1 (0.5)	0	0
Atrioventricular block first degree	2 (0.2)	0	1 (0.1)	2 (0.4)
Bundle branch block right	0	0	1 (0.1)	0
Cardiac flutter	0	0	0	1 (0.2)
ECG change	0	1 (0.5)	0	2 (0.4)
ECG p wave abnormal	1 (0.1)	0	0	0
ECG T wave inversion	1 (0.1)	0	0	0
Extrasystoles	1 (0.1)	1 (0.5)	0	3 (0.6)
Nodal arrhythmia	1 (0.1)	0	0	0
Supraventricular tachycardia	1 (0.1)	0	0	0
Tachycardia	4 (0.4)	1 (0.5)	0	0
Ventricular extrasystoles	1 (0.1)	0	0	1 (0.2)
Total # of AEs	13	4	3	9

Reviewer created table from datasets ADAE and ADSL where APERIOD=1 and AEDBODSYS= Cardiac Disorders or Investigations

Table 108 AEs related to ECG abnormalities in the Open-Label Period

Preferred Term	70mg only N=1301 n(%)	140mg only N=371 n(%)	70mg and 140mg* N=827 n(%)	Total N=2499 n(%)
Arrhythmia	1 (0.1)	0	0	1 (<0.1)
Atrial Fibrillation	1 (0.1)	0	0	1 (<0.1)
Atrioventricular block first degree	3 (0.2)	1 (0.2)	1 (0.1)	5 (0.2)
Bradycardia	1 (0.1)	0	0	1 (<0.1)
Bundle branch block left	0	0	1 (0.1)	1 (<0.1)
Cardiac flutter	0	0	1 (0.1)	1 (<0.1)
Conduction disorder	1 (0.1)	0	0	1 (<0.1)
ECG abnormal	1 (0.1)	0	1 (0.1)	2 (0.1)
ECG change	0	0	1 (0.1)	1 (<0.1)
ECG QT prolonged	0	0	1 (0.1)	1 (<0.1)

ECG T wave inversion	0	0	1 (0.1)	1 (<0.1)
Heart rate increased	1 (0.1)	0	0	1 (<0.1)
Sinus tachycardia	1 (0.1)	0	0	1 (<0.1)
Supraventricular extrasystoles	0	0	1 (0.1)	1 (<0.1)
Tachycardia	1 (0.1)	1 (0.2)	1 (0.1)	3 (0.1)
Total # AEs	11	2	9	22

Reviewer created table from datasets ADAE and ADSL where APERIOD=2 or 3 and AEDBODSYS= Cardiac Disorders or Investigations
* The doses in this column refer to patients who received both 70mg and 140mg at some point in the open-label portion of the studies

Reviewer Comment: I did not detect any clear dose response or relationship to drug treatment in ECG related AEs.

8.4.9. **QT**

Because this is a biologic, monoclonal antibody, a thorough QTc study was not performed. The sponsor provided summary statistics for QTcF at weeks 4, 8, and 12 for Pool A. One patient in the placebo group had a QTcF interval greater than 500msec, but no patients in the erenumab treatment groups had a QTcF greater than 500msec. One patient in the 70mg group had a QTcF interval increase from baseline greater than 60msec

QT: Mean Changes from Baseline

Table 109 Pool A: QTcF Interval Maximum Mean Post-baseline and Maximum Mean Increase from Baseline

QTcF(msec)	Placebo N=1043	7mg or 21mg N=213	70mg N=893	140mg N=507	All doses N=1613
Baseline					
Mean	408.30	406.20	408.66	408.32	408.23
Median	407	406	408	408	408
Min, Max	346, 487	356, 466	343, 485	360, 471	343, 485
Max Post-baseline					
Mean	417.77	415.96	417.25	417.42	417.13
Median	417	415	417	417	417
Min, Max	365, 505	371, 472	362, 484	356, 477	356, 484
Max Increase from					

Baseline					
Mean	9.48	9.73	8.76	9.18	8.97
Median	10	10	9	8	9
Min, Max	-39, 60	-41, 50	-36, 61	-24, 51	-41, 61

This table was summarized from the sponsor's data from the ISS table 14-8.4.7.1.

Analyses Focused on Outliers

Table 110 Pool A: Max QTcF Post-baseline and Max Increase from Baseline

QTcF (msec)	Placebo N=1043 n(%)	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)	All doses N=1613 n(%)
>450 to 480	33 (3.2)	5 (2.3)	26 (2.9)	11 (2.2)	42 (2.6)
>480 to 500	2 (0.2)	0	1 (0.1)	0	1 (<0.1)
>500	1 (<0.1)	0	0	0	0
Change 30 to 60	67 (6.4)	16 (7.5)	51 (5.7)	28 (5.5)	95 (5.9)
Change >60	0	0	1 (0.1)	0	1 (<0.1)

This table was summarized from the sponsor's data from the ISS table 14-8.4.8.1

Table 111 Pool C: Max QTcF Post-baseline and Max Increase from Baseline

QTcF (msec)	70mg or 140mg N=2499 n(%)
>450 to 480	106 (4.2)
>480 to 500	3 (0.1)
>500	0
Change 30 to 60	214 (8.6)
Change >60	4 (0.2)

This table was created from the sponsor's data from the ISS table 14-8.4.8.3

Reviewer Comment: Erenumab does not appear to have an effect on the QTc (Tables 109 through 111).

8.4.10. Immunogenicity

The sponsor tested for anti-AMG334 (erenumab) antibodies using a cell based assay for neutralizing antibody detection, and a electrochemiluminescence immunoassay for binding antibody detection. Samples were first tested for binding antibodies. Samples that were positive for binding antibodies were subsequently tested for neutralizing activity. If a post-dose sample was positive for binding antibodies, and had neutralizing activity at the same time point, the sample was defined as positive for neutralizing antibodies.

Development of anti-drug antibodies (ADAs) was infrequent in the double-blind treatment period and in the open-label period. The sponsor summarized the incidence of anti-AMG 334 antibodies (binding and neutralizing) and summarized adverse events for those patients who developed ADAs.

In the original BLA submission of dataset ADAB, 194/2484 (7.8%) patients were reported to be ADA positive. Of these, 17 (0.7%) had neutralizing antibodies. Results from the DBTP are shown below in Table 112. There seems to be increasing immunogenicity with decreasing dose. This may be a function of the presence of erenumab during the detection of antibodies. The presence of the drug decreases the ability of the assay to detect the antibody. It appears that at lower doses more ADAs are present, but this may be because there is less erenumab present in the sample at lower doses therefore making detection of ADAs easier.

Table 112 Patients Developing ADAs in the DBTP

ADAs	7mg or 21mg N=213 n(%)	70mg N=893 n(%)	140mg N=507 n(%)	All doses N=1613 n(%)
Positive	25 (11.7)	57 (6.4)	13 (2.6)	95 (5.9)

Reviewer created table from dataset ADAB where APERIOD=1, BASETYPE=DOUBLE-BLIND, AVALC=POSITIVE analysis by TRT01AN

When including all studies in the development program including phase 1, 2, and 3 studies, the sponsor reports that 242/3361 (7.2%) of those exposed to erenumab developed ADAs. Of the patients who had binding antibodies, 26% had a negative result at the last measured time point and 43% who had neutralizing antibodies had a negative result at the last measured time point.

Effect of ADAs on Safety: Analysis of AEs of Patients with ADAs

There was a total of 95 patients in the DBTP who were ADA-positive. Of those 95 patients, 53 patients reported any AE for a total of 160 AEs. The most common AEs reported by antibody positive patients was in line with the most common AEs reported in the overall database. There were no SAEs reported in the population of patients who were ADA positive in the DBTP.

120-day Safety Update

At the time of the 120-day safety update, 224/2515 patients (8.9%) developed anti-erenumab antibodies inclusive of studies 20120178, 20120295, 20120296, and 20120297. This number does not include all phase 1 and phase 2 studies. There were no additional cases of neutralizing antibodies that developed.

Of the 224 patients who developed antibodies, 178 patients reported an AE at any time during the development program. Of the 224 patients, 15 patients reported SAEs at any time during the development program. There were three malignancies (2 breast, 1 lung), 2 cases of non-cardiac chest pain, and 2 cases of visual impairment. All other SAEs occurred only once.

The most common adverse events were URI/cold/flu-like illness, injection site reactions, diarrhea, and arthralgia.

Reviewer Comment: Rate of development of erenumab antibodies is low, especially for neutralizing antibodies. Too few people developed antibodies to make any definitive statements about safety in the setting of antibody positivity. Preliminarily no safety concerns were identified.

OBP has identified that the assay for detecting neutralizing antibodies is underreporting the true number of neutralizing antibodies. The analysis conducted above was done on all patients with ADAs. If one assumed all patients with ADAs, also had neutralizing antibodies there is still insufficient information to make any definitive conclusions about the safety of erenumab in patients who have developed neutralizing antibodies.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiovascular, Cerebrovascular, and Peripheral Vascular Disease

CGRP is a potent vasodilator. For this reason, there is a theoretical cardiovascular safety risk potentially associated with antagonism of the CGRP receptor. This concern is centered around a potential lack of compensatory vasodilatation in the context of ischemia. Plasma CGRP levels

have been found to be increased during myocardial infarction and it is thought that these increased levels of CGRP may act as a defense mechanism (Mair et al. 1990).

Migraine has an association with increased risk of vascular disease especially in patients with migraine with aura (Scher et al. 2005). There is some evidence that migraine patients are at increased risk of cardiovascular events (ischemic heart disease, myocardial infarction) and increased risk of stroke. These epidemiological findings combined with the theoretical risk of CGRP antagonism have made cardiovascular and cerebrovascular safety issues of concern warranting a closer evaluation.

For this BLA, a cardiology consultation has been obtained to evaluate the two cardiovascular related deaths, and to evaluate study 20140254, a Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects with Stable Angina. (b) (4)

DCRP was asked to review this study, (b) (4)

Study 20140254: Exercise Time During Treadmill Test in Patients with Stable Angina

Study 20140254 evaluated the effect of a single dose of 140mg IV of erenumab compared to placebo on the exercise capacity of 88 patients with stable angina. This study enrolled 51 patients age 65 and older. Of these 51 patients, 23 received a single dose of 140mg of erenumab. Only one of the patients was ≥75. Of those 88 patients, 44 received a single dose of erenumab and 44 received placebo. The primary objective was to evaluate the effect of erenumab on total exercise time during an exercise treadmill test (ETT). Secondary objectives included time to onset of exercise-induced angina, and time to ≥1mm ST-segment depression. Patients were given a single dose of erenumab 140mg IV or placebo. Patients had to have a history of stable angina with at least one angina episode per month for at least three months prior to screening. Patients also had to complete two ETTs during screening. The results of these tests could not differ by more than one minute in total exercise time. Patients were given a single dose IV over 1 hour of 140mg of erenumab, and then began the ETT within 30 minutes (+/- 15minutes) of completing the dose.

The sponsor found no difference in total exercise time between patients who received 140mg and those who received placebo. According to the sponsor, the lower limit of the 90% confidence interval of the difference in total exercise time did not reach the non-inferiority margin of -90 seconds. The mean change in total exercise time for placebo was 8.2 seconds (i.e., improvement) while the mean change in total exercise time for 140mg was -2.7 seconds (i.e., worsening). The median time to exercise-induced angina for placebo was 508 seconds and slightly shorter for erenumab at 500 seconds. The median time to exercise-induced ST-segment depression was 420 seconds for placebo, and shorter for 140mg (407 seconds). There were 29

patients in placebo versus 33 in treatment who developed exercise induced angina during the ETT. There were 36 patients in placebo versus 35 in treatment who developed exercise induced ST segment depression.

In the safety follow up period, two patients in the 140mg experienced angina compared to none in the placebo group. One patient experienced angina starting on day 1 and ending on day 3. The second patient experienced unstable angina starting on day 15 and ending on day 18, followed by a second event on day 52 and ending on day 54. A third patient in the 140mg group experienced chest pain, while none in the placebo group did. One placebo patient was reported to have 'non-cardiac chest pain.' One SAE of atrial fibrillation was reported in the placebo group. One TIA was reported in the placebo group. Two AEs of hypotension were reported in the placebo group while one AE of hypertension was reported in the 140mg group. One patient each in placebo and 140mg arm reported use of post-baseline nitrates.

Reviewer Comment: The value of this study for assessing patients with CV disease is limited. The study is a single dose study, and does not give any information regarding the chronic antagonism of CGRP in patients with CV disease.

This study was reviewed in detail by Dr. Preston Dunnmon, DCRP. Please see his consult for more details. (b) (4) *Dr. Dunnmon states the sponsor has biased their study towards nominal success by increasing the non-inferiority margin from 60 seconds to 90 seconds, and by using the 90% confidence interval instead of 95%.*

At EOP2, the Division discussed the lack of data on patients over the age of 65. The sponsor agreed at EOP2 to obtain PK data in 25 patients ≥65 in this treadmill study. The sponsor fell just short of this number and only 23 patients received a single dose of 140mg in the treadmill study. Only one patient over the age of 75 was included. The study does not adequately address safety issues in patients over the age of 65.

Many patients in the database had cardiovascular risk factors such as diabetes, hypertension, cigarette use, high cholesterol, high triglycerides, or obesity (Table 113). However, the overall prevalence of pre-existing major cardiovascular disease in the entire database was very low (0.5%). There was a total of 13 patients in the entire database with pre-existing major cardiovascular disease. Of those with pre-existing major cardiovascular disease, there were three patients with coronary artery disease, and 11 with cerebrovascular or peripheral vascular disease (Appendix Table 147).

Table 113 Summary of Baseline Cardiac Risk Factors

	Placebo N=1043 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
Diabetes	21 (2.0)	17 (1.9)	6 (1.2)
History of hypertension	93 (8.9)	51 (5.7)	34 (6.7)
Current cigarette use	114 (10.9)	93 (10.4)	51 (10.1)
High cholesterol	489 (46.9)	438 (49.0)	241 (47.5)
BMI>30 kg/m²	253 (24.3)	230 (25.8)	133 (26.2)

This table is adapted from the sponsor's materials in the SCS

In the DBTP, there were no SAEs in the Cardiac SOC. In Pool C, there were 5 cardiac related SAEs: myocardial ischemia (2), atrial fibrillation, pericarditis, and hypertensive heart disease. I added a sixth SAE for cardiac failure for the patient who died of cardiac failure, but was not coded as such.

