CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761077Orig1s000

OTHER REVIEW(S)
Date: May 15, 2018

Reviewer(s): Hongliu Ding, MD, PhD, MPH
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS
Division of Epidemiology I

Division Deputy Director: Sukhminder K. Sandhu, PhD, MS, MPH
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name(s): Amovig (erenumab)

Application Type/Number: BLA 761077

Applicant/sponsor: Amgen Inc.

OSE RCM #: 2018-869
1. BACKGROUND INFORMATION

1.1. Medical Product

Amovig (erenumab) is a human immunoglobulin G2 (IgG2) monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor. CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilator associated with migraine pathophysiology.\(^1\)\(^-\)\(^3\) Plasma CGRP levels have been shown to increase significantly during migraine and return to normal when headache is relieved.\(^4\)\(^,\)\(^5\) Erenumab competes with the binding of CGRP and inhibits its function at the CGRP receptor, and thus, the proposed indication is for prophylaxis of episodic and chronic migraine in adults.

1.2. Describe the Safety Concern

Amovig (erenumab) exposure to women affected by migraine that are pregnant or of childbearing potential is possible. The data from a non-clinical study provided by the sponsor in which female monkeys were administered erenumab (0 or 50 mg/kg) twice weekly by subcutaneous showed that injection throughout pregnancy (gestation day 20-22 to parturition) did not observe adverse effects on offspring. However, several studies have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.\(^6\)\(^-\)\(^10\) During the clinical trials, 23 pregnancies were reported in female participants with exposure to erenumab. Among the 23 pregnancies, the outcomes of 6 pregnancies were not yet known and 5 pregnant women were lost to follow-up. The remaining pregnancies (N=12) ended with 5 full-term births without complications, 1 full-term birth with complications (no birth complication or congenital anomalies, but admitted to neonatal intensive care for unspecified reasons), 1 preterm birth without complications (infant was born via Caesarean section at 31 weeks due to the mother developing HELLP syndrome), 3 elective terminations, and 2 spontaneous abortions (1 was in a woman with a prior uterine ablation and 1 was in a woman who received a single dose of 140mg of erenumab and miscarried 3 months later). Women of childbearing potential were given monthly pregnancy tests and if the test was positive, they did not receive additional dosings. Therefore, it is likely that exposed pregnancies only received dosings during the first trimester, but the half-life of erenumab is 28 days. Overall, the evidence from animal studies and the clinical trials are limited, and thus, the developmental risk associated with use of erenumab in pregnant women is not known at this time. The goal of this pregnancy safety study is to obtain data on pregnancy and infant outcomes after erenumab exposure during pregnancy to inform prescribing for and counseling of women with migraine who are also pregnant or of childbearing potential.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS
2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ Signal detection – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ Signal refinement of specific outcome(s) – Important safety concern needing moderate level of statistical precision and certainty. †
☐ Signal evaluation of specific outcome(s) – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† If checked, please complete General ARIA Sufficiency Template.

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☐ Other, please specify:

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

☒ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools
For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

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

The following language has been proposed as of May 15, 2018 by the Division of Neurology Products for two PMRs related to pregnancy outcomes:

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

and

2. “Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3392-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Amovig (erenumab) during pregnancy compared to an unexposed control population.”

The finalized PMR language will be issued upon approval.
3. References

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/s/

HONGLIU DING
05/15/2018

KIRA N LEISHEAR
05/15/2018

SUKHMINDER K SANDHU
05/16/2018

JUDITH W ZANDER
05/16/2018

MICHAEL D NGUYEN
05/16/2018

ROBERT BALL
05/16/2018
Date: May 3, 2018

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Uses (IFUs)

Drug Name (established name): AIMOVIG (erenumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: 761077

Applicant: Amgen
INTRODUCTION

On May 17, 2017, Amgen submitted for the Agency’s review a new BLA submission, request for priority review. AIMOVIG (erenumab) is a potent and selective human IgG2 monoclonal antibody against the calcitonin gene-related peptide receptor. Amgen is seeking to market erenumab for the indication of prophylaxis of migraines in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on May 26, 2017 and May 25, 2017 respectively for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) and Instructions for Uses (IFUs) for AIMOVIG (erenumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on April 10, 2018.

MATERIAL REVIEWED

- Draft AIMOVIG (erenumab) PPI and IFUs received on May 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on April 23, 2018.

- Draft AIMOVIG (erenumab) PPI and IFUs received on May 17, 2017, revised by the Review Division throughout the review cycle and received by OPDP on April 20, 2018.

- Draft AIMOVIG (erenumab) Prescribing Information (PI) received on May 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on April 23, 2018.

- Draft AIMOVIG (erenumab) Prescribing Information (PI) received on May 17, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on April 20, 2018.

REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI and IFUs we:
4 CONCLUSIONS
The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

• Our collaborative review of the PPI and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFUs.

Please let us know if you have any questions.
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/s/

AMANPREET K SARAI
05/03/2018

MARCIA B WILLIAMS
05/03/2018

DHARA SHAH
05/03/2018

LASHAWN M GRIFFITHS
05/03/2018

Reference ID: 4257545
In response to DNP consult request dated May 25, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Uses (IFUs), and carton and container labeling for the original BLA submission for AIMOVIG (erenumab-aooe) injection, for subcutaneous use (Aimovig).

PI, PPI, and IFUs: OPDP’s comments on the proposed labeling are based on the draft PI, PPI and IFUs received by electronic mail from DNP (Lana Chen) on April 20, 2018, and are provided below. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFUs were sent under separate cover on May 3, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 29, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.
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/s/

DHARA SHAH
05/03/2018
DATE:      Date of Document:  5/17/2017  
          Date of Consult:  2/27/2018  
          Desired Completion Date:  3/13/ 2018  
          Date of Completion: 4/7/2018  

FROM:      Preston M. Dunnmon, M.D., M.B.A., Medical Officer  
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          Division of Cardiovascular and Renal Products, HFD-110  

TO:        Heather Fitter, MD, CDTL, DNP  

PRODUCT NAME:  Aimovig (erenumab, AMG 334)  

FORMULATION/DOSE:  140 mg IV, single dose  

PRODUCT CLASS:  IgG2 mAb antagonist of calcitonin gene-related peptide  

SPONSOR:  Amgen  

INVESTIGATIONAL INDICATION:  for the prophylaxis of migraine
EXECUTIVE SUMMARY

DCRP was asked to review the world’s literature and render an opinion regarding “the strength and quality of published evidence concerning a theoretical risk conferred by calcitonin gene-related peptide (CGRP) antagonism via any mechanism of worsened ischemia due to impairment of compensatory vasodilation in the setting of ischemic vascular events.” The nonclinical toxicology and clinical reviewers from DCRP have assessed this literature. There is consensus from well performed nonclinical models that CGRP is a potent microvascular vasodilator. These studies suggest that CGRP is one of multiple redundant control mechanisms of regional and tissue specific blood flow, and that lack of vasodilation from blocking this pathway does not result in tissue-threatening vasoconstriction. Specifically, CGRP is a vasodilator in coronary arteries, but its antagonism does not induce vasoconstriction nor affect the extent of ischemia secondary to coronary artery stenosis nor vasodilation secondary to a short period of ischemia (reactive hyperemia). Therefore, if CGRP plays a role in coronary flow regulation, there are redundant systems to override inhibition of this modulator – both in healthy and diseased animals. We can locate no information to suggest that the same is not true in the cerebral, renal, or splanchnic circulations. However, the information from which these observations and comments arise is imperfect – almost all the coronary flow data that we cited derives from in vivo canine studies using human CGRP and the peptide antagonist CGRT-(8-37). The human coronary vasculature study we cited used isolated tissue. Most of the in vivo studies we cited were from one lab, at Merck, but we do not think this impacted the results since the studies appeared well done, with some of the critical studies including positive controls to ensure assay sensitivity. Additionally, most all the studies are quite old, as these types of experiments are uncommon now.

There is no clinical safety data on the effect of CGRP-r blockers in subjects diagnosed with known Prinzmetal’s Angina or severe multivessel coronary artery disease (CAD). In this regard, we considered one of the most acutely life-threatening scenarios in clinical cardiology to discern worst-case scenario potential risk of antagonizing CGRP vasodilation – the hypothetical circumstance of unstable angina occurring in a patient taking one of these long-acting mAb CGRP-r blockers for migraine prophylaxis who also had severe three vessel native coronary artery disease and who was 10 years post-coronary artery bypass grafting (CABG) with an obstructed saphenous vein graft (SVG) to the right coronary artery, an obstructed SVG graft to the circumflex coronary artery, and therefore perfusing the entire heart with blood both antegrade and retrograde via left-to-right collateral flow through an left internal mammary artery graft to the proximal LAD. It is somewhat reassuring that data from normal healthy men suggests that NTG-induced vasodilation is not CGRP dependent, so that these subjects should be just as response to sublingual (and thus intravenous) nitrates as their non-CGRP-r blocked counterparts.

Given the limitations of the current datasets, we suggest that post-marketing assessment of cardiovascular event rates comparing subjects being treated with triptans (which carried labeled warnings for Myocardial Ischemia/Infarction, and Prinzmetal Angina) versus patients being treated with CGRP-r antagonists be considered using a Sentinel
approach. It may be the case that the CGRP-r blockers are in fact a safer alternative (as evidenced by a triptan-induced reduction of coronary reactive hyperemia secondary to a short period of ischemia, which contrasted to the lack of this effect by a CGRP-r blocker in that same model).

**REASON FOR CONSULT AND CONSULT QUESTION**

Calcitonin gene-related peptide (CGRP) is known to be a potent vasodilator and thought to play a role in cardiovascular homeostasis. Several sponsors have pending BLAs for mAb inhibitors of the CGRP receptor for the prophylaxis of migraine headaches. Given the mechanism of action of these products (prevention of vasodilation), the Review Division has asked DCRP to review the world’s literature to and render an opinion as to the strength and quality of published evidence concerning the theoretical risk that CGRP receptor antagonism (via any mechanism – this is a question concerning the mechanistic drug class) may worsen ischemia and/or cause MACE events due to impairment of compensatory vasodilation in the setting of ischemic vascular events.