The sponsor assessed the database for potential cardiovascular and cerebrovascular effects using Ischemic Cardiac and Ischemic Cerebrovascular Standard MedDRA Queries (SMQs). In the double-blind treatment period, the incidence rates for ischemic central nervous system vascular disorders and ischemic heart disease SMQs were very low. There was only one adverse event mapping to peripheral arterial disease.

In Pool C (all exposed to either 70mg or 140mg), the preferred terms mapping to cardiovascular, cerebrovascular, and peripheral arterial disease were all low (Table 114). This table is inclusive of DBTP and open-label data.

Table 114 Summary of Preferred Terms Mapping to the Cardiovascular, Cerebrovascular and Peripheral Arterial SMQ (Pool C)

	70mg		140mg	
Preferred term	# of patients	Rate (per 100 SY)	# of patients	Rate (per 100 SY)
Cerebral venous thrombosis	0	0	2	0.3
Cerebrovascular disorder*	0	0	1	0.1
Transient ischemic attack**	0	0	1	0.1

Myocardial ischemia	2	0.1	0	0
Arteriosclerosis	1	<0.1	0	0
Blood CPK increased	13	0.7	4	0.6
ECG T-wave inversion	1	<0.1	0	0
Raynaud's phenomenon	1	<0.1	1	0.1

This data was adapted from the sponsor's materials in the SCS.

*Incidental MRI finding of non-specific ischemic white matter disease was coded as cerebrovascular disorder.
**There was one additional AE that was coded as a TIA. This case occurred in study 20120178 in the 7mg dose case. Upon review of this case it is unlikely to be a TIA.

At the time of the 120-day safety update, the following new AEs in the Cardiovascular, Cerebrovascular and Peripheral Arterial SMQ occurred: angina, ECG T-wave abnormal, and three more cases of elevated CK. In reviewing these cases, the ECG T-wave abnormal had been previously coded at 'ECG change' and was updated to 'ECG T-wave abnormal'. All three cases of elevated CK were asymptomatic. For the case of angina, I cannot completely exclude the role of erenumab. The patient experienced two episodes of chest pain while on erenumab. She eventually discontinued erenumab, but it is unknown whether she continued to have episodes of chest pain after discontinuation of the drug.

In the entire ISS database, there were 11 patients with an a priori diagnosis of Raynaud's phenomenon. Two of these patients with a history of Raynaud's phenomenon reported a worsening of symptoms. One patient was receiving erenumab 140mg but did not discontinue from the study. Another patient who was receiving 70mg of erenumab had symptoms consistent with Raynaud's phenomenon. These symptoms were severe enough to discontinue the investigational product. This is a concerning phenomenon because a deficiency of CGRP release has been implicated in the 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).

Reviewer Comment: (b) (4) *There is biological plausibility to this worsening as described above.*

Hypertension

There is some suggestion that CGRP has a role in hypertension (Russell et al. 2014) although the understanding of the role of CGRP is unclear. It may be that CGRP release is enhanced early in the development of hypertension as a compensatory or protective effect. In the safety review, I examined changes in vital signs carefully (Section 8.4.7). There is some suggestion that patients treated with erenumab were more likely that placebo patients to have elevations in their DBP by 10 mmHg or more. I examined the database to see if there were clinical consequences of this related to hypertension AEs. There were 14 (1.3%) placebo patients, 9 (1.0%) 70mg patients and 1 (0.2%) 140mg patient who had hypertension-related AEs. Almost all the placebo patients took medication for this AE while half of the 70mg patients took medication, and none of the 140mg patients.

I conducted some additional analyses on the patients who had a baseline diagnosis of hypertension to see if the addition of erenumab exacerbated their hypertension. The addition of erenumab did not elevate the systolic blood pressure of patients with an a priori diagnosis of hypertension. However, it does appear that the 140mg dose increases the diastolic blood pressure in patients with hypertension (Appendix Table 133).

Reviewer Comment: Overall, I did not find any difference between placebo and treatment groups related to hypertension AEs or use of anti-hypertensives. It appears that the elevation in diastolic blood pressure did not have clinical significance in these studies. However, while this did not have clinical significance in young healthy people, this degree of blood pressure elevation may have consequences in patients with CV disease who were not adequately studied in these studies. There is some suggestion that the 140mg dose may increase the diastolic blood pressure in patients with hypertension.

Additional CV Considerations

At the pre-BLA meeting, the sponsor was asked to do an analysis of concomitant cardiovascular (CV) medications to identify a possible signal. The sponsor excluded cardiovascular concomitant medications that were being used for non-cardiovascular indications. The sponsor identified various categories to which the medication could belong:

1. no change: patient takes the same cardiovascular medication with no changes to dose, no replacements, and no additions
2. new CV medication
3. add on medication
4. replacement of medication

5. increase of dose
6. decrease of dose
7. stopping CV medication (no replacement)

Overall, less than 10% of patients were using a CV medication at baseline. The most common being anti-hypertensive and lipid lowering agents. In the DBTP, for the anti-hypertensive agents, 15 (1.4%) placebo patients, 9 (1.0%) 70mg patients, and 2 (0.4%) 140mg patients required a de novo anti-hypertensive medication. In categories 3 through 6, there were an additional 7 patients in the placebo group, 2 in the 70mg group, and none in the 140mg group. Only one placebo patient stopped anti-hypertensive treatment without replacement. In Pool C (all exposed to 70mg or 140mg), 2.4% of patients were started on a new anti-hypertensive agent at some point in the study.

Reviewer Comment: No cardiovascular signal was detected by analysis of concomitant CV medications in the DBTP. Of note, when the sponsor created the tables for section 4.3.2 in the SCS, they used the number of patients on CV meds as the denominator for calculating rates. These calculations provide the rate of change for patients previously taking anti-hypertensives. I used the number of patients receiving treatment with IP as the denominator to calculate the rate of patients in the study who required new anti-hypertensive agents.

Thromboses

There was a total of 11 thromboses/embolism reported in the entire ISS in 8 patients in the initial filing. Three of the patients experienced thromboses in the DBTP and 5 patients experienced thromboses in the open-label period. All three thromboses in the DBTP occurred in patients taking erenumab. There were no cases in placebo-treated patients. At the 120-day safety update, there were an additional 2 patients who had experienced a thrombosis/embolism. In total, there were 13 thrombi/emboli in 10 patients. Many of the cases has predisposing factors, or other confounders causing the thrombus (Table 115).

An information request (IR) was sent to the sponsor to clarify some of the cases of thrombosis, and provide more information including the three that occurred in the DBTP. One of these three cases recorded as DVT could not be confirmed on ultrasound. One of the cases was a superficial thrombophlebitis of a varicose vein initially reported as secondary to trauma. The trauma could not be confirmed by the sponsor. This case does not carry the same risk of pulmonary embolism as a DVT; however, the causes and risks factors are overlapping for this type of AE. The third case in the DBTP was a CVT and peripheral blot clot which is described in detail under SAEs. This case had many risk factors contributing to the clots, and is unlikely to be

drug related. Of the three cases in the DBTP, only one case could not clearly be attributed to something other than erenumab.

In this same IR, the sponsor provided some data to support that their rate of VTE is not different from that seen in the population of patients with migraine. The sponsor used the "Marketscan Commercial Claims Database" to mine clinical data on adult patients age 18-65 with migraine. Patients had to have at least one year of continuous enrollment in the database, and data up to five years of follow-up were evaluated if available. The rate of VTE/PE in that database was 3.32 per 1000SY. In the Amgen database, the rate was 3.38 per 1000SY. The sponsor utilized all 10 patients identified in Table 115 in the calculation of this rate. The rates between the two databases are equivalent.

Overall, after careful examination, there were too few cases of thromboses/emboli in the DBTP to make any definitive conclusion about the relatedness to drug treatment and the rate in the open-label period were similar to background rate. Most of the cases had plausible alternative causes to treatment with erenumab.

Table 115 Summary of All Cases of Thromboses in the ISS Inclusive of the 120-day Update

Subject ID	Diagnosis	Phase	Dose	OCP Y/N	Notes
(b) (6)	Post-procedural pulmonary embolism	OLE	70mg	N	Narrative summarized under SAEs; occurred during hospitalization/immobilization
	Cerebral venous thrombosis of sigmoid sinus	OLE	140mg	N	Narrative summarized under SAEs; occurred while hiking in association with closed head injury
	Left transverse and sigmoid sinus, peripheral blood clot right arm	DBTP	140mg	N	Narrative summarized under SAEs; CVT occurred 79 days after discontinuation of erenumab; prior history of DVT
	Deep vein thrombosis	OLE	70mg	N	Narrative summarized under SAEs; patient had prior history of pulmonary embolism, DVT, and IVC placement; heterozygous for prothrombin G20210A gene mutation
	Deep vein thrombosis of leg,	DBTP	70mg	N	Sprain of foot/muscular rupture (b) (6) prior to DVT

(b) (6)	foot after immobilization				(b) (6) immobilization was possible risk factor; per sponsor DVT could not be confirmed on ultrasound; anticoagulation was discontinued when DVT could not be confirmed
	Thrombosis left lower leg	OLE	70mg	N	Clarified by investigator to be thrombophlebitis; cause unknown
	Superficial vein thrombosis	DBTP	70mg	N	Superficial thrombophlebitis of varicose vein
	Several blood clots, acute occlusive deep venous thrombosis left peroneal vein; pulmonary embolism	OLE	70mg	N	Narrative summarized under SAEs; patient had possible family history of "clots;" patient had risk factor for DVT due to left foot fracture, and 6-weeks immobilization
	Deep vein thrombosis	OLE	140mg	N	Cause unknown, possible cause long car ride two weeks prior to the event
	Superficial blood clot of the left leg	OLE	70mg	Y	Patient on OCPs and was a smoker; patient fell and injured knee; clot occurred four days after knee injury

8.5.2. **Hepatotoxic Effects and Hepatobiliary Disorders**

There were no imbalances between placebo and treatment groups in the hepatobiliary SOC in the DBTP. As described in the SAEs there was one case of acute liver injury that occurred in a study that was not included in the ISS. The case was confounded by use of other hepatotoxic medications.

I searched the ISS database for any potential cases of DILI or Hy's Law. For the query and at the suggestion of our hepatology consultant from DGIEP, I used 30 U/L for the ULN for AST and ALT,

and 1.2 mg/dl for the ULN for Tbili. In the ISS, there were no cases of patients having an AST or ALT ≥3xULN with TBili ≥2x ULN. I did not detect any cases of Hy's Law in the ISS.

A consultation from DGIEP was obtained regarding the patient who had acute liver injury. Please see the consultation from Dr. Ruby Mehta, DGIEP for further details. Dr. Mehta has concluded that the cause of the patient's acute liver injury was unlikely to be erenumab given the half-life of the product, and the otherwise benign profile of the drug. However, she has concluded that the patient's cause of acute liver injury is likely unknown. She has suggested product labeling as per her consult because of this case and adding a limitation of use statement for patients with pre-existing liver disease. She has suggested the following statement be added to the label:

"If a patient experiences liver-related symptoms such as jaundice, right upper quadrant abdominal pain, nausea, or vomiting, this may be indicative of serious liver injury and should lead to erenumab discontinuation. The patient should be taught to identify these symptoms, not take further doses, and contact the physician immediately. If there is biochemical or clinical evidence of serious liver injury, the drug should be permanently discontinued and the patient should be followed to resolution of injury."

Reviewer Comment: I agree with Dr. Mehta that erenumab is not the likely cause of the acute liver injury, but I feel that the case is quite confounded by the patient's use of other hepatotoxic drugs (i.e., Augmentin) in proximity to the development of the acute liver injury. For this reason, I do not think this warning in the label is justified at this point by the data that we have.

8.5.3. Gastrointestinal Disorders

Nonclinical data suggest that CGRP has protective effects against gastric injury. Mechanisms of gastric protection include inhibition of gastric secretion of somatostatin, stimulation of gastric mucin synthesis, and mucosal hyperemia via direct vasodilation. Endogenous CGRP has been shown to reduce gastric acid secretion. Theoretically concerns with CGRP include increased risk of gastric ulcer, bowel ischemia, obstruction as CGRP has known roles in blood flow, inflammation, motility and secretion into the colon.

Incidence rates in the Gastrointestinal Disorders SOC were 9.1% 8.1% and 8.9%. The only notable imbalances were in the constipation group (see Section 8.4.5 TEAE table). There was one SAE related to constipation, and two additional patients discontinued from treatment secondary to constipation related AEs.

The sponsor assessed the database for potential gastrointestinal effects using gastrointestinal SMQs (gastrointestinal nonspecific inflammation and dysfunctional conditions, and

gastrointestinal perforation, ulceration, hemorrhage, or obstruction). There was no imbalance amongst placebo, and treatment groups for these two SMQs in Pool A.

There was one case of ischemic colitis in the database in a patient who continued treatment with erenumab. This case is reviewed in section 8.4.2. Because of biological plausibility, this case may warrant mention in the label.

8.5.4. Hypersensitivity

The sponsor performed SMQs of hypersensitivity and anaphylactic reactions, as well as Amgen specific queries of rash and urticaria. In Pool A and Pool B there were no imbalances in adverse events mapping to the Hypersensitivity SMQ. In the open-label experience, there was one SAE of urticaria (see narratives in Section 8.4.2). The Anaphylaxis SMQ identified 11 patients in the total database with preferred terms mapping to the SMQ. Of these, 4 were in the DBTP and 7 were in the OLE. In the DBTP of the four combined studies, there was 1 patient in placebo, 1 in the 70mg group, and 2 in the 140mg who had preferred terms that mapped to the algorithmic Anaphylaxis SMQ. In the 140mg group, one of these patients had an allergic reaction to penicillin. In the entire ISS, three patients had PTs of anaphylactic reaction. All three had alternative causes of their reaction (penicillin allergy, stinging insect, and food allergy). In the OLE, there were 5 patients in the 70mg and 2 patients in the 140mg group who had PTs that mapped to the anaphylaxis SMQ.

At the 120-day safety update, there were 3 additional patients who had PTs that mapped to the Anaphylaxis SMQ (pruritus, rash, and generalized rash). None of these were associated with SAEs suggestive of actual anaphylaxis.

8.5.5. Injection Site Reactions

Injection site reactions were reported more frequently in the treatment groups than in the placebo group during the DBTP. In the DBTP, the rates of injection site reactions were 3.3% for placebo, 5.9% for 70mg, and 4.9% for 140mg. When combining all treatment groups including 7mg, and 21mg, the total is 5.4% of patients receiving erenumab in the DBTP reported an injection site reaction.

There were many type of injection site reactions experienced by patients receiving erenumab including injection site pain, erythema, paresthesia, pruritus, hypersensitivity, swelling, induration, hematoma, warmth, and rash. In the DBTP, there was only one discontinuation due to injection site rash in a patient who received 70mg of erenumab and one interruption to treatment due to injection site erythema in a patient receiving 140mg. In the OLE, there were two discontinuations due to injection site reactions in patients receiving 70mg of erenumab (pain and urticaria).

8.5.6. **Suicidality Assessment**

The sponsor utilized the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess patients for suicidality in all the pivotal and phase 2 studies. See the Appendix 13.5 for details about the scale. Overall in the four studies presented in the ISS, there does not appear to be a signal for suicidal ideation or suicidal behavior (Table 116). This table summarizes the number of patients per study that had a score on the C-SSRS of 1 or higher at any time during the DBTP.

Table 116 Summary of Post Baseline Suicidal Ideation Anytime during DBTP

Study	Placebo n(%)	7mg or 21mg n(%)	70mg n(%)	140mg n(%)	Notes
20120178	1 (0.6)	3 (1.4)	1 (0.9)	N/A	Two patients on 21mg had baseline suicidal ideation
20120295	1 (0.3)	N/A	2 (1.0)	0	An additional 2 placebo patients engaged in non-suicidal self-injurious behavior
20120296	3 (0.9)	N/A	0	4 (1.3)	One placebo patient with actual attempt; highest score for 140mg arm was 3
20120297	0	N/A	1 (0.3)	N/A	This patient's post baseline was 1 (wish to be dead)

Reviewer created summary. N/A=These doses were not evaluated in the respective studies.

In the sponsor's analysis of Pool A (DBTP, 3-month data), there were 3 (0.3%) patients in placebo, and 4 (0.2%) patients in treatment who had no baseline suicidal ideation (C-SSRS score of 0), but had a post-baseline score of 1 (wish to be dead). There was one patient in the 70mg arm and one patient in the 140mg arm with no baseline suicidal ideation, but had a post-baseline score of 3 (active thoughts without plan). In total, there were 5(0.5%) of placebo patients and 11(0.7%) of treatment patients who had at least one score on the C-SSRS of 1 or greater at any point in the DBTP. This does not take into account their baseline score.

In the sponsor's analysis of Pool C (all exposed), 24 (1.0%) patients had a shift from a baseline C-SSRS of 0 to a score of 1 or higher. The largest number of these shifts (9 out of the 24) were from a C-SSRS of 0 to 1. Of these 24 patients who had a shift, 11 of them were from the CM study. There was one patient in the OLE who had a score of 7 (aborted suicide attempt). This score was recorded 40 days after discontinuation of erenumab

I reviewed the 120-day update dataset for the C-SSRS. There were 27 patients (i.e., 3 additional) patients who had a shift at some point from baseline of C-SSRS of 0 to 1 or higher.

Two of these patients had scores of 6 (preparatory acts or behaviors). One patient continued on erenumab and follow-up C-SSRS scores were 0. In the other patient with a score of 6, this was recorded 112 days after the last dose of erenumab.

In terms of AEs related to suicidality, there were 3 (0.1%) of patients in the all exposed who had suicidality related AEs. All three patients were on erenumab 70mg at the time of the AE. One patient was in the DBTP, and the other two were in the open-label. This is inclusive of the 120-day update.

8.6. Safety Analyses by Demographic Subgroups

The database overall has very few SAEs and AEs. In addition, the database had a very limited number of non-white patients. I have presented the rates of SAEs and AEs by sex, age, and race in the entire ISS provided at the 120-day safety update (Table 117). This table represents the 2499 patients who were exposed to at least one dose 70mg or 140mg of erenumab in the four pooled studies (20120295, 20120296, 20120178, 20120297). Of these 2499, 71.7% reported at least one AE and 5.0% reported at least one SAE. The rates of AEs and SAEs by sex, age, and race roughly reflects rates in the overall population in the entire ISS. Some of the race categories have too few patients to make any meaningful comparisons or conclusions.

Table 117 Rates of SAEs and AEs by Sex, Age, and Race in Patients Exposed to 70mg or 140mg

	Sex		Age		Race					
	M N=408 n(%)	F N=2091 n(%)	<median age N=1288 n(%)	≥ median age N=1271 n(%)	White N=2282 n(%)	Black N=160 n(%)	Asian N=25 n(%)	Multiple/ Other N=27 n(%)	American Indian/ Alaskan Native N=3 n(%)	Native Hawaiian N=2 n(%)
SAEs	12 (2.9)	114 (5.5)	49 (3.8)	77 (6.1)	122 (5.3)	3 (1.9)	0 (0)	1 (3.7)	0 (0)	0 (0)
AEs	268 (65.7)	1524 (72.9)	881 (68.4)	911 (71.7)	1649 (72.3)	104 (65.0)	15 (60.0)	20 (74.1)	2 (66.7)	2 (100)

*Reviewer created table using ISS dataset from 120-day update ADAE, and ADSL as denominator. For AEs where POOL2RFL=Y, and for SAEs where AESER=Y. This table is at the patient level. Some patients may have experienced more than one AE, but are only represented once in each category.

8.7. Specific Safety Studies/Clinical Trials

Clinical Home Use Study: 20120178 and 20130255

Study 20120178 and 20120255 had a substudy to assess the patient's ability to administer the 140mg dose of erenumab by either two prefilled syringes or two prefilled autoinjectors. Each substudy was 12 weeks long. Participants were taken from U.S. and German study sites. They were randomized 1:1 into either 140mg via PFS or AI. To assess the patient's ability to self-administer two injections at home, the site staff called the patients and assessed what injection site was used, and assessed whether a full, partial, or no dose was administered.

There were a total of 136 patients enrolled in the two studies (83 from study 20120178-EM and 53 from 20130255-CM) who received at least one dose of IP. A total of 69 patients administered at least one dose of erenumab by PFS, and 67 patients administered at least one dose by AI. A total of 129 patients completed the entire CHU substudy, which was defined as completing the week 12 visit (i.e., three administrations of erenumab).

Two patients reported device related problems. One patient reported that the product leaked from the device. Another patient reported that the product spilled out after pulling the AI out from the abdomen.

The sponsor provided a combined ADAE dataset for the two CHU substudies. There were 53 AEs reported in 38 unique patients. There were 7 patients (5.1%) who reported injection site reactions. Four of the reports were in patients using the PFS, and three were in patients using the AI. The patients using the PFS reported injection site erythema, hemorrhage, bruising, and swelling. The patients using the AI reported injection site erythema, hemorrhage, and urticaria. The overall rate of injection related adverse events was on par with what was seen in the overall development program.

Overall, the population that was included in the substudy was representative of the development program in terms of age, and sex. The only difference is that the overall development program included 50% of the patients from foreign countries. The CHU substudy only included U.S. patients (132/136) and German patients (4/136).

Reviewer Comment: No safety signals were identified by the CHU. Rates of injection site reactions were on par with what was seen in the overall development program.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Overall there were very few malignancies in the database (Table 118). In total, there were 6 basal cell carcinomas, 4 breast cancers, 2 thyroid cancers, 1 lung cancer, 1 squamous cell, 1 malignant sweat gland tumor, and 2 fibrous histiocytomas (not confirmed malignancies). In the DBTP, the only malignant neoplasms noted were three basal cell carcinomas and one fibrous histiocytoma (malignancy not confirmed). In the DBTP, the basal cell carcinomas all occurred in patients on placebo at the time of the diagnosis. The fibrous histiocytoma occurred in a patient on 70mg of erenumab. The rate of breast cancer in women exposed to erenumab was 0.2% (4/2091). The exposure adjusted rate was 0.1 per 100 SY (4/2967). According to the National Cancer Institute, Surveillance, Epidemiology, and End Results Program (SEER), the incidence rate of breast cancer in women is 125/100,000 (incidence rate of about 0.1%). The age-specific rates applicable to the women who developed breast cancer in these studies are slightly higher. The rates are 188/100,000 for women age 45-49 and 225/100,000 for women age 50-54 (incidence rates of about 0.2%). I do not detect a signal for the development of breast cancer in this development program.

Table 118 Listing of Malignancies of All Exposed Patients to Erenumab

Malignancy	Subject ID	Age/Sex	Country	Dose/length of treatment
Basal cell carcinoma	(b) (6)	56/F	USA	placebo
Basal cell carcinoma		55/F	Canada	placebo
Basal cell carcinoma		47/F	USA	placebo
Basal cell carcinoma		54/F	USA	70mg 6 to 12 mo
Basal cell carcinoma		55/F	USA	70mg 12 to 18 mo
Basal cell carcinoma		42/F	USA	140mg 6 to 12 mo
Breast cancer		48/F	Finland	70mg 3 to 6 mo
Breast cancer		47/F	USA	70mg 3 to 6 mo

	(b) (6)			
Breast cancer (invasive lobular)		49/F	USA	70mg 18 to 24 mo
Breast cancer		51F	Germany	140mg 12 to 18 mo
Lung cancer (adenocarcinoma)		58/F	USA	70mg 18 to 24 mo
Squamous cell carcinoma		55/F	USA	70mg 12 to 18 mo
Papillary thyroid cancer		48/F	Spain	70mg 0 to 3 mo
Papillary thyroid cancer		38/F	USA	70mg 3 to 6 mo
Malignant sweat gland neoplasm		46/F	USA	70mg 6 to 12 mo
Fibrous histiocytoma (malignancy not noted)		55/M	Germany	70mg 12 to 18 mo
Fibrous histiocytoma (malignancy not noted)		44/F	USA	70mg 0 to 3 mo

Reviewer created table

8.8.2. **Human Reproduction and Pregnancy**

Despite requirements for contraception, the erenumab development program had some pregnancies. The data are insufficient to support conclusions about the effect of erenumab on reproduction and pregnancy.

Pregnant and lactating women were excluded from erenumab studies. According to the sponsor, measurable erenumab concentrations were found in infant monkeys at birth, confirming that erenumab crosses into the placenta.

There were a total of 29 pregnancies reported at the initial BLA filing, 24 were maternal exposures and 5 were paternal exposures. At the 120-day safety update, there were an additional 5 new pregnancies (4 maternal exposures, and 1 paternal exposure) for a total of 34 pregnancies. Of the 28 maternal exposures, 5 were in patients on placebo leaving 23 pregnancies in women exposed to erenumab. All 6 paternal exposures were from patients on erenumab.

Of these 23 pregnancies (Table 119), 2 spontaneous abortions were reported. One was in a woman with a prior uterine ablation, and the other was in a woman who received a single dose 140mg of erenumab and miscarried 3 months after discontinuation of erenumab.

Table 119 Summary of Pregnancies and Outcomes in Patients Exposed to Erenumab

Birth Outcome	Maternal Exposure	Paternal Exposure
Full term birth without complications	5	2
Full term birth with complications	1	0
Preterm birth without complications	1	1
Elective termination	3	0
Spontaneous abortion	2	0
Delivered (no other info)	0	1
Follow up pending/pregnancy on going	6	1
Lost to follow up	5	1
Total	**23**	**6**

This table was adapted from the sponsor's materials from the SCS.

8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable to this review. Pediatric patients were not exposed to erenumab. Patients under age 18 were excluded from all studies.

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

There were no cases of overdose reported in the clinical studies. The highest dose received was a single dose of 280mg followed by two monthly doses of 210mg to healthy volunteers in phase 1 studies. No adverse events or dose limiting toxicities were noted per the sponsor.

A consult to the controlled substance staff (CSS) was placed when the BLA was received. CSS felt that they would not need to be involved in the review of the BLA and cited the following reasons in the filing checklist: 1. Erenumab is not anticipated to have any potential for abuse or dependence based on the mechanism of action. 2. A very small fraction crosses the blood-brain barrier. 3. Erenumab has no structural similarities with other known drugs of abuse. 4. No abuse-related signals were observed during clinical development.

In accordance with the Guidance for Industry, "Assessment of Abuse Potential of Drugs", the database was queried for abuse-related terms. No signal for abuse related potential was found (Table 120).

Table 120 Adverse Events Associated with Abuse Potential (Pool A)

Preferred Terms	Placebo N=1043 n(%)	70mg N=893 n(%)	140mg N=507 n(%)
Euphoric mood	1 (<0.1)	0	0
Dizziness	11 (1.1)	9 (1.0)	7 (1.4)
Affect lability	0	1 (0.1)	0
Irritability	1 (<0.1)	3 (0.3)	1 (0.2)
Mood altered	2 (0.2)	3 (0.3)	0
Disturbances in consciousness (HLT)	4 (0.4)	5 (0.6)	1 (0.2)
Mood swings	1 (<0.1)	1 (0.1)	1 (0.2)
Mental impairment (HLT)	3 (0.3)	4 (0.4)	1 (0.2)
Apathy	0	1 (0.1)	0
Aggression	0	1 (0.1)	0
Total AEs	23 (2.2)	28 (3.1)	11 (2.2)
Total # of patients	21 (2.0)	25 (2.8)	11 (2.2)

This table was adapted from the sponsor's materials SCS.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

This section is not applicable. Erenumab is not marketed in any country at the time of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

There are theoretical safety concerns related to the use of CGRP in patients who have cardiovascular disease. These patients were not explicitly excluded from the pivotal migraine trials; however, they were effectively excluded. There is also a concern for safety in patients over age 65 who were not studied in the pivotal trials either. Patients in this age bracket likely have higher rates of cardiovascular disease. We have little to no data on either group (age over 65 or patients with cardiovascular disease).

8.10. Additional Safety Issues from Other Disciplines

The nonclinical reviewer identified mild to moderate injection site irritation as the only finding in the nonclinical studies. At the time of this writing, I am not aware of other additional safety issues from other disciplines.

8.11. Integrated Assessment of Safety

The following safety issues were examined in detail in this review based on the theoretical concerns associated with the CGRP receptor antagonism, and the use of monoclonal antibodies and injectable products: cardiovascular, cerebrovascular, peripheral vascular, gastrointestinal, immunogenicity, hypersensitivity, and injection site reactions. Additional close attention was paid to hepatoxicity. The safety of erenumab has been evaluated in four large clinical trials. My review of these trials has not revealed a clear relationship to any serious safety issues related to the use of erenumab.