Since DCRP has recently completed another consult for this specific CGRP inhibitor (erenumab, BLA 761077), the current consult will be filed to that BLA. What follows below is an overview of CGRP physiology based on contemporary reviews, followed by more detailed literature analyses of CGRP-r manipulation effects on epicardial coronary vasodilatation, coronary arterioles (resistance vessels), collaterals; and, preconditioning. The final section summarizes two relevant clinical references regarding CGRP inhibition.

**PHYSIOLOGY OVERVIEW**

- Russell et al. CGRP Pathology and Pathophysiology. Physiol Rev 2013;94:1099–1142

As demonstrated by immunoreactive staining, CGRP is localized to sensory nerves innervating multiple organs, including the heart, allowing it to act in a sensory-efferent manner to local (tissue level stimuli). It is a microvascular vasodilator with a potency that is ~10-fold higher than the most potent prostaglandins and 10–100 times greater than other vasodilators such as ACh and neuropeptide substance P (SP). Russell therefore stated that CGRP was the most potent microvascular vasodilator known as of the writing of his article.

CGRP receptor (CDRP-r) is a G-protein coupled receptor (GPCR), thereby providing a mechanism for important transmembrane signal amplification. There is promiscuity in this receptor-G-effector system, as CGRP-r has been shown to stimulate intracellular adenylate cyclase (AC) activity and cAMP (mediated through GαS), but also appears to stimulate the IP3-PLC pathway via interaction with Gαq. The ramp-up of intracellular BLA 761077
cAMP production occurs by both NO and NO-independent mechanisms. In addition to these effects on both the AC and IP3 intracellular signaling pathways, other downstream G-protein-mediated intracellular effector targets include ATP sensitive potassium channels, L-type calcium channels, and mitogen-activated protein kinases (MAPKs). Accordingly, the physiologic effects observed following the administration of CGRP agonists have included positive inotropic and chronotropic responses in the heart, in addition to vasodilator effects (in human subjects and in cardiovascular patients).

Of note, however, is that data from studies of CGRP antagonists suggest that antagonism of CGRP receptors does not particularly affect systemic BP, though CGRP knockouts in the ANG II model have shown that CGRP deletion not only leads to increased hypertension, but enhances loss of eNOS. These observations have supported the concept that CGRP may be a microvascular modulator of regional or tissue level blood flow, acting in concert with other local influences on microvascular tone. This concept in turn has been supported by the observed by the following observations:

- The sensitivity of ET-1-induced arterial contractions to relaxation by CGRP receptor stimulation (an effect that is independent of NO, cyclic nucleotides, and K+ channels)
- The potency of CGRP receptor stimulation as a mediator of preconditioning - (the phenomenon whereby pre-exposure of the heart to a preconditioning agent can attenuate subsequent damage incurred by an ischemic episode), and
- Elevations of CGRP in human plasma following acute myocardial infarction (though somewhat paradoxically, CGRP serum levels in subjects with coronary artery disease are reduced compared to normal healthy individuals).

On a relevant historical note with respect to the development rationale for CGRP-r antagonists with respect to cardiovascular safety, the Russel review states the following:

“In 2000, Boehringer Ingelheim published the pharmacological profile of BIBN4096BS (Olcegepant), the first selective nonpeptide CGRP antagonist, which could block vasodilatation caused by stimulation of the trigeminal nerve in the marmoset. Trials showed that BIBN409BS had no effect on baseline regional or systemic hemodynamics in animal and human studies, suggesting that unlike the triptan class of drugs, the CGRP antagonists may not lead to problems with cardiovascular side effects...”

In the following section, we discuss specific articles that are germane to the questions to be addressed.
HUMAN CORONARY ARTERIES (IN VITRO)

Chan, et.al., Characterization of the Calcitonin Gene-Related Peptide Receptor Antagonist Telcagepant (MK-0974) in Human Isolated Coronary Arteries. JPET 334:746–752, 2010

Abstract
The sensory neuropeptide calcitonin gene-related peptide (CGRP) plays a role in primary headaches, and CGRP receptor antagonists are effective in migraine treatment. CGRP is a potent vasodilator, raising the possibility that antagonism of its receptor could have cardiovascular effects. We therefore investigated the effects of the antimigraine CGRP receptor antagonist telcagepant (MK-0974) [N-[(3R,6S)-6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl) azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-1-yl)piperidine-1-carboxamide] on human isolated coronary arteries. Arteries with different internal diameters were studied to assess the potential for differential effects across the coronary vascular bed. The concentration-dependent relaxation responses to human α-CGRP were greater in distal coronary arteries (i.d. 600–1000 µm; Emax =83±7%) than proximal coronary arteries (i.d. 2–3 mm; Emax =23±9%), coronary arteries from explanted hearts (i.d. 3–5 mm; Emax =11±3%), and coronary arterioles (i.d. 200–300 µm; Emax =15±7%). Telcagepant alone did not induce contraction or relaxation of these coronary blood vessels. Pretreatment with telcagepant (10 nM to 1 µM) antagonized α-CGRP induced relaxation competitively in distal coronary arteries (pA2 =8.43±0.24) and proximal coronary arteries and coronary arterioles (1 µM telcagepant, giving pKB =7.89 ± 0.13 and 7.78 ±0.16, respectively). α-CGRP significantly increased cAMP levels in distal, but not proximal, coronary arteries, and this was abolished by pretreatment with telcagepant. Immunohistochemistry revealed the expression and colocalization of the CGRP receptor elements calcitonin-like receptor and receptor activity-modifying protein 1 in the smooth muscle cells in the media layer of human coronary arteries. These findings in vitro support the cardiovascular safety of CGRP receptor antagonists and suggest that telcagepant is unlikely to induce coronary side effects under normal cardiovascular conditions.

Key findings: Human coronary arteries are sensitive to CGRP, but CGRP antagonism alone did not affect basal vascular tone.

Reviewer comments: This study in isolated human coronary arteries demonstrated differential sensitivity of these vessels to CGRP, with distal arteries being more sensitive than proximal arteries and arterioles. Lack of effect of a CGRP antagonist suggests that basal tone, at least in isolated coronary arteries and arterioles, is not CGRP-dependent.

EPICARDIAL CORONARY VASODILATION


BLA 761077
Abstract
Calcitonin gene-related peptide (CGRP) is a potent vasodilator, but its effects on in situ ventricular function are unknown. We studied effects of intracoronary CGRP, 200, and 600 pmole/min, for 10 min) in 21 open chloralose-anesthetized dogs. Systemic, pulmonary, ventricular (LVP), central venous, and pulmonary capillary wedge pressures were continuously monitored. Ventricular wall thickness (WT) and circumflex coronary blood flow were also measured. CGRP was infused into the proximal circumflex artery. During CGRP infusion there were no changes in heart rate, cardiac index, pulmonary artery pressure, or systemic vascular resistance, no percentage change in ventricular WT, and no changes in dWT/dt, peak dP/dt, or the slope of end systolic points on WT/LVP loops. But there were significant changes in coronary flow (CQ), coronary resistance (CRES) and mean arterial blood pressure (MAP) from control (C)* (all, P < 0.05).

CGRP is a potent coronary artery vasodilator causing notable dose-dependent decreases in coronary resistance and a rise in myocardial flow, despite a decreased MAP (all P< 0.05). CGRP does not affect ventricular contractility in vivo.

Key finding: Canine coronary arteries are sensitive to exogenous CGRP.

Reviewer comments: Intracoronary CGRP infusion in anesthetized dogs increased coronary flow measured using a Doppler flow probe, and decreased coronary vascular resistance.

CORONARY ARTERIOLES (RESISTANCE VESSELS)


Abstract
Background: Calcitonin gene-related peptide (CGRP) is a potent dilator of epicardial conduit vessels and is released during myocardial ischemia in humans. However, the effect of CGRP on coronary arterial microvessels is still unclear, and it is unknown if CGRP modulates the tone of coronary arterial microvessels during acute myocardial ischemia.

Methods and Results: Epimyocardial microvessels were observed through a microscope equipped with a floating objective system in anesthetized open-chest dogs. Heart rate and aortic pressure were maintained at control levels. Flow velocity of the left anterior descending coronary artery (LAD) was measured with a suction-cup Doppler probe. When CGRP was cumulatively infused into the LAD (0.05, 0.5, 5.0, and 50 pmol/kg per minute) or superfused (0.03, 0.3, 3.0, and 30 nmol/L) over the left ventricular surface, arterial control microvessels > 100 µm in diameter dilated dose dependently at dosages of 0.5 to 50 pmol/kg per minute (infused) or 0.3 to 30 nmol/L (superfused), but those <100 µm dilated only at the highest dose, and those > 100 µm had greater dilation in
both groups. Only the highest dose of CGRP (infused) significantly increased coronary flow. The superfusion of CGRP(8-37) (CGRP receptor antagonist, 300 nmol/L) did not affect the control diameters of coronary arterial microvessels but completely abolished CGRP-induced vasodilation at the same doses (infused and superfused). However, 300 nmol/L of CGRP(8-37) did not affect the response of coronary arterial microvessels to the LAD occlusion in any size.

Conclusions: CGRP preferentially dilates the coronary arterial microvessels >100 µm in diameter but has only a small effect on arterioles <100 µm diameter. Endogenous CGRP does not modulate the tone of coronary arterial microvessels during acute myocardial ischemia in beating canine hearts.

Key findings: CGRP dilated coronary epicardial arterioles, but CGRP antagonism alone did not induce vasoconstriction of these vessels.

Reviewer comments: CGRP dilated coronary epicardial microvessels (arterioles) in anesthetized dogs, with larger arterioles (> 100 µm diameter) being more sensitive than smaller arterioles (<100 µm diameter). Lack of effect of the CGRP antagonist (CGRP[8-37]) on baseline arteriole diameter and response to ischemia suggests that basal tone and control of coronary blood flow during ischemia are not CGRP dependent.

COLLATERALS AND/OR INFARCT SIZE REDUCTION


Abstract
This study was performed to examine the effect of calcitonin gene-related peptide (CGRP) on blood flow through well-developed coronary collateral vessels. Studies were performed in 9 adult mongrel dogs 4-6 months after embolic occlusion of the left anterior descending coronary artery (LAD) with a hollow intravascular plug to stimulate collateral vessel growth. At the time of study, the LAD was cannulated to determine interarterial collateral flow from measurement of retrograde blood flow. Radioactive microspheres were injected during retrograde flow collection to determine continuing tissue flow in the collateral dependent region. CGRP was infused into the left main coronary artery in a dose of 0.2 μg/kg/min to reach collateral vessels originating from the left coronary system. Retrograde blood flow was 40 ± 9 ml/min during basal conditions and increased 22 ± 9% in response to infusion of CGRP (n = 9, p < 0.05). Tissue flow to the collateral-dependent myocardial region did not change in response to CGRP infusion. Isolated rings of epicardial collateral vessels contracted with prostaglandin F2" (PGF2a) underwent relaxation in response to CGRP which was similar in magnitude to that of normal coronary arteries of comparable size. These data demonstrate that CGRP causes vasodilation of well-developed epicardial coronary collateral vessels, resulting in an increase in collateral blood flow.

BLA 761077
Key finding: Canine coronary collaterals are sensitive to CGRP; however, the effect of CGRP antagonism was not evaluated in this model.

Reviewer’s comment: This was the only rigorously performed hemodynamic study of drug effect on CGRP effects on well-formed collaterals in the heart. It demonstrates that well-formed collaterals react the same way to CGRP exposure as do the native epicardial coronary arteries, and the ability of CGRP relax the coronary contraction induced by PGF2α. The microsphere assessment showed no endocardial to epicardial steal phenomenon. No antagonist was administered.


Abstract
Objective: In myocardial ischaemia, slow conducting capsaicin-sensitive C-fibres are activated. Apart from the mediation of pain, activation of these fibres causes release of various peptides, such as calcitonin gene-related peptide (CGRP), which is a potent vasodilator. The aim of this study was to investigate the role of CGRP in the context of myocardial ischaemia in vivo.

Methods: The left anterior descending coronary artery (LAD) was occluded during 45 min in 27 anaesthetised open-chest pigs. LAD flow, mean arterial pressure (MAP), heart rate, peak dP/dt, arterial and coronary venous concentration of CGRP was measured prior to ischaemia, and during 4 h of reperfusion. The extent of myocardial infarction was measured using staining with triphenyl tetrazolium chloride.

Results: Retroinfusion of CGRP (100 µg) into the ischaemic myocardium was associated with a more pronounced hyperaemia, and systemic hypotension, during early reperfusion. The infarct size in relation to the area at risk was not affected by CGRP or the CGRP antagonist CGRP(8–37), and averaged 67±3%. There were no changes in plasma CGRP levels during ischaemia or reperfusion.

Conclusion: Exogenously administered CGRP can cause systemic hypotension and augments postischaemic coronary flow. In this model, no cardioprotective effect of CGRP could be proven.

Key finding: though retroperfusion with CGRP was associated with more pronounced hyperemia, the area at risk was not affected by CGRP or the CGRP antagonist CGPR(8-37). There were no changes in plasma CGRP levels during ischemia or reperfusion.

Reviewer’s comment: This was one of the few published studies in this field that was not sponsored by Merck (this one was supported by grants from the Swedish Medical Research Council, the Heart–Lung Foundation, the Wallenberg Foundation, and funds from the Karolinska Institute). There were four treatment groups of pigs that received retroinfusion this study with either 0.9% NaCl (vehicle, n=6), 100 µg CGRP (CGRP 100, n=5), 10 µg CGRP (CGRP 10, n=6),
or 2 mg CGRP(8–37) (CGRP(8–37) retro, n=5). A fifth group of pigs (CGRP(8–37) i.v, n=5) received 2 mg of CGRP(8–37) as an intravenous infusion over 5 min. In the dose–response experiments three consecutive doses of CGRP (1, 10 and 100 mg, respectively) were administered as a bolus in 5 ml saline via the central venous catheter. MAP, CVP and CO was recorded prior to and after each dose of CGRP. The author reports that, “For all five groups, there was a significant ($P<0.001$) change in LAD flow over time, with peak values occurring 15-30 minutes of reperfusion per the following figure:

There was neither demonstration of CGRP infusion-related benefit, nor demonstration of CGRP antagonist-induced harm from the five treatment groups, as shown in the figure below:

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**Fig. 6.** Area at risk expressed as percent of the LV, and infarct size expressed as percent of the area at risk after 45 min of ischemia followed by 4 h of reperfusion in the five groups. IS = infarct size, AAR = area at risk, LV = left ventricle. Values are expressed as mean ± s.e.m.
CORONARY BLOOD FLOW – REACTIVE HYPEREMIA


Abstract
The triptans, serotonin 5-HT1B/1D receptor agonists exemplified by sumatriptan, are a mainstay migraine therapy but have class labeling contraindicating their use in patients with coronary artery disease. Triptans constrict human coronary artery in vitro, and there are case reports of myocardial infarction in patients using sumatriptan. However, preclinical studies with sumatriptan in normal dogs have failed to demonstrate effects on resting coronary flow. Calcitonin gene-related peptide (CGRP) receptor antagonism, exemplified by the prototype CGRP receptor antagonist peptide CGRP8–37, is a new antimigraine mechanism which also has been reported to have no effect on coronary flow in normal, non-stressed animals. The goal of the present studies was to compare the effects of sumatriptan (10 μg/kg/min i.v.) and CGRP8–37 (30 μg/kg/min i.v.) on systemic and coronary hemodynamics in conscious dogs under resting conditions and during myocardial reactive hyperemia following a brief 15 s of coronary artery occlusion. Neither CGRP8–37 nor sumatriptan affected resting coronary flow. However, whereas CGRP8–37 had no effect on myocardial reactive hyperemic response, sumatriptan reduced peak reactive hyperemic coronary artery blood flow (baseline vs treatment: 75.4±12.7 vs 60.0±10.3ml/min, P<0.05), reactive hyperemic flow (16.7±5.2 vs 11.6±3.3 ml, P<0.05) and the repayment of coronary blood flow debt following coronary artery occlusion (484±76 vs 369±57%, P<0.05), indicating an impairment in coronary blood flow reserve. The positive control nitric oxide synthase inhibitor L-NNA (30 mg/kg/30 min i.v.) likewise significantly attenuated myocardial reactive hyperemic response. These findings provide evidence for a differentiation between CGRP receptor antagonism and triptan effects on coronary vascular function.
Key findings: CGRP antagonism did not affect myocardial reactive hyperemia in dogs. In contrast, sumatriptan blunted the reactive hyperemic response.

Reviewer’s comments: In this in vivo conscious dog study, the CGRP antagonist CGRP-(8-37) did not affect myocardial reactive hyperemia following a 15 second coronary artery occlusion. In contrast, sumatriptan reduced the reactive hyperemic response, indicating that it decreased coronary flow reserve under these conditions. The dose selection for the drugs evaluated seemed reasonable. The dose of CGRP (8-37) utilized was sufficient to block the systemic vasodilator effect of exogenous CGRP. The dose of sumatriptan utilized yielded a plasma drug concentration similar to that seen clinically. Although sample sizes were small (n= 5 and 6 dogs per treatment arm), they were sufficient to capture effects of sumatriptan and the positive control nitric oxide synthase inhibitor, L-NNA.

CORONARY BLOOD FLOW – MYOCARDIAL ISCHEMIA (CORONARY STENOSIS AND RAPID ATRIAL PACING)

Regan, et.al. Calcitonin Gene-Related Peptide Receptor Antagonism Does Not Affect the Severity of Myocardial Ischemia during Atrial Pacing in Dogs with Coronary Artery Stenosis. JPET 328:571–578, 2009

Abstract
Calcitonin gene-related peptide (CGRP) is a sensory neuropeptide that also has potent vasodilator activity. There are conflicting preclinical reports regarding the effect of CGRP receptor antagonism in the setting of myocardial ischemia. The present study was conducted in a canine model in which regional myocardial ischemia was reproducibly...
evoked by serial periods of atrial pacing (80 beats per min above baseline rate) in the presence of a 40% stenosis of the left anterior descending (LAD) coronary artery. Ischemia severity was quantitated by changes in unipolar epicardial electrograms (EG) recorded in the area of ischemia. In validation studies, the calcium entry blocker diltiazem reduced ischemia severity (before versus after treatment: ΔEG, 1.92 ±0.23 versus 0.54 ±0.24 mV; p < 0.05) and tended to increase LAD flow (7.7 ± 0.7 versus 9.4 ±1.4 ml/min; p = 0.10), whereas the coronary constrictor serotonin increased ischemia severity (before versus after treatment: ΔEG, 2.11±0.44 versus 4.90 ±1.46 mV; p < 0.05) concomitant with a reduction in LAD flow (9.1 ±1.1 versus 5.4 ±1.5 ml/min; p < 0.05). A 30 µg/kg/min i.v. infusion test dose of the CGRP receptor antagonist CGRP(8-37) was validated by demonstrating complete block of the depressor effects of exogenous i.v. 0.03 to 0.3 µg/kg CGRP. This dose of CGRP(8-37), administered either intravenously or intra-atrially, had no effect on ischemia severity or paced LAD flow, indicating no intrinsic effect of CGRP receptor antagonism on the severity of acute myocardial ischemia. Likewise, the administration of a hemodynamically active dosing regimen of CGRP (0.03 µg/kg/min i.v.) had no effect on paced coronary flow or ischemia severity, suggesting no major role of CGRP in regulating ischemic blood flow.