The review focusing on cardiovascular and cerebrovascular disorders revealed no potential safety concerns in regards to toxicity associated with erenumab use. However, this review is extremely limited as the population studied was primarily young, and healthy. Two cases of cardiac related death were reviewed by our cardiology consultant and are felt to have plausible alternative causes to the use of erenumab. Although for one of the cases, a contribution of CGRP antagonism cannot be completely excluded. For peripheral vascular disorders, there were two cases of worsening symptoms of Raynaud's phenomenon with one possibly related to treatment with erenumab. There is biological plausibility to this worsening, and I recommend monitoring this in the postmarketing setting. There is some suggestion that patients treated with erenumab were more likely than placebo patients to have elevations in their diastolic blood pressure by 10 mmHg or more. Although this did not have clinical significance in young healthy people, this degree of blood pressure elevation may have consequences in patients with CV disease who were not adequately studied.

The primary safety concern of gastrointestinal toxicity associated with erenumab use was constipation. This occurred in a dose dependent fashion. One patient experienced an SAE related to constipation that resulted in hospitalization. There were two additional cases of discontinuation of treatment with erenumab due to constipation. There was one case of ischemic colitis in a patient treated with erenumab. However, this patient was able to continue treatment with erenumab. While this is not enough information to implicate erenumab in the case of ischemic colitis, it is something that may need monitoring in the postmarketing setting as there is biological plausibility to it being drug related.

Not enough data is available to make definitive conclusions on the safety of erenumab in the setting of anti-drug antibodies. Preliminarily the safety profile of patients who developed ADAs is similar to those patients who did not.

No clear cases of anaphylaxis related to erenumab were identified. No acute hypersensitivity reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) were reported.

One case of acute hepatic injury occurred in the development program. A thorough review of the development program revealed no safety signals related to hepatotoxicity in erenumab treated patients. Transient elevations of serum creatine kinase were noted without any associated clinical symptoms of concern.

There are still many uncertainties that remain with the use of erenumab that may come out in the postmarketing period, and will need to be monitored carefully. There was one case of acute liver injury in the development program. The information available at the time of this review does not suggest that erenumab was the cause of this case. The theoretical concerns related to the cardiovascular risk of erenumab remain as well. Patients older than age 65 were explicitly excluded from clinical studies and those with major cardiovascular disease were effectively (although not explicitly) excluded from clinical studies. The theoretical risk of CGRP antagonists lies with the potential loss of compensatory vasodilatation in the setting of ischemia. The data available at this time is primarily with the 70mg group with exposures for up one year. There is some limited data available with up to 18 months of exposure in primarily healthy individuals. However, there is no data available on the consequence of chronic CGRP antagonism in patients with cardiovascular disease.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting is not anticipated for this product.

10 Labeling Recommendations

10.1. Prescribing Information

The final label was not available at the time of this review. After reviewing the sponsor's submitted application, I had the following recommendations

DOSAGE AND ADMINISTRATION: The sponsor has provided instructions for administration of the 140mg dose. I recommend inclusion of the 70mg dose, and adjustment to the instructions for administration.

WARNINGS AND PRECAUTIONS: Due to the mechanism of action of erenumab, there is a theoretical concern about the use of erenumab in patients with major cardiovascular or cerebrovascular disease and in patients with high risk for major cardiovascular or cerebrovascular disease. Patients who have experienced a stroke, myocardial infarction, transient ischemic attack, unstable angina or had coronary artery bypass surgery within the last year should not use erenumab.

Reviewer Comment: At the EOP2 meeting, the sponsor was made aware that if the cardiovascular risks associated with the mechanism of action remain theoretical, then this information would be conveyed in the warning and precautions section of the product label. I do not think the sponsor has provided adequate evidence that erenumab is safe to use in patients with major cardiovascular disease.

This issue of whether to include a warning in section 5 of the label was discussed in detail at a meeting with the Medical Policy and Program Review Council (MPPRC). I discuss the outcome of this meeting below in section 10.2.

10.2. Medical Policy and Program Review Council (MPPRC)

DNP considered inclusion of a warning in section 5 of the FDA label to address the theoretical risk of CGRP receptor antagonism in patients with major cardiovascular disease. Per FDA guidance, a theoretical warning may be included in the label if the animal data raises substantial concern about the potential for occurrence of the adverse reaction in humans. DNP requested a consult from the Division of Cardiovascular and Renal Products (DCRP) to assess whether the available nonclinical literature supported inclusion of this warning in the label. DCRP concluded that there is consensus that CGRP is a potent microvascular vasodilator, but that CGRP is one of multiple redundant control mechanisms regulating blood flow. They concluded that in animal models, loss of vasodilatation from CGRP antagonism does not result in tissue threatening ischemia. Please see the consult from DCRP by Drs. Dunnmon and Koerner for further details of this literature review.

DNP requested a meeting with the MPPRC to discuss whether the animal data was compelling enough to include a warning in section 5 describing the theoretical risk of CGRP receptor antagonism in patients with major cardiovascular disease. The animal data was presented to the MPPRC as were details about the mechanism of CGRP. The Council agreed with DCRP's assessment that CGRP is a potent vasodilator, and that, in animal models, loss of vasodilatation from CGRP antagonism does not result in tissue threatening ischemia. The Council unanimously

felt that the animal data was not compelling enough to include a warning in section 5 of the label.

Reviewer Comment: After reviewing the consult from DCRP and listening to the opinions of the MPPRC members, I agree that the animal data is not compelling enough to consider inclusion of the theoretical risk of CGRP receptor antagonism in section 5 of the label.

10.3. Patient Labeling

A medication guide is not needed. Instructions for use are being reviewed.

10.4. Nonprescription Labeling

N/A

11 Risk Evaluation and Mitigation Strategies (REMS)

This section is not applicable to this review.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

N/A

11.2. Conditions of Use to Address Safety Issue(s)

N/A

11.3. Recommendations on REMS

I do not anticipate a REMS for this product.

12 Postmarketing Requirements and Commitments

PMR

1. Deferred pediatric studies required under the Pediatric Research Equity Act
2. Pregnancy registry

My recommendation:

Safety study in patients over age 65. As per ICH E7, and Guidance for Industry: Studies in Support of Special Populations: Geriatrics (Questions and Answers), for drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences. Per this guideline, elderly is considered over age 75. This suggests that the group age 65 through 75 is part of the adult, non-geriatric population and should be studied.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 20120295, 20120296, and 20120297

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 219		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
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) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. MPFID Questions and Scoring Rubric

The possible responses are:

Without any difficulty (1pt)
With a little difficulty (2pts)
With some difficulty (3pts)
With much difficulty (4pts)
Unable to do (5pts)

The following are the questions for the MPFID:

1. In the past 24 hours, were you able to do your usual household chores?
2. In the past 24 hours, were you able to do your usual activities outside your home? (For example, shopping or doing errands)
3. In the past 24 hours, were you able to keep to your daily routine or schedule?
4. In the past 24 hours, were you able to do activities that required you to concentrate?
5. In the past 24 hours, were you able to get yourself ready for the day?
6. In the past 24 hours, how much of the time did you avoid interacting with other people?
7. In the past 24 hours, how much of the time did you need to rest or lie down during your normal waking hours?
8. In the past 24 hours, overall, how difficult was it to do your usual activities?
9. In the past 24 hours, how much of the time did you have difficulty moving your head?
10. In the past 24 hours, how much of the time did you have difficulty moving your body?
11. In the past 24 hours, were you able to get out of bed?
12. In the past 24 hours, were you able to bend over?
13. In the past 24 hours, were you able to do your usual activities that required physical effort?

Questions 1 through 7 contributed to the domain "Impact on Everyday Activities." Question 8 is a global assessment of "Overall Impact on Everyday Activities." Questions 9 through 13 contribute to the domain "Physical Impairment."

Each item is score on a scale of 1 to 5 with 5 being a more negative impact on function. Raw scores for the "Impact of Everyday Activities" domain range from 7 to 35 and 5 to 25 for the domain "Physical Impairment." Each MPFID domain score is then transformed and scaled to a 100-point score. The score for the MPFID is calculated by averaging the daily MPFID score over a 28-day period. The transformed score is calculated by the following equation:

Transformed score= ((raw score-lowest possible raw score)/(highest possible raw score-lowest possible raw score))*100

The missing data for the MPFID is handled as follows:

When estimating the average score for a monthly interval, if fewer than 14 days of MPFID are recorded then the monthly MPFID score is considered missing. For each MPFID domain, if ≥50% of items in that domain are missing then the daily domain score will be considered missing.

Table 121 MPFID Reviewer Created Table Comparing Raw Score to Transformed Score

Impact on Everyday Raw Score	Transformed Domain Score		Physical Impairment Raw Score	Transformed Domain Score
7	0		5	0
8	4		6	5
9	7		7	10
10	11		8	15
11	14		9	20
12	18		10	25
13	21		11	30
14	25		12	35
15	29		13	40
16	32		14	45
17	36		15	50
18	39		16	55
19	43		17	60
20	46		18	65
21	50		19	70
22	54		20	75
23	57		21	80
24	61		22	85
25	64		23	90
26	68		24	95
27	71		25	100
28	75			
29	79			
30	82			
31	86			
32	89			
33	93			
34	96			
35	100			

13.4 Additional Tables

Table 122 Study 20120295: Analysis of the Primary Endpoint by Age

	Placebo		70mg			140mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
18-40	126	-4.59	82	-7.62	-3.03	68	-7.11	-2.52
41-55	116	-3.70	89	-6.05	-2.35	96	-6.25	-2.55
56-65	40	-3.99	19	-3.87	+0.12	24	-6.3	-2.31

Reviewer calculated using ADMONPRI for study 20120295 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 123 Study 20120296: Analysis of the Primary Endpoint by Age

	Placebo		70mg			140mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
18-40	151	-1.59	138	-2.99	-1.40	149	-3.21	-1.62
41-55	129	-1.65	143	-3.29	-1.64	143	-3.88	-2.23
56-65	38	-2.42	32	-2.07	+0.35	27	-3.99	-1.57

Reviewer calculated using ADMONPRI for study 20120296 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 124 Study 20120297: Analysis of the Primary Endpoint by Age

	Placebo		70mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO

18-40	123	-1.92	118	-2.72	-0.8
41-55	123	-1.83	124	-3.29	-1.46
56-65	43	-2.48	41	-1.95	+0.53

Reviewer calculated using ADMONPRI for study 20120297 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 125 Studies 20120296 and 20120297: Pooled Analysis of the Primary Endpoint by Age Quartile

	Placebo		70mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
18-33	163	-1.85	153	-3.04	-1.19
34-42	147	-1.52	143	-2.84	-1.32
43-50	148	-1.62	161	-3.12	-1.50
51-65	151	-2.29	145	-2.68	-0.39

Reviewer calculated using ISE dataset ADMONPRI where PARAMCD=MMD, and AVISIT=WEEK 12, evaluating CHG by TRT01PN

Table 126 Study 20120295: Analysis of the Primary Endpoint by Age Quartile

	Placebo		70mg			140mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
18-34	79	-4.79	54	-7.81	-3.02	44	-5.70	-0.91
35-43	67	-3.94	51	-6.98	-3.04	38	-8.02	-4.08
44-50	66	-3.40	40	-5.54	-2.14	59	-6.49	-3.09
51-65	70	-4.29	45	-5.27	-0.98	47	-6.30	-2.01

Reviewer calculated using ADMONPRI for study 20120295 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 127 Study 20120296: Analysis of the Primary Endpoint by Age Quartile

	Placebo		70mg			140mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
18-33	84	-1.82	84	-3.17	-1.35	100	-2.84	-1.02
34-42	83	-1.45	78	-3.10	-1.65	73	-3.98	-2.53
43-50	83	-1.53	78	-2.75	-1.22	78	-3.79	-2.26
51-65	68	-2.12	76	-2.98	-0.86	68	-3.98	-1.86

Reviewer calculated using ADMONPRI for study 20120296 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 128 Study 20120297: Analysis of the Primary Endpoint by Age Quartile

	Placebo		70mg		
Age group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
18-33	79	-1.88	69	-2.88	-1.00
34-42	64	-1.62	65	-2.54	-0.92
43-50	65	-1.75	83	-3.48	-1.73
51-65	83	-2.43	69	-2.35	+0.08

Reviewer calculated using ADMONPRI for study 20120297 where PARAMCD=MMD, and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 129 Studies 20120296 and 20120297: Pooled Analysis of the Primary Endpoint by BMI quartiles

	Placebo		70mg		
BMI	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
16 to 23	159	-1.22	165	-2.58	-1.36
>23 to 26	154	-1.10	120	-3.04	-1.94
>26 to 31	145	-2.11	167	-3.12	-1.01
>31 to 55	148	-2.93	148	-3.01	-0.08

Reviewer calculated using ADMONPRI where PARAMCD=MMD joined with ADVS where PARAMCD=BMI for study 20120296 and 20120297 and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 130 Study 20120295: Analysis of the Primary Endpoint by BMI Quartiles

	Placebo		70mg			140mg		
BMI	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
15 to 22	61	-4.89	52	-6.61	-1.72	48	-6.96	-2.07
>22 to 25	65	-3.47	44	-5.96	-2.49	40	-5.22	-1.75
>25 to 29	83	-4.08	47	-6.30	-2.22	49	-7.45	-3.37
>29 to 40	73	-4.17	47	-7.13	-2.93	51	-6.41	-2.24

Reviewer calculated using ADMONPRI where PARAMCD=MMD joined with ADVS where PARAMCD=BMI for study 20120295 and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 131 Study 20120296: Analysis of the Primary Endpoint by BMI Quartiles

	Placebo		70mg			140mg		
BMI	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO	N	Change from Baseline in MMD	Difference from PBO
16 to 23	85	-0.95	88	-2.47	-1.51	97	-4.13	-3.18
>23 to 26	79	-1.31	59	-3.42	-2.11	78	-3.56	-2.25
>26 to 31	82	-1.81	92	-3.21	-1.40	69	-3.36	-1.55
>31 to 55	72	-2.94	77	-3.05	-0.11	75	-3.07	-0.13

Reviewer calculated using ADMONPRI where PARAMCD=MMD joined with ADVS where PARAMCD=BMI for study 20120296 and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 132 Study 20120297: Analysis of the Primary Endpoint by BMI Quartiles