Key finding: CGRP antagonism did not worsen myocardial ischemia in dogs in the setting of coronary artery stenosis and rapid pacing to increase oxygen demand.

Reviewer Comments: In this in vivo anesthetized dog study, the CGRP antagonist did not affect severity of ischemia (based on changes in a surface ECG) induced by LAD stenosis and rapid atrial pacing at 80 bpm higher than baseline, which increases myocardial oxygen consumption and thus need for coronary flow. In contrast, the positive control drugs (diltiazem and serotonin), attenuated and exacerbated ischemic changes in the ECG, respectively, commensurate with changes in LAD coronary flow. The dose of CGRP (8-37) utilized was sufficient to block the systemic vasodilator effect of exogenous CGRP. Although sample sizes were small (n=6 for each drug treatment group, n=13 for the saline group) they were sufficient to capture effects of the positive control drugs, diltiazem and serotonin.

HEART FAILURE

Shen, et al., Effects of Inhibition of -CGRP Receptors on Cardiac and Peripheral Vascular Dynamics in Conscious Dogs with Chronic Heart Failure. (J Cardiovasc Pharmacol 2003,42: 656–661)

Abstract
Whether endogenous calcitonin gene-related peptide (CGRP) plays a role in heart failure is unclear. Seven dogs were instrumented with left ventricular (LV) pressure gauges, pacers, coronary occluder and aortic, atrial, and coronary sinus catheters.

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Hemodynamic recordings and response to α-CGRP challenge were obtained for baseline in the conscious state. Rapid pacing (240 beats/min) was then initiated. The coronary artery was occluded for 90 minutes followed by reperfusion after 2 weeks of pacing. After 6 weeks of pacing, LV pressure (−11 ± 6%), LV dP/dt (−53 ± 5%), and mean arterial pressure (−15 ± 4%) decreased (P < 0.01), while left atrial pressure (+19±3mmHg from7±1mmHg) and heart rate (+53 ± 16%) increased (P < 0.01). Infusion of the α-CGRP receptor antagonist α-CGRP[8-37] (30 μg/kg/min, iv), which blocked the exogenous α-CGRP challenge, did not affect any of these indices. Regional blood flow, as measured by the microsphere technique, in the nonischemic myocardium, as well as cerebral and renal vasculatures were unaltered during the infusion of α-CGRP[8-37]. Plasma concentrations of CGRP from both arterial and coronary sinus samples were unchanged after 6 weeks of pacing as compared with control. Thus, we conclude that endogenous α-CGRP does not appear to play a major role in the regulation of cardiac and peripheral vascular dynamics in the late stage of heart failure.

Key finding: CGRP antagonism did not affect coronary flow in a canine heart failure model.

Reviewer’s comments: Administration of a CGRP antagonist (CGRP[8-37]) tested negative for effects on hemodynamics, regional non-ischemic coronary flow (microspheres) and LV contractility (LV dP/dtmax) in an in vivo conscious canine heart failure model.

PRECONDITIONING


Abstract
Aim: To examine the role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning induced by prostaglandins in isolated guinea pig hearts.
Methods: The isolated guinea pig hearts were perfused in a Langendorff model. The heart rate, coronary flow, left ventricular pressure, and its first derivatives (± dp/dtmax) were recorded and the calcitonin gene-related peptide like immunoreactivity (CGRP-LI) and 6-keto-PGF1α were measured.
Results: Endothelin-1 (200 pmol in 1 mL K-H buffer) reduced the left ventricular developed pressure and its first derivatives (± dp/dtmax) heart rate, and coronary flow. Preconditioning with two cycles of 5-min global ischemia and 5-min reperfusion attenuated endothelin-1-induced myocardial injury, and concentrations of both CGRP and 6-keto-PGF1α in the coronary effluent were markedly raised in the preconditioning periods. Pretreatment with capsaicin, which depletes endogenous CGRP, abolished the elevated level of CGRP concomitantly with loss of the cardioprotection induced by ischemic preconditioning. CGRP[6-37] (100 nmol/L), a selective CGRP receptor antagonist, also abolished the protective effects of ischemic preconditioning. After pretreatment with indomethacin (10 μmol/L), an inhibitor of cyclooxygenase, the protective effects of
ischemic preconditioning were abolished and the release of 6-keto-PGF\(_{1\alpha}\) was no longer elevated. Pretreatment with indomethacin abolished the elevated level of CGRP in the coronary effluent.

Conclusion  Endogenous prostaglandins are involved in the protective effects of ischemic preconditioning, and the beneficial effect of prostaglandins are mediated by CGRP in the guinea pig heart.

Key findings: Endogenous prostaglandins are involved mechanistically in the generation of ischemic preconditioning, and this effect appears associated with and/or mediated through the release of CGRP in the Langendorff model.

Reviewer’s comment: This is one of the earliest studies that gave rise to the concern for possible CV risk with therapeutic CGRP antagonism. However, the ex-vivo model may limit the activity of other compensatory mechanisms during ischemic preconditioning that are present in vivo.

Ren et al.  Cardioprotection by ischemic postconditioning is lost in isolated perfused heart from diabetic rats: Involvement of transient receptor potential vanilloid 1, calcitonin gene-related peptide and substance. Regulatory Peptides 2011;169:49–57

Abstract
We previously found that the expression of transient receptor potential vanilloid 1 (TRPV1) and contents of calcitonin gene-related peptide (CGRP) and substance P (SP), two main neuropeptides released from TRPV1, were decreased in diabetic hearts. This study aimed to test whether decreased TRPV1, CGRP and SP levels were responsible for the loss of cardioprotection by ischemic postconditioning (IPostC) in isolated perfused heart from streptozotocin-induced diabetic rats. IPostC effectively protected non-diabetic hearts against ischemia/reperfusion injury by improving cardiac function and lowering creatine kinase (CK) and cardiac troponin I (cTnI) release, which could be abolished by inhibiting TRPV1, CGRP receptor or SP receptor. However, IPostC had no effect on cardiac function and the release of CK and cTnI in diabetic hearts regardless of whether TRPV1, CGRP receptor or SP receptor were inhibited. CGRP or SP-induced postconditioning significantly prevented both non-diabetic and diabetic hearts from ischemia/reperfusion injury by improving cardiac function and lowering CK and cTnI release. Additionally, IPostC markedly increased CGRP and SP release in non-diabetic hearts, which could be reversed with TRPV1 inhibition, but not CGRP receptor or SP receptor inhibition. However, IPostC failed to affect CGRP and SP release in diabetic hearts in the presence or absence of TRPV1, CGRP receptor or SP receptor inhibition. These results indicate that the loss of cardioprotection by IPostC during diabetes is partly associated with a failure to increase CGRP and SP release, likely due to decreased TRPV1 expression and CGRP and SP contents in diabetic hearts.

Key findings: A lack of increase in CGRP release associated with IPostC during diabetes may be due to decreased TRPV1 expression and CGRP contents in diabetic hearts.
Reviewer’s comment: This is one in a series of studies from this group demonstrating the impact of ischemia on CGRP release.

Chai et al. The role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning in isolated rat hearts. European Journal of Pharmacology 2006;531:246–253

Abstract
Brief coronary artery occlusion can protect the heart against damage during subsequent prolonged coronary artery occlusion; ischemic preconditioning. The role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning is investigated in isolated perfused rat hearts, by measuring CGRP release during ischemic preconditioning and mimicking this by exogenous CGRP infusion, either in the absence or presence of the CGRP antagonist BIBN4096BS. CGRP increased left ventricular pressure and coronary flow in a concentration dependent manner, which was effectively antagonized by BIBN4096BS. Rat hearts (n=36) were subjected to 45 min coronary artery occlusion and 180 min reperfusion, which was preceded by: (1) sham pretreatment, (2) BIBN4096BS infusion (1 μM), (3) preconditioning by 15 min coronary artery occlusion and 10 min reperfusion, (4) as 3, but with BIBN4096BS, (5) 15 min CGRP infusion (5 nM) and 10 min washout, (6) as 5, but with BIBN4096BS. Cardiac protection was assessed by reactive hyperaemia, creatine kinase release, infarct size related to the area at risk (%), and left ventricular pressure recovery. Preconditioning increased CGRP release into the coronary effluent from 88±13 to 154±32 pg/min/g, and significantly protected the hearts by decreasing reactive hyperaemia (35%), reducing creatine kinase release (53%), limiting infarct size (48%), and improving left ventricular pressure recovery (36%). Exogenous CGRP induced preconditioning-like cardioprotection. BIBN completely abolished the cardioprotection induced by preconditioning as well as by exogenous CGRP. In conclusion, since cardioprotection of preconditioning-induced CGRP release can be mimicked by exogenous CGRP, and both can be blocked by a CGRP antagonist, results indicate an important role for CGRP in ischemic preconditioning.

Key findings: Cardioprotection of preconditioning-induced CGRP release can be mimicked by exogenous CGRP, and both can be blocked by a CGRP antagonist, results indicate an important role for CGRP in ischemic preconditioning.

Reviewer’s comment: This is a confirmatory observation that CGRP appears to have a mechanistic role in ischemic preconditioning in isolated perfused rat hearts. However, the author demonstrates no difference in the area at risk as a percent of the left ventricle, as excerpted from the paper below (somewhat difficult to ascertain because risk area was placed on the same table as the incidence of V-fib):
Table 2

| Incidence of ventricular fibrillation group identification as in Fig. 3 |
|-------------------------------------|-----------------|------------------|
| Number | Risk area (% to left ventricle) | Ventricular fibrillation |
| Control | 6 | 49.8±4 | 5/6 |
| BIBN | 6 | 52.6±6 | 6/6 |
| PC | 6 | 51.4±5 | 2/6^a |
| BIBN+PC | 6 | 51.1±5 | 5/6 |
| CGRP | 6 | 53.5±2 | 2/6^a |
| CGRP+BIBN | 6 | 52.6±2 | 6/6 |

^a p<0.01.