	Placebo		70mg		
BMI group	N	Change from Baseline in MMD	N	Change from Baseline in MMD	Difference from PBO
16 to 23	74	-1.54	77	-2.71	-1.17
>23 to 26	75	-0.87	61	-2.67	-1.80
>26 to 31	63	-2.51	75	-3.00	-0.49
>31 to 55	76	-2.92	71	-2.96	-0.04

Reviewer calculated using ADMONPRI where PARAMCD=MMD joined with ADVS where PARAMCD=BMI for study 20120297 and AVISIT=Week 12, analysis of CHG by TRT01AN

Table 133 Mean Change from Baseline in DBP in Patients with Hypertension

	Placebo	70mg	140mg
Week 4	0.05 (n=55)	-2.06 (n=35)	0.94 (n=32)
Week 8	-0.78 (n=55)	-1.74 (n=34)	0.03 (n=33)
Week 12	-0.76 (n=55)	-0.65 (n=34)	1.94 (n=31)
Week 24*	-0.72 (n=32)	-0.05 (n=20)	1.59 (n=17)

Reviewer created table from ADMH where MHTERM=HYPERTENSION join with ADVS where PARAMCD=DIABP, analysis of CHG by TRT01AN and AVISIT; Pooled data from studies 20120295 and 20120296 except where noted
*Study 20120296 only

Table 134 Full Analysis Set Disposition for Study 20120296

	Placebo (N = 319) n (%)	AMG 334 70 mg (N = 317) n (%)	AMG 334 140 mg (N = 319) n (%)	Total (N = 955) n (%)
Efficacy analysis set inclusion	316 (99.1)	312 (98.4)	318 (99.7)	946 (99.1)
Efficacy analysis set exclusion	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Did not receive at least one dose of IP	0 (0.0)	3 (0.9)	0 (0.0)	3 (0.3)
Did not have at least one change from baseline measurement in monthly migraine day during DBTP	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Per protocol analysis set inclusion	262 (82.1)	273 (86.1)	273 (85.6)	808 (84.6)
Per protocol analysis set exclusion	57 (17.9)	44 (13.9)	46 (14.4)	147 (15.4)
Excluded from efficacy analysis set	3 (0.9)	5 (1.6)	1 (0.3)	9 (0.9)
Incomplete data on primary endpoint	39 (12.2)	33 (10.4)	35 (11.0)	107 (11.2)
Did not receive IP at the primary time point per protocol	39 (12.2)	31 (9.8)	28 (8.8)	98 (10.3)
Migraine or headache frequency at baseline did not meet eligibility criteria	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)
Important deviation from eligibility criteria	4 (1.3)	1 (0.3)	3 (0.9)	8 (0.8)
Received excluded therapies	7 (2.2)	6 (1.9)	3 (0.9)	16 (1.7)
Important GCP deviations	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)

These tables are taken from the sponsor's material: CSR for study 20120296

Table 135 Protocol Deviations for Study 20120296

	Placebo (N = 319) n (%)	AMG 334 70 mg (N = 317) n (%)	AMG 334 140 mg (N = 319) n (%)	Total (N = 955) n (%)
Number of subjects with at least one important protocol deviation	20 (6.3)	26 (8.2)	18 (5.6)	64 (6.7)
Entered study even though entry criteria was not satisfied	10 (3.1)	10 (3.2)	9 (2.8)	29 (3.0)
Used prohibited migraine prophylactic therapy prebaseline	1 (0.3)	2 (0.6)	3 (0.9)	6 (0.6)
Baseline migraine frequency outside specified range	1 (0.3)	2 (0.6)	2 (0.6)	5 (0.5)
Excluded medical condition-psychiatric	1 (0.3)	3 (0.9)	0 (0.0)	4 (0.4)
Possible medication overuse	3 (0.9)	1 (0.3)	0 (0.0)	4 (0.4)
Unstable prophylactic medication use	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.3)
Excluded medical condition-neurologic	1 (0.3)	2 (0.6)	0 (0.0)	3 (0.3)
Excluded medical condition-malignancy	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)
Excluded medical condition-hepatic	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Risk of selfharm or harm to others	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Unwilling to use contraception	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Inappropriate pre-baseline headache frequency	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Received botulinum toxin	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)

	Placebo (N = 319) n (%)	AMG 334 70 mg (N = 317) n (%)	AMG 334 140 mg (N = 319) n (%)	Total (N = 955) n (%)
Received an excluded concomitant treatment	8 (2.5)	7 (2.2)	5 (1.6)	20 (2.1)
Received excluded treatment during double-blind treatment phase	7 (2.2)	6 (1.9)	3 (0.9)	16 (1.7)
Received excluded treatment during active treatment phase while on IP	1 (0.3)	1 (0.3)	2 (0.6)	4 (0.4)
Received the wrong treatment or incorrect dose	2 (0.6)	8 (2.5)	4 (1.3)	14 (1.5)
Temperature excursion	2 (0.6)	6 (1.9)	4 (1.3)	12 (1.3)
Dosed with incorrect IP box ID[a]	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)
Other deviations	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)
Important GCP deviations	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)

These tables are taken from the sponsor's material: CSR for study 20120296.

Table 136 Full Analysis Set Disposition for Study 20120297

	Placebo (N = 291) n (%)	AMG 334 70 mg (N = 286) n (%)	Total (N = 577) n (%)
Efficacy analysis set inclusion	288 (99.0)	282 (98.6)	570 (98.8)
Efficacy analysis set exclusion	3 (1.0)	4 (1.4)	7 (1.2)
Did not receive at least one dose of IP	2 (0.7)	3 (1.0)	5 (0.9)
Did not have at least one change from baseline measurement in monthly migraine day during DBTP	3 (1.0)	3 (1.0)	6 (1.0)
Per protocol analysis set inclusion	260 (89.3)	262 (91.6)	522 (90.5)
Per protocol analysis set exclusion	31 (10.7)	24 (8.4)	55 (9.5)
Excluded from efficacy analysis set	3 (1.0)	4 (1.4)	7 (1.2)
Incomplete data on primary endpoint	21 (7.2)	18 (6.3)	39 (6.8)
Did not receive IP at the primary time point per protocol	19 (6.5)	17 (5.9)	36 (6.2)
Migraine or headache frequency at baseline did not meet eligibility criteria	5 (1.7)	3 (1.0)	8 (1.4)
Important deviation from eligibility criteria	1 (0.3)	0 (0.0)	1 (0.2)
Received excluded therapies	4 (1.4)	2 (0.7)	6 (1.0)
Important GCP deviations	0 (0.0)	0 (0.0)	0 (0.0)

These tables are taken from the sponsor's material: CSR for study 20120297

Table 137 Protocol Deviations for Study 20120297

	Placebo (N = 291) n (%)	AMG 334 70 mg (N = 286) n (%)	Total (N = 577) n (%)
Number of subjects with at least one important protocol deviation	15 (5.2)	6 (2.1)	21 (3.6)
Entered study even though entry criteria was not satisfied	11 (3.8)	4 (1.4)	15 (2.6)
Baseline migraine frequency outside specified range	3 (1.0)	3 (1.0)	6 (1.0)
Excluded medical condition- neurologic	1 (0.3)	1 (0.3)	2 (0.3)
Inappropriate baseline headache frequency	2 (0.7)	0 (0.0)	2 (0.3)
Used prohibited migraine prophylactic therapy pre-baseline	2 (0.7)	0 (0.0)	2 (0.3)
Risk of self-harm or harm to others	0 (0.0)	1 (0.3)	1 (0.2)
Excluded medical condition- hepatic	1 (0.3)	0 (0.0)	1 (0.2)
Excluded medical condition- psychiatric	1 (0.3)	0 (0.0)	1 (0.2)
Unstable prophylactic medication use	1 (0.3)	0 (0.0)	1 (0.2)
Received an excluded concomitant treatment	4 (1.4)	2 (0.7)	6 (1.0)
Received excluded treatment during double-blind treatment phase	4 (1.4)	2 (0.7)	6 (1.0)
Received the wrong treatment or incorrect dose	1 (0.3)	0 (0.0)	1 (0.2)
Temperature excursion	1 (0.3)	0 (0.0)	1 (0.2)

These tables are taken from the sponsor's material: CSR for study 20120297

Table 138 Full Analysis Set Disposition for Study 20120295

		AMG 334		
	Placebo (N = 286) n (%)	70 mg (N = 191) n (%)	140 mg (N = 190) n (%)	Total (N = 667) n (%)
Efficacy analysis set inclusion	281 (98.3)	188 (98.4)	187 (98.4)	656 (98.4)
Efficacy analysis set exclusion	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)
Did not receive at least one dose of IP	4 (1.4)	1 (0.5)	2 (1.1)	7 (1.0)
Did not complete at least one post-baseline monthly migraine day measurement during DBTP	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)

Per protocol analysis set inclusion	262 (91.6)	173 (90.6)	177 (93.2)	612 (91.8)
Per protocol analysis set exclusion	24 (8.4)	18 (9.4)	13 (6.8)	55 (8.2)
Excluded from efficacy analysis set	5 (1.7)	3 (1.6)	3 (1.6)	11 (1.6)
Incomplete data on primary endpoint	19 (6.6)	13 (6.8)	8 (4.2)	40 (6.0)
Did not receive IP at the primary time point per protocol	15 (5.2)	7 (3.7)	6 (3.2)	28 (4.2)
Migraine or headache frequency at baseline did not meet eligibility criteria	4 (1.4)	2 (1.0)	1 (0.5)	7 (1.0)
Important deviation from eligibility criteria	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.3)
Received excluded therapies	3 (1.0)	3 (1.6)	2 (1.1)	8 (1.2)
Important GCP deviations	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)

These tables are taken from the sponsor's material: CSR for study 20120295

Table 139 Protocol Deviations for Study 20120295

	Placebo (N = 286) n (%)	AMG 334 70 mg (N = 191) n (%)	AMG 334 140 mg (N = 190) n (%)	Total (N = 667) n (%)
Number of subjects with at least one important protocol deviation	20 (7.0)	16 (8.4)	13 (6.8)	49 (7.3)
Entered study even though entry criteria was not satisfied	12 (4.2)	11 (5.8)	9 (4.7)	32 (4.8)
Excluded medical condition SCR	4 (1.4)	1 (0.5)	5 (2.6)	10 (1.5)
Used prohibited migraine prophylactic therapy or device SCR	3 (1.0)	4 (2.1)	2 (1.1)	9 (1.3)
Inappropriate headache and migraine frequency BL	4 (1.4)	2 (1.0)	1 (0.5)	7 (1.0)
Excluded medical condition BL	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.3)
Received botulinum toxin SCR	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.3)
Anticipated to require excluded medication/ device or procedure	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Evidence of drug or alcohol abuse SCR	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Inappropriate distinct headache episodes	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Use of excluded concomitant medication BL	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Received the wrong treatment or incorrect dose	6 (2.1)	2 (1.0)	2 (1.1)	10 (1.5)
Temperature excursion	6 (2.1)	2 (1.0)	2 (1.1)	10 (1.5)
Received an excluded concomitant treatment	3 (1.0)	3 (1.6)	2 (1.1)	8 (1.2)
Received excluded treatment during study	3 (1.0)	3 (1.6)	2 (1.1)	8 (1.2)
Received daily excluded medication for migraine prophylaxis	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other deviations	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Important GCP deviations	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)

Table 140 Decrease by ≥10mmHg from Baseline DBP over Time in the DBTP

	Placebo n/N (%)	70mg n/N (%)	140mg n/N (%)
Week 4	93/1024 (9.1)	69/881 (7.8)	41/502 (8.2)
Week 8	110/999 (11.0)	80/873 (9.2)	49/498 (9.8)
Week 12	104/988 (10.5)	88/861 (10.2)	53/484 (11.0)
Week 24*	38/284 (13.4)	34/286 (11.9)	33/289 (11.4)

Reviewer created table using ISS ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN *Study 20120296 only

Table 141 Decrease by ≥10mmHg from Baseline DBP over Time in DBTP of Studies 20120295 and 20120296 Combined

	Placebo n/N (%)	70mg n/N (%)	140mg n/N (%)
Week 4	50/589 (8.5)	44/497 (8.9)	41/502 (8.2)
Week 8	60/575 (10.4)	52/494 (10.5)	49/498 (9.8)
Week 12	64/569 (11.2)	59/489 (12.1)	53/484 (11.0)
Week 24*	38/284 (13.4)	34/286 (11.9)	33/289 (11.4)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN
*Study 20120296 only

Table 142 Decrease by ≥10mmHg from Baseline DBP over Time in DBTP of Study 20120295

	Placebo n/N (%)	70mg n/N (%)	140mg n/N (%)
Week 4	20/273 (7.3)	20/183 (10.9)	17/186 (9.1)
Week 8	31/270 (11.5)	14/185 (7.6)	20/185 (10.8)
Week 12	27/274 (9.9)	18/185 (9.7)	24/183 (13.1)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, or Week 12; analysis of CHG by TRT01AN

Table 143 Decrease by ≥10mmHg from Baseline DBP over time in DBTP of Study 20120296

	Placebo n/N (%)	70mg n/N (%)	140mg n/N (%)
Week 4	30/311 (9.6)	24/308 (7.8)	24/314 (7.6)
Week 8	29/298 (9.7)	38/306 (12.4)	29/305 (9.5)
Week 12	37/295 (12.5)	41/304 (13.5)	29/301 (9.6)
Week 24	38/284 (13.3)	34/286 (11.9)	33/289 (11.4)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12, or Week 24; analysis of CHG by TRT01AN

Table 144 TEAEs from Study 20120295 with a Risk Difference of 1% or Greater

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=282	n=190	n=188		
Cramps, muscle spasms	4 (1%)	2 (1%)	7 (4%)	0	2
Constipation	1 (0%)	0 (0%)	8 (4%)	0	4
Injection site reaction	6 (2%)	9 (5%)	14 (7%)	3	5
Pruritis (inc inj site)	1 (0%)	1 (1%)	4 (2%)	0	2
Infection, viral	3 (1%)	7 (4%)	5 (3%)	3	2
Abdominal pain, distention, bloating	3 (1%)	5 (3%)	4 (2%)	2	1
Epistaxis	0 (0%)	3 (2%)	0 (0%)	2	0
Bleeding	2 (1%)	4 (2%)	0 (0%)	1	-1
Influenza	0 (0%)	5 (3%)	1 (1%)	3	1
Dizziness, lightheadedness	3 (1%)	4 (2%)	2 (1%)	1	0
Insomnia, sleep disturbance	2 (1%)	3 (2%)	3 (2%)	1	1
Cough	3 (1%)	1 (1%)	6 (3%)	-1	2
bronchitis	3 (1%)	2 (1%)	4 (2%)	0	1
arthralgia, arthritis, arthrosis	3 (1%)	2 (1%)	3 (2%)	0	1
dyspepsia, N, V, indigestion, epigastri	12 (4%)	7 (4%)	10 (5%)	-1	1
headache	7 (2%)	4 (2%)	6 (3%)	0	1
Rash	1 (0%)	0 (0%)	3 (2%)	0	1
UTI	7 (2%)	4 (2%)	6 (3%)	0	1
Nausea and vomiting	8 (3%)	5 (3%)	7 (4%)	0	1

Reviewer created table from study 20120295

Table 145 TEAEs from Study 20120296 with a Risk Difference of 1% or Greater

	Placebo	Erenumab		Risk Difference	
		70 mg	140 mg	70mg/placebo	140mg/placebo
	n=319	n=314	n=319		
Infection, all	92 (29%)	89 (28%)	102 (32%)	0	3
Infection, viral	11 (3%)	13 (4%)	19 (6%)	1	3
Injection site reaction	6 (2%)	19 (6%)	11 (3%)	4	2
Constipation	4 (1%)	5 (2%)	11 (3%)	0	2
Influenza	6 (2%)	4 (1%)	8 (3%)	-1	1
Pruritus	4 (1%)	5 (2%)	7 (2%)	0	1
abdominal pain, distention, bloating	4 (1%)	6 (2%)	7 (2%)	1	1
bronchitis	3 (1%)	5 (2%)	6 (2%)	1	1
infection, bacterial	3 (1%)	6 (2%)	7 (2%)	1	1
dizziness	5 (2%)	2 (1%)	6 (2%)	-1	0
arthralgia, arthritis, arthrosis	9 (3%)	11 (4%)	11 (3%)	1	1
URI, cold, flu	60 (19%)	63 (20%)	69 (22%)	1	3

Reviewer created table from study 20120296

Table 146 TEAEs from Study 20120297 with a Risk Difference of 1% or Greater

	Placebo	Erenumab	Risk Difference
		70 mg	70mg/placebo
	n=283	n=289	
injection site reaction	15 (5%)	20 (7%)	2
infection, viral	15 (5%)	18 (6%)	1
infection, all	70 (25%)	74 (26%)	1
somnalence, fatigue	7 (2%)	10 (3%)	1
URI, cold, flu	42 (15%)	49 (17%)	2

Reviewer created table from study 20120297

Table 147 Summary of Cardiovascular, Cerebrovascular, or Peripheral Arterial Disease Medical History

Category Diagnosis/Procedure	Placebo (N = 1043) n (%)	AMG 334 7 mg or 21 mg (N = 213) n (%)	AMG 334 70 mg (N = 893) n (%)	AMG 334 140 mg (N = 507) n (%)	Total (N = 2656) n (%)
Number of subjects reporting cardiovascular medical history	8 (0.8)	0 (0.0)	2 (0.2)	3 (0.6)	13 (0.5)
Coronary artery disease	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.1)
Coronary artery disease (CAD)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (<0.1)
Angina pectoris (stable and unstable)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (<0.1)
Myocardial infarction (MI)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary artery bypass (CABG)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Percutaneous coronary artery intervention (PCI)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cerebrovascular or peripheral arterial disease	7 (0.7)	0 (0.0)	2 (0.2)	2 (0.4)	11 (0.4)
Transient ischemic attack (TIA)	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.2)	2 (<0.1)
Cerebrovascular accident (CVA)	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Carotid or vertebro-basilar artery disease	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Other cerebrovascular conditions (eg.: AV malformation, aneurysm)	4 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	5 (0.2)
Peripheral artery disease	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (<0.1)

Integrated safety analysis set: all subjects in the studies/pool who have received at least one dose of IP.
N = Number of subjects in the analysis set.
n = Number of subjects reporting that diagnosis/procedure; % = n/N * 100.
For studies which do not have a dedicated cardiovascular medical history CRF page, manual review has been performed on the medical history data.

Sponsor's table from the SCS

Table 148 Increase by ≥10mmHg from Baseline DBP over time in the DBTP in Study 20120297

	Placebo n/N (%)	70mg n/N (%)
Week 4	22/284 (7.7)	29/279 (10.4)
Week 8	27/279 (9.7)	22/273 (8.1)
Week 12	28/275 (10.2)	29/270 (10.7)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12; analysis of CHG by TRT01AN where CHG≥10

Table 149 Increase by ≥10mmHg from Baseline DBP over time in the DBTP in Study 20120178

	Placebo n/N (%)	70mg n/N (%)
Week 4	9/148 (6.1)	6/105 (5.7)
Week 8	11/145 (7.6)	12/102 (11.8)
Week 12	8/147 (5.4)	10/106 (9.4)

Reviewer created table using ADVS where PARAMCD=DIABP and APERIOD=1 and BASETYPE=DOUBLE-BLIND, AVIST=Week 4, Week 8, Week 12; analysis of CHG by TRT01AN where CHG≥10

13.5 Columbia-Suicide Severity Rating Scale

0: No suicidal ideation or behavior
1: Wish to be dead
2: Non-specific active suicidal thoughts
3: Active suicidal ideation with any methods without intent to act (no plan)
4: Active suicidal ideation with some intent to act, without specific plan
5: Active suicidal ideation with specific plan and intent
6: Preparatory acts or behavior
7: Aborted attempt
8: Interrupted attempt
9: Actual attempt (non-fatal)
10: Completed suicide

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/s/

LAURA A JAWIDZIK
05/17/2018

HEATHER D FITTER
05/17/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

MEDICAL OFFICER CONSULT

BLA	761077
Sponsor	Amgen
Drug	Erenumab, Aimovig, AMG 334
Requesting Division	Division of Neurology Products
Indication	Migraine
Safety Issue for Consult	Drug-Induced Liver Injury (DILI)
Date Received	November 11, 2017
Date review Completed	January 22, 2018
Clinical Reviewer	Ruby Mehta, MD
Team Leader	Kathleen Donohue, MD
Acting Associate Division	Lisa Soule, MD
Project Manager	Cheronda Cherry-France, RN BSN MHA

Executive Summary

This DGIEP addendum is to the consult review submitted to Division of Neurology Products (DNP) on 11-7-2017, for BLA 761077 Erenumab, which is currently being reviewed by the DNP for the indication of migraine. The NDA is submitted by Amgen. DGIEP requested that DNP send out the IR below, because the information and details of testing were missing. The overall impression remains unchanged; the reviewer thinks that the drug seems unlikely to be the cause for worsening of the liver function. With this information, no alternative causes for the elevation of liver enzyme could be found. With the review of current information, and the lack of Hy's Law cases, currently, we think the drug does not appear to have a drug-induced liver injury signal. However, ongoing pharmacovigilance is still required during the post-marketing period as DILI is rare event, and might be detected as a higher number of patients are exposed during the post marketing period.

The IR was sent out to Amgen on 10-25-2017 and below-noted questions were asked by DGIEP:

1. Please provide the following information for Subject (b) (6) including a complete narrative with a timeline for drug initiation, symptom initiation and laboratory evaluations and include the following information:
    a. The initial admitting diagnosis(ses), and physical exam findings
    b. Vitals signs
    c. The laboratory tests results -complete blood count and electrolytes values
    d. Dates and results for:
        1. For repeat hepatitis C antibody, and ceruloplasmin
        2. Hepatitis C RNA-PCR to confirm absence of Hepatitis C and Hepatitis E IgM antibody
2. Provide an anonymized copy of the patient's medical records from the hospital admission for liver injury.

DGIEP Review of Amgen's Response:

A 51-year-old Hispanic female participated in a healthy volunteer trial, Study 20160349, and received a single subcutaneous dose 140 mg of Erenumab on (b) (6) One week later, on (b) (6) the subject developed elevated transaminases and bilirubin with clinical symptoms; a picture consistent with acute hepatitis. In the previous consult, the reviewer stated that the event seemed unlikely secondary to Erenumab. Noted below are the additional details provide by the sponsor in response to the IR.

Hepatitis C

- Sponsor provided their rationale for not performing the Hepatitis C RNA-PCR - because the Hep C antibody was non-reactive on (b) (6)
- However, the sponsor performed the Hepatitis C RNA-PCR test with the sample that was collected when the liver biochemical enzymes rose on (b) (6) and the Hepatitis C PCR was negative.

- Hepatitis IgE was not tested as a part of the diagnostic workup for the patient; however, a retained blood sample obtained on (b) (6) was tested and the resulted in non-reactive antibody.

- A repeat serum ceruloplasmin was tested from the blood sample from (b) (6) and the result was 28 mg/dL, which is in the normal range.

- Hepatitis B surface antigen was non-reactive at enrollment. Hepatitis B surface antigen and core IgM antibody were non-reactive (b) (6)

- Physical exam:
    - The subject was admitted to the hospital on (b) (6) from the emergency department and was found to have elevated liver function tests that were concerning. Physical exam performed up on admission noted the subject was alert, cooperative and

in no distress. The abdomen was soft and non-tender to palpation, and bowel sounds were active in all four quadrants. Lungs were clear with respirations unlabored and heart was of regular rate and rhythm. Skin color, texture and turgor was normal and the neurologic exam was grossly normal.

- On (b) (6), the physical exam note stated the subject was alert and oriented to time, place and person, and in no distress. The abdomen was soft, mildly tender to palpation in right upper quadrant, bowel sounds active in all four quadrants with no masses or organomegaly, and jaundice was present. Respirations were unlabored, heart sounds were normal and skin color, texture, and turgor were normal with no rashes or lesions.

- On (b) (6), following test were done and were found normal:
  - Hepatitis A IgM antibody
  - CMV-PCR and EBV-PCR was undetected
  - ANA and LDH were normal
  - N-acetylcysteine was started
  - Iron/TIBC/Ferritin were noted to be high, reference range not provided. However, on repeat testing done on (b) (6), all the three were normal.
  - Peripheral eosinophil count was borderline-5.9 (normal range 0.07-5.8%)
  - Serum ammonia was normal
  - Doppler ultrasound demonstrated the direction of blood flow was normal
  - Subject's PMH was positive for migraines
  - The past medical history in the H&P on (b) (6) stated that patient had colonoscopy which was positive for ulcerative colitis but subject denies any medications for treatment

- On (b) (6) the EBV panel was repeated- EBV capsid antigen antibody IGM was negative, EBV capsid antigen antibody IGG was positive at 4.53 and EBV nuclear antigen antibody IgG positive at >5.00, indicative of past EBV infection.

Table 1: Trends of the Laboratory Enzymes and Vital Signs During Subject's Hospitalization.

Date	ALT U/L	AST U/L	TB mg/dL	DB mg/dL	INR	ALP U/L	GGT U/L	Vitals
Reference range	6-40	10-35	0.2-1.2	<0.2	0.9-1.1	33-130	3-70	BP/RR/HR/Temp
(b) (6)	15	17	0.3	0.1		85	44	
	1626	1713	1.3	0.5		100	217	128/84; 16 breaths/min; 87 bpm; 36.61C
	6025 (150 x ULN)	2065 (~60 x ULN)	4.9 (4 x ULN)	3.1 (15 x ULN)	2.0 (2x ULN)	168→ 228	349	138/73; 16 bpm; 100 bpm; 36.7C
								105/61; 18 bpm; 81 bpm; 37C
			4.3		1.79	115		
	1528	152	3.3		1.41			
	541	64	3	1.4	1	166	453	122/80; 18; 69; 37C
	245	60	2	0.8	1	113	335	
	88	41	1.2	0.4		97	193	
	40	28	0.7	0.2		57		
	35	23	0.5	0.1		82		
	36	30	0.8	0.1		78		

Source: generated from the data provided by the sponsor

The vital signs were stable overall, with exception on (b) (6) when the BP and HR were mildly elevated relative to baseline and these resolved spontaneously. The liver enzymes stabilized on (b) (6) and continued to remain normal on (b) (6) the event was considered resolved. The repeat values on (b) (6) were also normal.

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/s/

RUBY MEHTA
01/29/2018

KATHLEEN M DONOHUE
01/30/2018

LISA M SOULE
01/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION

DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS (DGIEP)

MEDICAL OFFICER CONSULT

BLA	761077
Sponsor	Amgen
Drug	Erenumab, Aimovig, AMG 334
Requesting Division	Division of Neurology Products
Indication	Migraine
Safety Issue for Consult	Drug-Induced Liver Injury (DILI)
Date Received	August 11, 2017
Date review Completed	November 7, 2017
Clinical Reviewer	Ruby Mehta, MD
Team Leader	Kathleen Donohue, MD
Acting Associate Division Director	Lisa Soule, MD
Project Manager	Cheronda Cherry-France, RN BSN MHA

Executive Summary

This is a DGIEP response to the request for consultation from the Division of Neurology Products for BLA 761077 for Erenumab for migraine from Amgen. DGIEP was asked to evaluate a case of acute liver injury. One patient experienced acute hepatitis ten days after Erenumab administration as evidenced by biochemical testing and a clinical picture consistent with hepatocellular injury. The differential diagnosis for the etiology of this case of acute liver injury is complex, and includes four possibilities. This reviewer believes an unidentified cause may be the most likely explanation. The second most likely explanation is a bile duct stone, because of the rapid rise and fall of liver enzymes; however, the pace of recovery was more prolonged than is typically seen with bile duct stones, these stones classically do not elevate INR, and ultrasound did not

detect signs of a passed a stone. Erenumab and amoxacillin are far less likely culprits. Erenumab was temporally associated, but the injury would not be expected to have resolved so rapidly given the prolonged half-life of erenumab. The least likely explanation is amoxicillin-clavulanic acid, because the rapid rise and fall of liver enzymes is atypical and the pattern of injury with this drug is typically cholestatic or mixed rather than hepatocellular.