REGULATION OF CARDIOVASCULAR SYSTEM


Abstract
It remains unknown whether the extent of vasoactive response to exogenous calcitonin gene-related peptide (CGRP) varies among different regional vascular beds. It is also unclear whether endogenous CGRP plays a functional role in regulating basal vascular activity. To address these two issues, experiments were conducted in 27 anesthetized rats instrumented with a carotid flow probe and catheters in a jugular vein, left ventricle (LV), and femoral artery, and in 6 conscious dogs, chronically instrumented with LV pressure gauge, aortic and atrial catheters, and ascending aortic, coronary, carotid, and renal flow probes. In both species, administration of human a-CGRP (0.1–0.5 mg/kg, i.v.) induced a dose-dependent peripheral vasodilation that was completely abolished by pretreatment with a-CGRP[8-37] (30 mg/kg/min, i.v.), a competitive antagonist of CGRP receptors. Regional blood flow measured by the radioactive microsphere technique in rats showed that the a-CGRP (0.3 mg/kg, i.v.)-induced increase in blood flow was greater (p≤0.05) in the heart (53 ± 16%) than in the brain (14 ± 6%). In the presence of β-adrenergic receptor blockade with propranolol, however, the increases in blood flow in these two vascular beds were identical. In conscious dogs, a-CGRP (0.3 mg/kg, i.v.) produced similar increases in coronary (24 ± 6%), carotid (26 ± 3%), and renal (26 ± 6%) blood flow, which were different from the patterns induced by other vasodilators; at an equivalent level of reduction in mean arterial pressure and total peripheral resistance, a-CGRP increased coronary and carotid blood flow significantly less (p≤0.05) than adenosine or nitroprusside. Unlike a-CGRP, adenosine and nitroprusside, as expected, induced pronounced differential blood flow changes in these vascular beds. Neither systemic hemodynamics nor regional blood flow distribution was altered by the administration of a pharmacological blocking dose of a-CGRP[8-37] in the two species.

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Reference ID: 4246390
Thus, we conclude that endogenous a-CGRP does not play an important role in cardiovascular regulation under normal, resting conditions, although exogenous a-CGRP induces a marked, comparable vasorelaxation in different regional vascular beds.

Key findings: Systemically administered CGRP increased coronary and cerebral blood flows in rats and dogs, but CGRP antagonism alone did not affect these blood flows.

Reviewer comments: Infusion of CGRP in anesthetized rats and conscious dogs produced increases in carotid and coronary blood flows that were abolished by pretreatment with CGRP-[8-37], a competitive CGRP inhibitor. Administration of CGRP-[8-37] alone did not affect systemic hemodynamics nor regional blood flow distribution, suggesting that CGRP does not affect regional blood flow distribution in resting conditions in healthy animals.

CLINICAL STUDIES


Abstract
Aims: To assess the effect of the calcitonin gene-related peptide (CGRP) receptor antagonist, telcagepant, on the haemodynamic response to sublingual nitroglycerin (NTG).
Methods: Twenty-two healthy male volunteers participated in a randomized, placebo-controlled, double-blind, two-period, crossover study. Subjects received 500 mg telcagepant or placebo followed, 1.5 h later, by 0.4 mg NTG. To assess the haemodynamic response the following vascular parameters were measured: blood pressure, aortic augmentation index (AIx) and brachial artery diameter (BAD). Data are presented as mean (95% confidence interval, CI).
Results: The aortic AIx following NTG decreased by -18.50 (-21.02, -15.98) % after telcagepant vs. -17.28 (-19.80, -14.76) % after placebo. The BAD fold increase following NTG was 1.14 (1.12, 1.17) after telcagepant vs. 1.13 (1.10, 1.15) after placebo. For both AIx and BAD, the hypothesis that telcagepant does not significantly affect the changes induced by NTG is supported (P < 0.0001). In addition, no vasoconstrictor effect of telcagepant could be demonstrated.
Conclusions: Telcagepant did not affect NTG-induced haemodynamic changes. These data suggest that NTG-induced vasodilation is not CGRP dependent.

Key finding: In this model, CGRP inhibition does not inhibit indices of vasodilation in healthy men.
Reviewer comments: In this GCP, Merck-sponsored study, the AIx was defined as the proportion of central pulse pressure that results from arterial wave reflection as a commonly used measure for arterial stiffness. The author remarks that this method has been shown to be more reliable in detecting arterial triptan and nitrate-induced vascular effects than the classically used brachial artery diastolic (DBP) and systolic blood pressure (SBP). Only subjects with a positive AIx during screening were enrolled.

The blood pressure data appears to have been rigorously acquired, per the following description:

Before performing baseline measurements, subjects rested for 30 min in the supine position on a comfortable bed for acclimatization (flow chart in Figure 1). Fifteen minutes prior to drug administration, BAD followed by PWF measurements were performed in triplicate. Three PWF measurements were repeated 73 min after the administration of telcagepant or placebo. Thereafter and 5 min prior to NTG administration (i.e. 85 min post-dose), three BAD recordings were performed. The same image of the brachial artery was maintained by use of a probe-holder and arm supports throughout the sublingual administration of 0.4 mg NTG at exactly 90 min after drug intake. The time point of NTG administration was chosen at the expected time of maximal plasma concentration of telcagepant. Between 2 and 6 min following NTG administration (i.e. between 92 and 96 min post-dose), a maximum of nine BAD measurements was performed, followed by four PWF recordings. All brachial oscillometric SBP and DBP values were obtained before and after PWF recordings and used for calibration of the PWFs.

In addition, the analytical plan seemed well-conceived and reasonable, as per the following description:

Primary analyses to evaluate the effect of telcagepant on NTG-induced vascular changes. The study was powered to detect changes in the maximal vasodilatory NTG response due to telcagepant for the parameters aortic AIx and BAD. Therefore, in the primary analyses, only aortic AIx and BAD were used. As NTG causes a decrease in aortic AIx and the baseline aortic AIx was positive (cf. inclusion criteria), the change in aortic AIx is a negative value. Therefore, the maximum effect on aortic AIx for a subject in a given treatment period was defined as the largest negative difference between the post- and pre-NTG measurements over the two predefined post-NTG time points. The maximum increase in BAD induced by NTG was defined as the maximum fold-change obtained over the four predefined post-NTG time points. Individual maximal effect values were analyzed in a mixed effects analysis of variance (ANOVA) with fixed effects for treatment, period and treatment sequence and a...
random effect for subject nested within treatment sequence. For BAD, values were ln-transformed, whereas for AIx the data were analyzed on the original scale. Results for BAD were back-transformed to the original scale to obtain a geometric mean and corresponding 95% confidence interval (95% CI).

For aortic AIx, the hypothesis was tested that at least 50% of the maximum NTG effect was maintained following administration of telcagepant as compared with placebo, where 50% was predefined as the threshold for significance. The P value is for the test that the fold treatment difference (effect of NTG with telcagepant/effect of NTG with placebo) is less than 0.50 (null hypothesis) vs. at least 0.50 (alternative hypothesis). P < 0.05 signifies that at least 50% of the NTG effect is maintained when administered with telcagepant.

In addition, the hypothesis was tested that at least 50% of the maximum NTG effect on BAD is maintained following administration of telcagepant as compared with placebo. Therefore, a two-sided 90% CI (equivalent to a one-sided lower 95% CI) for the difference (effect of NTG with telcagepant – effect of NTG with placebo) in ln-BAD maximum effect was calculated using the mean square error from the ANOVA and referencing a t-distribution. These confidence limits were exponentiated to obtain a 90% CI for the fold treatment difference (effect of NTG with telcagepant/effect of NTG with placebo). It was predefined that if the lower bound of the 90% CI was >0.50, the hypothesis that telcagepant has no effect on NTG-induced vascular changes would be supported.

Regarding the dose of telcagepant administered, there were no PK/PD assessments in this study. However, this reviewer concludes that the pharmacologic target was engaged appropriately based on the following description of phase 2 PK/PD data obtained by the sponsor:

It was recently demonstrated, both in a dose finding phase II study and in a confirmatory phase III study, that a 300 mg dose of telcagepant has an efficacy comparable with that of the triptans for the treatment of acute migraine headache. The anticipated clinical dose of telcagepant (relative to the formulation used in this study) is a single 300 mg dose, with an optional second 300 mg dose 2h later, if needed. A single 500 mg dose, as used in this study, achieves pharmacokinetic exposures similar to 2 x 300 mg doses, administered 2 h apart.

We are confident that the single 500 mg dose of telcagepant adequately blocks the peripheral CGRP receptor in healthy men based on a previous study conducted by our group in which we used topical capsaicin applications to elicit CGRP release in human skin and assessed the increase in dermal blood flow (DBF) using laser Doppler. Telcagepant...
inhibited the increase in DBF following capsaicin application and the subsequent analysis of the pharmacokinetic/pharmacodynamic relationship suggested that telcagepant engages the CGRP receptor with an EC90 of approximately 900 nM [42]. The concentration–response curve above 900 nM was relatively flat indicating that at or above this plasma concentration, telcagepant is maximally blocking the peripheral CGRP receptor in healthy men. In the capsaicin study, an early formulation of telcagepant was used that had lower bioavailability than the formulation used in this trial. The plasma concentrations achieved in this study are estimated to be approximately two- to four-fold higher than 900 nM and we are therefore confident that adequate blockade of the peripheral CGRP receptor was achieved.

While the choice of the AIx treatment effect ratio seemed arbitrary, review of the raw results does demonstrate the lack of a measurable vasoconstrictor effect of the active drug using this model. A weakness of this study was the lack of a triptan positive control. In addition, the author points out that “central pressure effects were not measured invasively but were estimated by use of a generalized transfer function. This transfer function has received some criticism and has not been convincingly validated in young healthy subjects.”


Abstract
Migraine is the most prevalent neurological disorder worldwide and it has immense socioeconomic impact. Currently, preventative treatment options for migraine include drugs developed for diseases other than migraine such as hypertension, depression and epilepsy. During the last decade, however, blocking calcitonin gene-related peptide (CGRP) has emerged as a possible mechanism for prevention of migraine attacks. CGRP has been shown to be released during migraine attacks and it may play a causative role in induction of migraine attacks. Here, we review the pros and cons of blocking CGRP in migraine patients. To date, two different classes of drugs blocking CGRP have been developed: small molecule CGRP receptor antagonists (gepants), and monoclonal antibodies, targeting either CGRP or the CGRP receptor. Several trials have been conducted to test the efficacy and safety of these drugs. In general, a superior efficacy compared to placebo has been shown, especially with regards to the antibodies. In addition, the efficacy is in line with other currently used prophylactic treatments. The drugs have also been well tolerated, except for some of the gepants, which induced a transient increase in transaminases. Thus, blocking CGRP in migraine patients is seemingly both efficient and well tolerated. However, CGRP and its receptor are abundantly present in both the vasculature, and in the peripheral and central nervous system, and are involved in several physiological processes. Therefore, blocking CGRP
may pose a risk in subjects with comorbidities such as cardiovascular diseases. In addition, long-term effects are still unknown. Evidence from animal studies suggests that blocking CGRP may induce constipation, affect the homeostatic functions of the pituitary hormones or attenuate wound healing. However, these effects have so far not been reported in human studies. In conclusion, this review suggests that, based on current knowledge, the pros of blocking CGRP in migraine patients exceed the cons.

Key findings: While evidence from animal studies suggests that blocking CGRP may induce constipation, affect the homeostatic functions of the pituitary hormones or attenuate wound healing.

Reviewer’s comments: This statement from the European Headache Federation School of Advanced Studies (EHF-SAS) states that “...no cardiovascular concerns have been disclosed with any of these drugs (CRRP antagonists).” However, these authors also opine that “...studies testing the cardiovascular safety of the long-term blockade are warranted in order to answer the numerous questions on the possibility of higher risk in cardio- and cerebrovascular compromised patients. For example, it is unknown whether blocking CGRP could potentially transform transient mild cerebral ischemia into a full-blown brain infarct and whether these risks are higher in women. To investigate these aspects, future studies should include patients with preexisting cardiovascular conditions.” They conclude, however, by stating that “…based on current knowledge, we believe that the benefits of blocking CGRP – including the perspectives of improving the lives of those suffering from frequent headaches – seems to be greater than the disadvantages.” From this reviewer’s perspective, this review is reassuring in that these authors are also unaware of any clinical cardiotoxicity imparted by the use of CGRP-r antagonists.


Abstract
Telcagepant is a calcitonin gene-related peptide (CGRP) receptor antagonist being evaluated for acute migraine treatment. CGRP is a potent vasodilator that is elevated after myocardial infarction, and it delays ischemia during treadmill exercise. We tested the hypothesis that CGRP receptor antagonism does not reduce treadmill exercise time (TET). The effects of supratherapeutic doses of telcagepant on TET were assessed in a double-blind, randomized, placebo-controlled, two-period, crossover study in patients with stable angina and reproducible exercise-induced angina. Patients received telcagepant (600 mg, n = 46; and 900 mg, n = 14) or placebo and performed treadmill exercise at Tmax (2.5 h after the dose). The hypothesis that telcagepant does not reduce TET was supported if the lower bound of the two-sided 90% confidence interval (CI) for the mean treatment difference (telcagepant–placebo) in TET was more than −60 s. There were no significant between-treatment differences in TET (mean treatment difference: BLA 761077
−6.90 (90% CI: −17.66, 3.86) seconds, maximum exercise heart rate, or time to 1-mm ST-segment depression using pooled data or with stratification for dose.

Key finding: The mean TET for the pooled 600-mg and 900-mg telcagepant vs. placebo treatment groups were 405.38 s (95% confidence interval (CI): 375.91, 434.85) vs. 412.28 s (382.72, 441.85), respectively. The mean treatment difference for telcagepant pooled over both doses minus placebo was −6.90 s (90% CI: −17.66, 3.86).

Reviewer’s comment: This was a Merck-sponsored study that demonstrated a small and non-statistically significant reduction in placebo-corrected treadmill time, the lower bound of which did not violate the prespecified -60 s difference for concluding that TET was decreased.
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/s/

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PRESTON M DUNNMONT
04/10/2018

JOHN E KOERNER
04/10/2018

JEAN Q WU
04/10/2018

MARTIN ROSE
04/10/2018

NORMAN L STOCKBRIDGE
04/11/2018

Reference ID: 4246390
1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised carton labeling for Aimovig (Appendix A) to determine if the carton labeling is acceptable from a medication error perspective. The revisions are in response to recommendations we provided in a previous labeling memo.\(^b\)

2 CONCLUSION

The revised carton labeling for Aimovig is acceptable from a medication error perspective. We have no further recommendations at this time.

\(^a\) The proposed nonproprietary name suffix ‘aooe’ was found to be conditionally acceptable on February 15, 2018.

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

/s/

EBONY A WHALEY
04/10/2018

LOLITA G WHITE
04/10/2018
HUMAN FACTOR RESULTS AND LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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<td>DMEPA Associate Director for Human Factors:</td>
<td>QuynhNhu Nguyen, MS</td>
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* The proposed nonproprietary name suffix ‘aooe’ was found to be conditionally acceptable on February 15, 2018.

***The proposed proprietary name Aimovig was found to be conditionally acceptable on August 18, 2017.

Reference ID: 4238517
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report, Prescribing Information (PI), Instructions for Use (IFU), container labels, and carton labeling for BLA 761077, Aimovig (erenumab-aooe) prefilled syringe and autoinjector, submitted on May 17, 2017.

The Division of Neurology Products (DNP) requested that we review the HF validation study results and proposed labels and labeling submitted by Amgen to determine if they are acceptable from a medication error perspective.

1.1 PRODUCT BACKGROUND

Amgen proposes a prefilled syringe (PFS) and autoinjector (AI) presentation for Aimovig (erenumab-aooe), which is intended for the prophylaxis of migraines in adults. The product is intended for subcutaneous administration once every four weeks by patients, caregivers. In this BLA submission, Amgen intends to seek approval of the Aimovig (erenumab-aooe) 70 mg/mL PFS and AI;  

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
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<tr>
<td>Previous DMEPA Reviews</td>
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<tr>
<td>Human Factors Study</td>
<td>C</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D – N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F – N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

Reference ID: 4238517
3 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide a summary of the study design, errors observed with critical tasks (Tables 2 and 3), and our analysis of the HF validation study results.

3.1 SUMMARY OF STUDY DESIGN-AIMOVIG PREFILLED SYRINGE

The objective of this simulated use human factors (HF) validation study was to test the participants’ ability to safely and accurately use the proposed Aimovig 70 mg/mL. The HF validation study included a total of 95 representative untrained users within the following user groups: injection-naïve patients, injection-experienced patients, injection-naïve caregivers, injection-experienced caregivers, and injection-experienced healthcare providers. Participants were assigned to administer a dose of 140 mg in one of the following scenarios: 2 injections of the 70 mg/mL PFS (2-count carton with IFU and Reference Guide [RG]).

Table 2 below summarizes and focuses on the results observed with critical tasks, including IFU knowledge assessment, that were evaluated in the HF validation study along with the Applicant’s provided root cause analysis for each failure.

\[\text{Reference ID: 4238517}\]
Table 2: List of critical tasks where failures occurred with the Aimovig prefilled syringe

<table>
<thead>
<tr>
<th>Task</th>
<th>Use Scenario</th>
<th>Number of Failures</th>
<th>Participants Committing the Errors (Number of failures)*</th>
<th>Root Cause Analysis and Sponsor’s Assessment</th>
<th>Additional Analysis and General Recommendations from DMEPA</th>
</tr>
</thead>
</table>
| Step 6. Dispose of device without needle stick injury | (b) (4) | 1/47 | PINN (1) | Four participants failed to dispose of the PFS properly and one of those four use errors resulted in a needle stick injury. The sponsor did not propose mitigations in response to the failures.  
- **Negative transfer**: One participant experienced a needle stick injury while attempting to recap the needle. The participant stated they recapped the needle out of habit. The sponsor attributed this failure to negative transfer.  
- **Intentional misuse**: One participant did not dispose of the PFS in the sharps container. The participant did not believe they needed to safely dispose of the PFS at home because they lived alone. The sponsor attributed this failure to intentional misuse.  
- **Study artifact**: One participant did not dispose of the PFS in the sharps container on the 1st and 2nd injections (counted as 2 failures). The participant stated that they did not notice the sharps container in the room. The sponsor attributed this failure to study artifact and noted that the study moderator pointed out the sharps container at the beginning of the session. | While we acknowledge the residual risk of needle stick injuries, the submitted root cause information does not suggest that the user interface contributed to the failures. Based on our evaluation of use-related risks, we find the proposed PFS does not have unique risks regarding its disposal as compared to other marketed PFS products. In addition, we find that the IFU labeling adequately describes how to dispose of the PFS. As such, we agree with the sponsor’s assessment and do not have recommendations at this time. |
| Two 70 mg injections + IFU + RG | 3/48 | PINE (1), PINN (2) |  |  |  |
Step 7. When required, repeat essential steps 1—6 as applicable to administer a complete dose.

| Two 70 mg injections + IFU + RG | 1/48 | CINE (1) |

One participant did not administer 2 injections as prescribed in the simulated-use scenario.

- The sponsor indicated that based on carton labeling and study prescription language (e.g. “140 mg; Take two injections once monthly”), the participant interpreted the study task as that they should administer two 140 mg injections per month and interpreted that each PFS contained 140 mg. However, the correct interpretation is that the participant should administer two 70 mg injections to complete a dose of 140 mg and each PFS contained 70 mg. The sponsor attributed this error to “study artifact with labeling confusion”. The sponsor noted that the participant was not a native English speaker and experienced difficulty interpreting the prescription. The sponsor did not propose mitigations.