Approximately 3,000 subjects have been exposed to Erenumab across different trials to support this BLA. The case described above was the only Hy's Law case observed in the program. A total of 13/1785 (0.7%) subjects exposed to Erenumab 70 mg and 3/644 (0.4%) who received Erenumab 140 mg for 3 months experienced ALT >3 x ULN. A total of 3/1025 (0.3%) subjects exposed to Erenumab 70 mg dosing, and 3/644 (0.4%) dosed with Erenumab 140 mg for >3 to 6 months experienced ALT >3 x ULN. A total of 7/1042 (0.7%) subjects exposed to Erenumab 70 mg dosing, and 4/556 (0.7%) dosed with Erenumab 140 mg for >6 to 12 months experienced ALT >3 x ULN. Some patients were found to have alternative etiologies for the transaminase elevations such as alcoholic hepatitis, hemangioma, etc., while a few patients did not have any attributable etiology for liver enzyme elevations. Based on these findings, we recommend the following for labeling:

1. If a patient experiences liver-related symptoms such as jaundice, right upper quadrant abdominal pain, nausea, or vomiting, this may be indicative of serious liver injury and should lead to Erenumab discontinuation. The patient should be taught to identify these symptoms, not take further doses, and contact the physician immediately. If there is biochemical or clinical evidence of serious liver injury, the drug should be permanently discontinued and the patient should be followed to resolution of injury.
2. Consider including in labeling a Limitation of Use statement for patients with pre-existing liver disease, as there are no data to support use of Erenumab in patients with hepatic impairment.

DNP Question

"Please refer to the IND report for Subject (b) (6) (liver case usact (b) (6)) and the Safety information Amendment in response to a May 2, 2017 information request that describe a case of acute liver injury approximately 1 week after a single dose of AMG 334 (erenumab), an anti-calcitonin gene-related peptide receptor antibody that is currently being evaluated under BLA 761077 for prevention of migraine. This case occurred in the absence of an overall signal of liver injury in the clinical trials database. Please provide your assessment of whether a role for erenumab can be ruled out it in this case and of whether any other factor could have contributed to the liver injury."

DGIEP Response:

A 51-year-old Hispanic female, participated in a healthy volunteer trial, Study 20160349, and received a single subcutaneous dose 140 mg of AMG 334 on (b) (6). One week later, on (b) (6), the subject developed elevated transaminases and bilirubin in association with symptoms, a clinical picture consistent with acute hepatitis.

Table 1 Trajectory of the Liver Enzymes in Subject (b) (6)

Date	ALT U/L	AST U/L	TB mg/dL	DB mg/dL	INR	ALP U/L	GGT U/L
Reference range	6-40	10-35	0.2-1.2	<0.2	0.9-1.1	33-130	3-70
(b) (6)	15	17	0.3	0.1		85	44
	1626	1713	1.3	0.5		100	217
	6025 (150 x ULN)	**2065 (~60 x ULN)**	**4.9 (4 x ULN)**	**3.1 (15 x ULN)**	**2.0 (2x ULN)**	**168→228**	**349**
			4.3		1.79	115	
	1528	152	3.3		1.41		
	541	64	3	1.4	1	166	453
	245	60	2	0.8	1	113	335
	88	41	1.2	0.4		97	193

Source: Sponsor's submission

1. Evaluation for alternative etiology:
    a. Serum acetaminophen and salicylate negative
    b. LDH and CPK normal
    c. Acute viral hepatitis (Hepatitis A IgM ab, Hepatitis B surface antigen, Hepatitis B core IgM ab, Hepatitis C ab, CMV) serology negative
    d. Acute EBV IgM infection negative
    e. ANA, Liver-kidney microsomal ab, IgG, SMA antibody - all negative

f. For evaluating for Wilson's disease - serum ceruloplasmin was done. Ceruloplasmin was borderline low at 16 mg/dL (normal range >20 mg/dL). No other testing to confirm Wilson's was done.

g. History negative for mushroom consumption, chemical agent, environmental agents, international travel, fasting and dietary changes

h. Urine screen positive for benzodiazepine, negative for opiates, cocaine, amphetamine, cannabinoids, barbiturates, methadone, PCP and oxycodone

i. No drug abuse; Alcohol 1-7 beverages per week

j. History negative for weight gain, cardiac failure, shock or septicemia

k. Ultrasound of liver is normal, no biliary dilatation

l. Doppler abdominal ultrasound was performed and the visualized main portal veins, main hepatic veins, splenic vein, hepatic artery, aorta and inferior vena cava in the upper abdomen appeared patent with normal direction of blood flow.

Concomitant medication:

a. Amoxicillin-clavulanic acid (started (b) (6) for 10 days)
b. Metronidazole (unknown duration) started on (b) (6)
c. Librium (dose unknown),
d. Fluconazole 200 mg 1 tablet 1x/week for 2 weeks (started (b) (6))
e. Atenolol 25 mg daily,
f. Gabapentin 300 mg twice a day
g. Voltaren 1% gel

Reviewer's comments:

1. Time to onset - 9 days after single dose administration (b) (6))
2. Symptoms: nausea, vomiting, abdominal pain, decreased appetite and jaundice (clinically symptomatic)
3. Time to event recovery - total bilirubin and INR normalized over a period of one month, transaminases and GGT were rapidly trending down (within 5 days of onset of elevations) and were near normal about one month after the single dose
4. Concomitant medication as potential confounders:

a. Amoxicillin-clavulanic acid (started (b) (6) for 10 days)

5. Evaluation for alternative etiology: very thorough evaluation (laboratory and imaging) for alternative etiology performed, no cause detected. However, a liver biopsy was NOT performed.
6. Clinical phenotype: Acute hepatitis
7. Injury pattern: Hepatocellular injury (↑ALT>>>↑ALP)

Amoxicillin-clavulanic acid[1] is known to cause DILI.

Features that support Amoxicillin-clavulanic acid leading to acute liver injury in this case:

1. The onset of injury with amoxicillin-clavulanate occurs typically within a few days to as long as 8 weeks (average ~3 weeks) after initiation of therapy and often occurs after the course of antibiotic is completed.
2. The liver injury caused by amoxicillin-clavulanate is typically associated with jaundice and can be severe and prolonged (with jaundice lasting 4 to 24 weeks), but rarely results in lasting injury or death.

Features that argue against Amoxicillin-clavulanic acid leading to acute liver injury in this case:

1. The typical pattern of injury is cholestatic or mixed injury.
2. If hepatocellular or mixed[2] injury is seen, the resolution is very slow, unlike the subject in question where rapid injury and rapid resolution were noted.
3. Peak values of ALT are typically not as high as were seen in this subject.

Atypical presentation of liver injury by Amoxicillin-clavulanic acid is less likely but a possibility.

Fluconazole, Atenolol, Gabapentin and Metronidazole: unlikely as causative agents for this SAE.

[1] deLemos AS, Ghabril M, Rockey DC, et al. Amoxicillin–Clavulanate-Induced Liver Injury. *Digestive diseases and sciences*. 2016;61(8):2406-2416. doi:10.1007/s10620-016-4121-6.

The Sponsor consulted [redacted] (b) (4)

1. The reviewer disagrees with the following assessments made by the consultants:
    a. [redacted] (b) (4) If the subject failed to disclose the use of Librium, the subject also may have not disclosed use of other hepatotoxic agents.
        i. Reviewers assessment:
            1. There is no evidence of use of another hepatotoxic agent.
            2. No evidence of renal injury, which is common with significant liver injury like this
    b. [redacted] (b) (4) suggest that the subject had passed a retained bile duct stone as a possible cause of the clinical picture.
        i. Reviewers assessment:
            1. The subject did not have residual biliary dilation as observed by ultrasound, especially after such significant increase in liver biochemistry
            2. INR elevation is typically not seen during acute passage of ductal stones.
            3. Resolution of liver biochemical enzymes over 4 weeks is a long duration for recovery post-bile duct stone passage. Recovery within days is the norm after passing a bile duct stone.
            4. However, this remains a possible etiology.
    c. [redacted] (b) (4) There is a lack of toxicity of AMG 334 in knock-out (KO) mice and lack of other cases in 3,000 subjects exposed with AMG 334.
        i. Reviewers assessment:
            1. KO mice models are not good models to predict injury from human monoclonal antibody products.
            2. Idiosyncratic DILI is a rare event; even one case in 3,000 is concerning.
    d. [redacted] (b) (4) The serum half-life of AMG 334 is 4 weeks, so a quick resolution of liver indices makes it unlikely as a cause of liver injury.
        i. The reviewer agrees with this assessment; however, the PK of the drug is linear and as the drug concentration decreased, the biochemical parameters improved.
2. The reviewer agrees with the following assessments made by the [redacted] (b) (4)
    a. Ischemic cardiac disease is not an etiology for her SAE.

i. Additionally, the subject would have not improved spontaneously, i.e., without any medical intervention, if the etiology were cardiac in origin.

b. Unlikely to be Wilson's disease (WD), consistent with the rationale the consultants have suggested
   i. This reviewer notes if a patient presents with INR >2 and massive elevation of transaminases, spontaneous reversal of acute liver failure in WD is rare.

c. The resolution in 4 weeks makes this unlikely to be viral hepatitis, autoimmune hepatitis, or inherited liver disease (e.g. hemochromatosis).

d. This is not ischemic liver disease (LDH was normal).

e. This is not an acute toxic exposure, as there was no evidence of renal injury.

Background:

AMG 334 (Erenumab) is a monoclonal human Ig G2 that binds with high affinity to Calcitonin gene-related peptide (CGRP) receptor complex and inhibits the action of CGRP. Following SC administration, peak serum concentration is reached between 4 and 11 days post-dose. The effective half-life is approximately 28 days with 140 mg once every 4 weeks dosing. Elimination of AMG 334 occurs via two pathways: degradation by reticuloendothelial cells, and breakdown within lysosomes of cells bearing the CGRP receptor.

Drug and similar moieties discussion: Development of several small molecule CGRP antagonists was halted due to hepatotoxicity. There are three other monoclonal antibodies currently in development and hepatotoxicity has not been observed in ongoing clinical trials.

Pre-clinical findings:

1. In the 1 to 6-month cynomolgus nonclinical toxicology studies, there was no evidence of hepatic toxicity (either by histopathology or clinical chemistries [e.g., bilirubin, transaminase elevation]) or any evidence of immunomodulation at doses resulting in systemic exposures (based on serum AUC) that are approximately 123-fold higher than those achieved in humans with the clinical dose of 140 mg.
2. Although the hepatotoxicity signal was not observed in the CGRP KO mice model, the reviewer notes that this information is not relevant, as Erenumab is a humanized monoclonal antibody and targets the CGRP receptors.

Brief introduction of drug development program:

AMG has been administered to ~3,000 subjects in single or multiple doses at 21 mg, 70 mg and 140 mg doses, administered subcutaneously (SQ) in controlled and open-label studies. In subjects and patients who received multiple doses, the SQ injection was given every 4 weeks for 12 or 24 weeks. An additional study using doses of 7 mg, 21 mg, 70 mg and 140 mg was conducted in patients with migraine.

In the integrated summary of safety, phase 2 and 3 studies are presented in four pools:

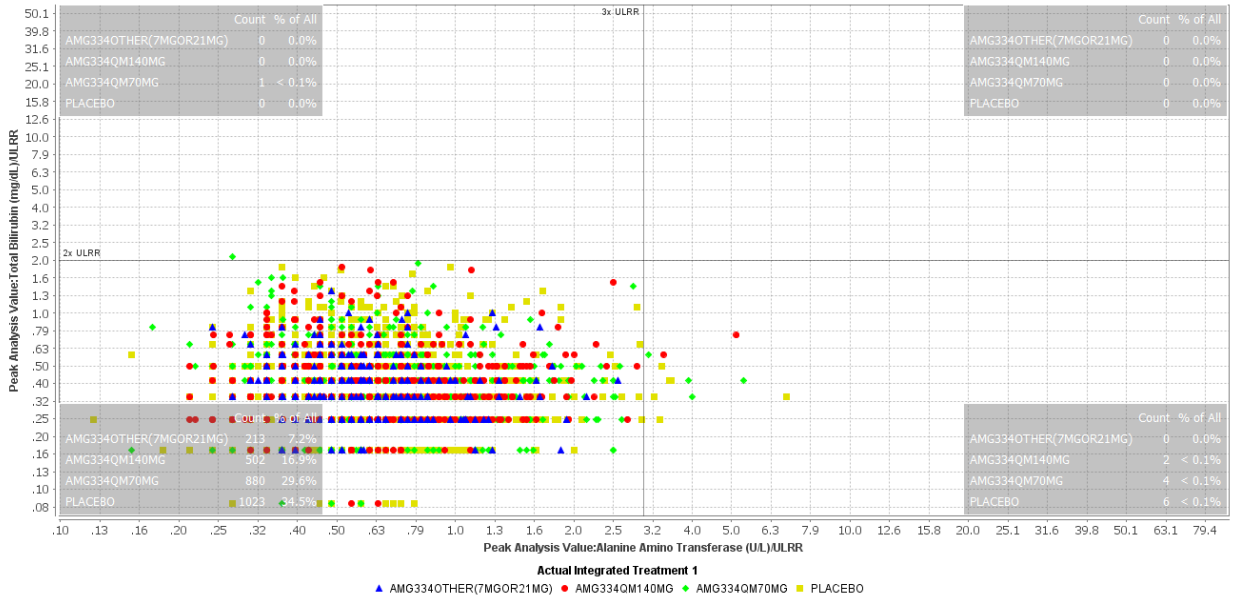
Pool A: 12-week, placebo-controlled trial, and data from the first 3 months of the double-blind, placebo-controlled phases from Studies 20120178, 20120295, 20120296, 20120297

Pool B: 24-week placebo-controlled pool from the double-blind phase of Study 20120296

Pool C: Double blind and open-label extension/active treatment phases of Studies 20120178, 20120295, 20130255, 20120296 and 20120297

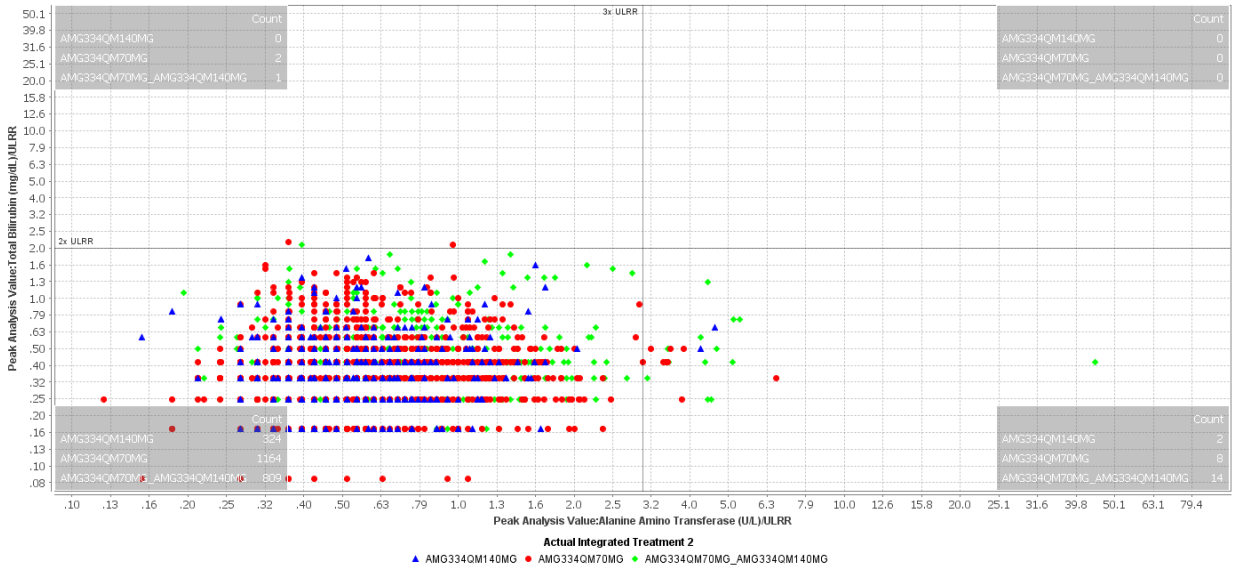
Pool D: Subjects with continuous exposure to AMG 334 70 mg or 140 mg for a minimum of 1 year through the data cutoff (subset of Pool C).

Figure 1 Hy' Law ALT Vs TB - Double Blind Period



Hy's Law Post Baseline- Treatment Period 1

Figure 2: Hy' Law ALT Vs TB - Open Label Extension Period



Hy's Law plot ALT Vs TB -Open label extension period

Source: reviewer generated in JReview

The patient on the lower far right represented by the green dot was found to have "alcoholic hepatitis."

The reviewer has summarized below some of the cases in which AST/ALT elevations were found to understand time to onset of transaminase elevation, time to recovery, maximum elevations, and outcomes. The reviewer selected these cases with the following rationale:

a. Depict magnitude of transaminase elevations
b. To assess if there was adaptation
c. To note whether a positive de-challenge occured
d. Cases with transaminase elevations at baseline were selected to understand whether fluctuation were any greater than in subjects who had normal liver enzymes at baseline.

The sponsor reported narratives on 40 subject who experienced hepatic disorders, of which 21 subjects were coded as transaminase elevation; other subjects were reported to experience hemangioma, exercise-induced transaminase elevation, isolated elevation of bilirubin, diverticulitis with hepatic fibrosis, fatty liver etc. Some had ALT/AST or TB elevations at baseline, which remained elevated during the treatment. Some subjects who had abnormal transaminases at baseline normalized the liver biochemical abnormalities during the trial. Subjects on the placebo arm who experienced ALT/AST elevations had lower peak values for transaminases relative to subjects treated with Erenumab.

The 12-week trials were open label: 20120178, 20120295, 20120296, 20120297.

Phase 3-The 24-week double blind placebo controlled trial was Study 20120296.

Table 2: Patients with Liver Enzyme Elevation -Time to Event for Elevations of Liver Enzymes:

Patient Id/Study number	Dose of AMG334	Baseline ALT/AST/TB/DB/ALP	Time to onset of elevation of biochemical indices	Time to recovery of rise in biochemical indices	Maximum elevation of TB/DB value	Maximum elevations of ALT/AST/ALP Value	Last observed value for TB/DB	Last observed value for ALT/AST/ALP	Concomitant medications (started 4 weeks prior to elevation of liver enzymes)	Reviewer comment
(b) (6) **Study ID # 20120178**	21mg →70 mg	16/13/0.4/0.2/79	2 years	1 month	0.6/0.2	36/30/78	0.6/02	21/21/69		Minimal elevation, adaptation
(b) (6) **Stud ID # 20120178**	70 mg (DB) & 140 mg (OLE)	48/35/0.5/0.2/68 29/24/0.4/0.1/66	2 years	No values provided after Last abnormal value	0.9/0.2	177/127/104	0.9/0.2	177/127/104	eletriptan, ibuprofen, oxazepam, paracetamol, tramadol, zopiclone, frovatriptan, rizatriptan, anacin, metformin, metoclopramide, losartan and liraglutide.	All liver indices slowly rose after dosing with AMG 334 Concerning –no follow up laboratory data provided
(b) (6) **Study ID# 20120178**	Placebo →70 mg	51/31/0.3/<0.1/86 41/24/0.3/na/86	4 weeks	4 weeks	0.6/0.1	67/44/124	0.4/<0.1	26/21/77	ibuprofen, thomapyrin N, multivitamin and vicks formula 44.	At baseline the enzymes were elevated, however, were trending down. The enzymes started rising again after AMG334 was started and enzymes

										normalized while on treatment
(b) (6) **Study # 20130255**	70 mg	17/19/0.5/0.1/60	1 year	No follow up after	0.4/0.3	1472/1937/81	0.4/0.3	1472/1937/81	alprazolam, bromazepam, bromocriptine, diclofenac sodium, escitalopram, ibuprofen, indomethacin, lenoltec with codeine no 1, levothyroxine, metamizole, metoclopramide, paracetamol, promethazine hydrochloride, sumatriptan, thiethylperazine, tiapride, tramadol, and trazodone hydrochloride.	Alcoholic hepatitis Patient consumed 200 ml of 38% alcohol daily and one beer daily. Reviewer concurs with possibility of alcoholic hepatitis. Patient discontinued from the trial after enzyme elevations.
(b) (6) Study Id # **20130255**	70 mg→ 140 mg	58/34/1.7/0.3/49	Week 20	Week 36	baseline	83/47/1.1/0.2/ 54	1..3/0.2	34/23/53	indometacin, sumatriptan, lornoxicam, troxerutin and perindopril	Enzymes variability was noted throughout the trial
(b) (6) Study # **20130255**	140 mg	21/21/0.3/0.1/95	Week 12 AST ↑>>ALT↑	Week 40	0.5/0.2	46/174/96	0.4/0.1	8/13/35	indomethacin, anacin and tolfenamic acid.	Possibility: alcohol consumption giving rise to enzymes
(b) (6) Study # **20130255**	70 mg→ 140 mg	36/29/0.4/0.1/75	Week 24	Never recovered, but ALT kept on fluctuating throughout the trial	0.5/0.1	154/67/107	0.3/0.1	70/38/107	paracetamol, eletriptan hydrobromide, diazepam, diclofenac, dexketoprofen trometamol, amitriptyline hydrochloride, bisoprolol fumarate, zolpidem tartrate,	No reason to explain these elevations can be found in the narrative.

									melatonin and esomeprazole.	
(b) (6) Study id# **20130255**	70 mg→140 mg	51/34/1.1/0.3/81	Week 36	Never but reached close to baseline at week 52	1.5/0.3	71/36/79 146/71/70 Week 64	1/0.2	146/71/70	eletriptan hydrobromide, naproxen sodium, desogestrel, tacrolimus and cetirizine hydrochloride.	Rise in liver enzymes- etiology unexplained by the data provided
(b) (6) **Study ID: 20130255**	70 mg	33/25/0.4/0.1/64	Week 4	Week 8	0.4/0.2	116/72/102	0.3/01	27/31/47	paracetamol, zolmitriptan, silybum marianum, ramipril, doxycycline, levothyroxine sodium, metamizole sodium and ciprofloxacin.	Adaptation
(b) (6) **Study ID: 20130255**	70 mg→ 140 mg	13/17/0.3/0.1/75	Week 65- Post drug discontinuation	Not provided	0.3/0.1	149/214/209	0.2/0.1	149/214/209	sumatriptan and eletriptan hydrobromide.	Rise in liver enzymes- etiology unexplained by the data provided- but the elevation occurred after discontinuation of the drug, unlikely to be related to Erenumab
(b) (6) **Study ID: 20130255**	140 mg	15/31/1.1/0.2/113	Week 4	Week 12	1.3/0.3	None	0.4/0.1	22/33/97	ibuprofen, paracetamol, eletriptan, lansoprazole, azathioprine, clonazepam, amoxicillin/clavulanate potassium, miconazole	The total bilirubin is unrelated to Erenumab use
(b) (6) **Study ID: 20130255**	140 mg	23/26/0.3/0.1/157	Week 36	Continued to fluctuate to week 56, no follow up values post	0.5/0.1	169/145/147	0.4/0.1	89/92/132	paracetamol, rizatriptan, naratriptan, macrogol, atorvastatin,	Partial adaptation

				week 56 provided					levothyroxine, pantoprazole, loratadine, enalapril, dextromethorphan hydrobromide and naproxen sodium/pseudoephedrine hydrochloride	
(b) (6) **Study ID: 20130255**	70 mg→ 140 mg	41/39/0.3/0.1/77	Week 52	Week 65	0.3/0.1 0.4/0.1	48/35/86	0.4/0.1	34/29/96	ibuprofen, naproxen sodium, rizatriptan, zolmitriptan, loperamide hydrochloride, loratadine, omeprazole and ondansetron	Most likely AE seems unrelated to drug, because of elevations of liver enzymes prior to drug use.
(b) (6) **Study ID: 20101267**	140 mg	16/18/0.35/0.17/56	Day 8	Day 15	0.6/0.17	69/66/63	0.3/0.17	25/17/70	marvelon, domperidone and paracetamol	adaptation
(b) (6) (male) **Study ID: 20120295**	140 mg	15/24/0.9/0.2/58	Week 4	Week 8	0.8/0.2	170/102/170	0.9/0.2	14/23/59	NSAIDs	adaptation
(b) (6) ***Study ID: 20120296 Phase 3 trial***	140 mg→70 mg	20/18/0.2/<0.1/60	Week 4	Week 8	0.3/<0.1	64/45/66	0.4/<0.1	20/21/57	NSAIDs	adaptation
(b) (6) (male) ***Study ID: 20120296 Phase 3 trial***	140 mg	54/33/0.4/nv/67	Week 4	No resolution	08/0.2	189/90/77 (6 months post starting txt) CK 1044	0.5/0.1	125/69/76 CK-normal	NSAIDs	No resolution of AE CK was elevated on (b) (6) however, patient continued to have elevated ALT/AST prior and after one abnormally elevated CK value. All CK values prior and after this one value are normal.
(b) (6) **Study ID:**	Placebo →70 mg	13/18/0.2/<0.1/60	Week 24 from enrollment	Resolution not documented	0.4/0.1	68/49/43	0.3/0.1	68/49/43	naproxen, dexketoprofen	Transaminase Elevation seen at week 24 after

20120297			and week 12 from starting the Erenumab						sumatriptan, levothyroxine sodium, finasteride, ivabradine, rosuvastatin, flavia	enrollment or at week 12 after starting Erenumab. Patient had normal enzymes at enrollment and continued to have normal liver enzymes while on placebo arm, enzymes started rising 12 weeks after Erenumab administration
(b) (6) **Study ID: 20120297**	Placebo (12 week)→ 70 mg	9/11/0.3/0.1/65 Was on placebo arm for 12 weeks, had normal enzymes at enrollment as well as when patient was treated with placebo.	Week 40 Week 28 after starting Erenumab	Resolution not documented	0.4/0.1	220/101/82	0.3/0.1	220/101/82	acetylsalicylic acid, ibuprofen, sumatriptan and escitalopram oxalate.	Transaminases elevations were observed weeks after starting the Erenumab
(b) (6) **Study ID: 20120297**	Placebo (12 week) →70 mg	74/43/0.6/0.2/96	Week 4 (while on placebo) + at Week 16 (4 weeks after starting Erenumab) further ALT increases were noted	Resolution not documented, transaminases continue to fluctuate throughout the study period	0.5/0.2	114/73/101	0.5/0.2	106/47/95	thomapyrin N, ibuprofen, furosemide and iron.	Transaminases fluctuation were noted though out the study and no resolution observed. The rise in transaminases were observed while patient received placebo and Erenumab
(b) (6) **Study ID: 20140477 (male)**	70 mg	16/22/15.3 µmol/L/3.42 µmol/L/73	Week 16	Resolution not documented a downward trend was documented	6.84/1.71 µmol/L	232/183/78		109/146	No concomitant medications	Downward trend noted after discontinuing the drug. Seems Positive dechallenge.

Source: Reviewer generated from data provided by sponsor

OLE: open label extension

The following conclusions can be drawn from the cases noted above:

1. The time to onset of liver enzyme elevation was variable after starting the drug. Eight subjects had elevations after the first dose, another eight after the second dose, and seven had elevations as late as one or two years after starting therapy.

2. There seems to be an "adaptation response" in some subjects.
3. Of the 21 subjects noted above, 11 had normalization of their transaminases despite continuing therapy.
4. Three subjects who had baseline liver enzymes elevations continued to have post-baseline elevations of liver enzymes that were higher than their baseline transaminase levels.
5. Isolated bilirubin elevations were observed in only 3 subjects, and were minimally elevated (all three were <2 x ULN).
6. Positive dechallenge was observed in one subject.

The case was discussed with Dr. Mark Avigan. The subject's full follow-up was not provided in the narrative. Dr. Avigan and the reviewer requested further information from the sponsor. A final update to the consult will be provided when the Applicant's response to the IR has been received and reviewed.

The following IR was sent on 10-25-2017:

1. Please provide the following information for Subject (b) (6) including a complete narrative with a timeline for drug initiation, symptom initiation and laboratory evaluations and include the following information:
    a. The initial admitting diagnosis(ses), and physical exam findings
    b. Vitals signs
    c. The laboratory tests results -complete blood count and electrolytes values
    d. Dates and results for:
        1. For repeat hepatitis C antibody, and ceruloplasmin
        2. Hepatitis C RNA-PCR to confirm absence of Hepatitis C and Hepatitis E IgM antibody
2. Provide an anonymized copy of the patient's medical records from the hospital admission for liver injury.

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

/s/

RUBY MEHTA
11/16/2017

KATHLEEN M DONOHUE
11/16/2017

LISA M SOULE
11/16/2017