We note that the sponsor did not assess this task as critical. We disagree with the sponsor’s assessment that the task is not critical and that mitigations are not needed. We find the task to administer two injections to achieve one full dose pose risk of underdose if performed incorrectly or omitted and as such, should be categorized as critical.

The sponsor’s assessment of this task included any failure that occurred with the 2nd injection (including failures reported under the previously mentioned critical task). To avoid redundancy, our assessment focuses only on failures in which the participant did not attempt to administer the 2nd injection.

We find that the Aimovig PFS IFU labeling does not prominently inform users that 2 injections must be administered to complete a 140 mg dose. We recommend that the Aimovig PFS IFU labeling be improved to more prominently indicate that users must inject 2 syringes to complete the 140 mg dose. We provide recommendation A.1. in Section 5.2 below to improve the prominence of this task. Given that the modifications are intended to increase the prominence of the instruction regarding the administration of 2 PFS to complete the 140 mg dose, we do not require additional human factors validation data.
<table>
<thead>
<tr>
<th>IFU Knowledge Assessment</th>
<th>IFU Step 1D: If you want to use the same injection site, make sure it is not the exact same spot on the injection site you used for a previous injection.</th>
<th>(b) (4) 11/47</th>
<th>Not fully described by the sponsor</th>
<th>The sponsor noted that several participants stated that they would give a subsequent injection in the same injection area as a previous injection. The sponsor also noted that during the injection task, several participants found the IFU unclear and were unsure whether the instruction applied to 2 injections administered on the same day or 2 injections administered one month apart. The sponsor did not identify failures with the simulated-use testing of the associated task (e.g. injection site rotation of the second injection if applicable). However, the sponsor indicated that during simulated-use testing, there were four close calls in which participants were uncertain whether they could inject the second syringe into the same exact location as the previous injection. The sponsor noted that after the moderator’s prompts, the participants read the IFU and were unable to locate additional information. The sponsor did not provide root-cause analysis information regarding the incorrect responses to this IFU Knowledge Assessment question or the observed difficulty in the simulated-use testing. The sponsor did not propose mitigations.</th>
<th>We note if the associated task (e.g. injection site rotation) is not performed correctly or omitted, there may be a risk of injection site irritation. The subjective feedback provided by the participants indicate a lack of clarity in the IFU. Our review of the IFU finds that the IFU does not clearly indicate whether the instruction to rotate the injection site for subsequent injection applies to consecutive injections given on the same day, consecutive injections given one month apart, or both. The IFU also does not indicate whether consecutive injections should be separated by a certain distance (e.g. specify how many inches apart). We determined that the IFU can be improved to further minimize the residual risk. <strong>We provide recommendation A.2. in Section 5.2 below to increase the clarity of the injection site rotation instructions in.</strong> Given that this revision is intended to provide additional clarity surrounding the administration of consecutive injections, we do not require additional HF validation testing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two 70 mg injections + IFU + RG</td>
<td>10/48</td>
<td>Not fully described by the sponsor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CINN: caregiver injection-naive  
PINN: patient injection-naive  
HCP: healthcare professional injection-experienced  
CINE: caregiver injection-experienced  
PINE: patient injection-experienced*
3.2 SUMMARY OF STUDY DESIGN-AIMOVIG AUTOINJECTOR RESULTS

The objective of this simulated use HF validation study was to evaluate whether the intended user can safely and effectively use the proposed Aimovig 70 mg/mL autoinjector (AI). The HF validation study included a total of 286 representative users within the following groups: (1) self-trained injection-naïve patients, (2) moderator-trained injection-naïve patients, (3) self-trained injection-experienced patients, (4) moderator-trained injection-experienced patients, (5) self-trained injection-naïve caregivers, (6) moderator-trained injection-naïve caregivers, (7) self-trained injection-experienced caregivers, (8) moderator-trained injection-experienced caregivers, (9) self-trained injection-naïve HCPs, (10) moderator-trained injection-naïve HCPs, (11) self-trained injection-experienced HCPs, and (12) moderator-trained injection-experienced HCPs. Participants were assigned to administer a dose of 70 mg or 140 mg in one of the following scenarios: 1 injection of the 70 mg/mL AI (using the 1-count carton with IFU), 2 injections of the 70 mg/mL AI (using the 2-count carton with IFU), or 2 injections of the 70 mg/mL AI (using the 2-count carton with the IFU and RG).

Table 3 below summarizes and focuses on the results observed with critical tasks, including IFU knowledge assessment, that were evaluated in the HF validation study along with the Applicant’s provided root cause analysis for each failure.
### Table 3: List of critical tasks where failures occurred with the Aimovig autoinjector

<table>
<thead>
<tr>
<th>Task</th>
<th>Use Scenario</th>
<th>Number of Failures</th>
<th>Participants Committing the Errors*</th>
<th>Root Cause Analysis and Sponsor’s Assessment</th>
<th>Additional Analysis and General Recommendations from DMEPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 3. Push the AI down firmly at the injection site to unlock the device (by triggering the needle guard)</strong></td>
<td>One 70 mg injection with IFU</td>
<td>3/95</td>
<td>CINN-S (1; session 1), PINN-M (1; session 1), PINE-S (1; session 1)</td>
<td>9 participants did not press the AI firmly enough to trigger the needle guard and subsequently unlock the device. Below, we note significant objective and subjective feedback associated with certain failures with this task.</td>
<td>According to the sponsor, pushing the AI down firmly at the injection site will unlock the device (by triggering the needle guard). We disagree with the sponsor’s assessment that the failure to perform this task is low risk and that mitigations are not needed. We find the task to push the AI down firmly at the injection site to unlock the device is a critical task. Failure of this task may pose risk of delay of therapy if performed incorrectly or omitted and as such, should be categorized as critical. We note that most failures occurred on first injections for the use scenario for which 2 injections are required. This demonstrated to us that the users improve their performance with repeated use. Our review of the IFU finds that the IFU labeling does not adequately instruct users to firmly press down the AI to trigger the device. We find that the instructions are not clear and may pose risk for confusion. We determined that the IFU can be (continued to next row below)</td>
</tr>
<tr>
<td></td>
<td>Two 70 mg injections with IFU</td>
<td>4/95</td>
<td>CINN-S (1; session 1—failed on both injections) HAIE-S (1; session 1—failed on both injections; 1, session 2—failed on 1st injection only) PINE-S (1; session 1—failed on 1st injection only)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **IFU confusion:**
  - One participant stated that they thought Step H in the IFU was directing them to press the AI until the skin stops moving (instead of until the AI stops moving). The study moderator noted that the participant failed on both injections but did hold the second AI to the site longer than the first. The participant indicated that they did not hold the AI down long enough because they believed that the word “autoinjector” meant that the medicine would be administered quickly.
  - One participant noted Step H in the IFU, ‘Firmly push … down’, did not make it clear that there was a firm resistance and that they had to apply more pressure.
  - One participant stated that because the needle guard was not called out in the steps that instruct how to hold the AI (G and H), they did not realize that the AI needed to be pushed down hard enough to compress the needle guard.
  - One participant indicated that they believed Step H in the IFU (e.g. “Firmly push...down”) mean to press firmly into the skin.
- **Study artifact:** Two participants were confused regarding the scenario and whether to simulate the use task
  - “I was simulating…I wasn’t sure if it was an actual (continued to next row below)”

Reference ID: 4238517
| Two 70 mg injections with IFU + RG | 2/96 | HAIE-S (1, session 1--failed on both injections), PINN-S (1, session 2--failed on 1st injection only) | device or it was just to demonstrate what my technique would be”. After moderator intervention, the participant was able to successfully administer the injections.  
  
  o "I thought it was a sample...They usually give you three: one to practice and get comfortable, so you don't waste the medicine practicing."

The sponsor categorized the associated task as “low risk” and noted that the consequence of this use error is failing to successfully perform the injection leading to decreased efficacy. The sponsor did not propose mitigations in response to the failures and finds the residual risk acceptable. | improved to further minimize the residual risk. We provide recommendation B.2. in Section 5.2 below to improve the instructions to press down the AI to trigger the device in Section 5.2 below. Given that this revision is intended to provide additional clarity regarding unlocking the device, we do not require additional HF validation testing. |
<table>
<thead>
<tr>
<th>Step 5. Hold until injection is complete</th>
<th>7/95</th>
<th>One 70 mg injection with IFU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7/95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CINE-M (2; session 2),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CINE-S (1, session 1),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CINN-M (1; session 2),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAIE-S (1; session 1),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PINN-S (1; session 1),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PINE-S (1, session 2)</td>
</tr>
</tbody>
</table>

18 participants did not hold the AI down long enough to allow for the injection to complete (approximately 15 seconds). The majority of the participants who failed this task noted that they did not expect the injection to take 15 seconds and/or noted confusion regarding the “click” sounds. Below, we note significant objective and subjective feedback.

- **Did not expect 15-second injection period:** Six participants stated that they did not expect the injection delay (e.g. 15 second time to completion) and some noted that the time to complete the injection is longer than from other marketed devices they were familiar with.
  - “Did not expect that delay”
  - Previous experience with other devices that inject instantly

- **Confusion regarding the click sound:** Five participants misinterpreted the 1st “click” sound as an indication that the injection was complete or were not expecting more than 1 “click” sound.
  - Heard a click sound that indicated to them that the medication was “released”

- **Did not expect 15-second injection period and confusion regarding the click sound:** Two participants stated that they did not expect the injection delay and also misinterpreted the “click” sound.
  - Expected the delivery of medication to be “instant”
  - “…even though [it] says SubQ, when I’m at work, we don’t wait the 15 seconds”

- **Study artifact:** One participant injected the AI into the
  (continued to next row below)

We disagree with the sponsor’s assessment that the failure to perform this task is low risk and that mitigations are not needed. We find the task to hold the AI down firmly until the injection is complete is a critical task. Failure of this task may pose risk of patient harm or delay of therapy if performed incorrectly or omitted and as such, should be categorized as critical.

Our review of the IFU finds that the IFU labeling includes prominent instructions and graphics to indicate to users that the injection takes up to 15 seconds. However, we find that the IFU labeling does not provide clear instruction regarding the number of “click” sounds that might be heard during the injection process (e.g. users hear a click when pressing the button and may hear a 2nd click when the injection is complete). We recommend revising the proposed Aimovig AI IFU to include the number of clicks heard to help mitigate the risk of failures leading to use error.

We provide recommendation B.3. in Section 5.2 below to improve the (continued to next row below)
| Two 70 mg injections with IFU + RG | 6/96 | CINE-M (1, session 1—failed on 1st injection only), CINE-S (1, session 1--failed on 1st injection only; 1, session 1--failed on both injections), HAIE-S (1, session 1—failed on 1st injection only), PINE-M (1, session 1--failed on 1st injection only), PINN-S (1, session 1--failed on 1st injection only) | upper portion of injection pad and injected the mannequin’s arm causing the AI needle to bend. The moderator noted that the participant held the AI for approximately 25 seconds; however, fluid sprayed from the AI. The sponsor noted that the consequence of use errors with this task is failing to successfully perform the injection leading to decreased efficacy, which the sponsor categorized as “low risk”. The sponsor did not propose mitigations in response to the failures and finds the residual risk acceptable. | IFU labeling in Section 4 below. Given that this revision is intended to provide additional clarity regarding the “click” sounds and dose completion, we do not require additional HF validation testing. |

Reference ID: 4238517
| Step 7. Dispose of AI without needle-stick injury | One 70 mg injection with IFU | 3/95 | CINE-M (1; session 1), CINE-S (1; session 2), CINN-S (1; session 2) | Nine participants discarded the AI in the trash can instead of the sharps container. None of the participants experienced a needle stick injury with this task. Several of the participants noted that they discarded the AI improperly due to habit (negative transfer) or do to forgetting to use the sharps container. The sponsor noted that the consequence of use errors with this task is the possibility of infection (e.g. due to needle stick), which the sponsor categorized as low risk. The sponsor did not propose mitigations in response to the failures. |
| | Two 70 mg injections with IFU | 4/95 | CINE-S (2; session 1) PINN-S (1; session 1), PINN-M (1; session 2) | |
| | Two 70 mg injections with IFU + RG | 2/96 | CINE-S (1; session 1) CINN-S (1; session 1) | |

While we acknowledge the residual risk of needle stick injuries, the submitted root cause information did not suggest that the user interface contributed to the failures. Based on our evaluation of use-related risks, we find the proposed AI does not have unique risks regarding its disposal as compared to other similar AI devices. In addition, we find that the IFU labeling adequately describes how to dispose of the AI. As such, we find the residual risk acceptable and have no recommendations at this time.
<table>
<thead>
<tr>
<th>Step 8. Repeat of essential steps 1 through 7 for 2 injections only (140 mg dose)</th>
<th>Two 70 mg injections with IFU</th>
<th>7/95 CINE-S (1, session 1) HAIE-M (2, session 1) PINE-S (1, session 1) CINN-M (3, session 1)</th>
<th>Twelve participants did not administer 2 injections as prescribed in the simulated-use scenario. Below we note significant objective and subjective feedback.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>IFU text difficult to visualize or unclear:</strong> One participant stated that the IFU step regarding a 2nd injection was “a little small”. Another participant noted that they read “Finish” in Step 4 of the IFU after the 1st injection, which led them to believe they were complete.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Confusion regarding dose:</strong> One participant stated that they believed that each injection was 140 mg. Another participant stated that they thought each AI held the full dose and noted that the IFU only shows the process with one AI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• <strong>Study prescription confusion:</strong> Three participants expressed confusion regarding the study prescription (e.g. one participant noted stated that they understood that the full dose was 140 mg, but believed that the 2nd injection could be administered at a different time within the same month and stated that the prescription was “a little vague”).</td>
</tr>
</tbody>
</table>
| | | | • **Unfamiliar with administering 2 consecutive injections:** One participant stated that they have never received 2 injections in a row and stated “most people would say that it’s just one injection and then you’re done”.

The sponsor’s URRA notes that failure to complete this task might result in decreased efficacy (e.g. underdose). The sponsor categorized the use errors as close calls and did not propose mitigations.

We disagree with the sponsor’s categorization of certain use errors with this task as close calls. We find the study moderator used methodology which prompted the participants to administer a second dose and as such should be categorized as failures. Specifically, in cases where the participants initially did not attempt a 2nd injection, the study moderator probed participants to inquire whether the participants administered the full dose (e.g. “Have you given the full dose of 140 mg?”), which prompted participants to complete the 2nd injection.

We note that the sponsor did not assess this task as critical. We disagree with the sponsor’s assessment that the task is not critical and that mitigations are not needed. We find the task to administer two injections to achieve one full dose pose risk of underdose if performed incorrectly or omitted and as such, should be categorized as critical.

The sponsor’s assessment of this task included any failure that occurred (continued to next row below) with the 2nd injection (including failures reported under the previously mentioned critical task).
| Two 70 mg injections with IFU + RG | 5/96 | HAIE-S (1, session 1), PINN-M (2, session 1), PINE-M (1, session 1), PINN-S (1, session 1) |

To avoid redundancy, our assessment focuses only on failures in which the participant did not attempt to administer the 2nd injection.

Our review of the Aimovig AI IFU labeling finds the labeling does not prominently inform users that 2 injections must be administered to complete a 140 mg dose. We recommend that the AI IFU labeling be improved to more prominently indicate that users must inject 2 AIs to complete the 140 mg dose. We provide recommendation B.1. in Section 5.2 below to improve the prominence of this task. Given that the modifications are intended to increase the prominence of the instruction regarding the administration of 2 AI to complete the 140 mg dose, we do not require additional HF validation testing.
IFU Knowledge Assessment

**IFU Step 1D:** If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.

<table>
<thead>
<tr>
<th>One 70 mg injection with IFU</th>
<th>6/95</th>
<th>Not fully described by the sponsor; however, we note that failures were committed by HCP, patient and caregiver participants</th>
</tr>
</thead>
</table>

Eight participants did not correctly answer the IFU knowledge assessment regarding the administration of consecutive injections. The sponsor noted that the majority of the participants were confused regarding the differentiation between different spot on an injection site vs. different injection site.

The sponsor stated that some participants indicated that they would give a subsequent injection in the same injection area as a previous injection. The sponsor also noted that during the injection task, several participants found the guidance within the IFU unclear and were unsure whether it applied to 2 injections administered on the same day or 2 injections administered one month apart. The sponsor did not propose mitigations.

We note if the associated task (e.g. injection site rotation) is not performed correctly or omitted, there may be a risk of injection site irritation. The subjective feedback provided by the participants indicate a lack of clarity in the IFU.

Our review of the IFU finds that the IFU does not clearly indicate whether the instruction to rotate the injection sites for subsequent injection applies to consecutive injections given on the same day, consecutive injections given one month apart, or both. The IFU also does not indicate whether consecutive injections should be separated by a certain distance (e.g. two inches apart). We determined that the IFU can be improved to further minimize the residual risk. **We provide recommendation B.1. in Section 5.2 to increase the clarity of the injection site rotation instructions in Section 4 below.** Given that this revision is intended to provide additional clarity surrounding the administration of consecutive injections, we do not require additional HF validation testing.

Reference ID: 4238517
<table>
<thead>
<tr>
<th>Two 70 mg injections with IFU</th>
<th>0/95</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two 70 mg injections with IFU + RG</td>
<td>2/96</td>
<td>Not fully described by the sponsor; however, we note that failures were committed by patient and caregiver participants</td>
</tr>
</tbody>
</table>

*CINN-S*: caregiver injection-naïve self-trained  
*CINE-S*: caregiver injection-experienced self-trained  
*HAIE-S*: HCP autoinjector-experienced self-trained  
*PINN-S*: patient injection-naïve self-trained  
*PINE-S*: patient injection-experienced self-trained  
*CINN-M*: caregiver injection-naïve moderator-trained  
*CINE-M*: caregiver injection-experienced moderator-trained  
*HAIE-M*: HCP autoinjector-naïve moderator-trained  
*PINN-M*: patient injection-naïve moderator-trained  
*PINE-M*: patient injection-experienced moderator-trained
4  LABELS AND LABELING

4.1  AIMOVIG PRESCRIBING INFORMATION

Our review of the Aimovig Prescribing Information identified the following areas of needed improvement that should be addressed to decrease the risk of medication error.

1. The Prescribing Information does not include the conditionally acceptable nonproprietary name suffix ‘aooe’.
2. The Highlights of Prescribing Information and Section 2.1 Recommended Dosing use an abbreviation (e.g. “QM”) that might confuse users.
3. Section 3 Dosage Forms and Strengths does not correctly display the product strength.

4.2  AIMOVIG PREFILLED SYRINGE AND AUTOINJECTOR CONTAINER LABEL AND CARTON LABELING

Our review of the proposed carton labeling and container labels for the Aimovig PFS and AI identified the following areas, which should be improved to decrease risk of medication error:

1. The container label and carton labeling do not include the trade name Aimovig.
2. The presentation of the trade name, proper name, and dosage form on the container label and carton labeling is not displayed in the proper format.
3. The strength display on the carton labeling lack prominence, which pose risk of wrong strength medication error.
4. The storage information on the container label does not contain the temperature scale designation (i.e., “°C”) after each numerical value.
5. The carton labeling references the total dose of Aimovig which may be confused with the product strength, which pose risk of wrong dose errors.

We communicated the aforementioned carton labeling and container label revisions to the sponsor via email correspondence on November 20, 2017.

(c) Labeling PMR/PMC Discussion Comments for Aimovig BLA 761077. Silver Spring (MD): FDA, CDER, OND, ODE I, DNP (US); 2017 NOV 20.
5 CONCLUSION & RECOMMENDATIONS

Based on the results of the HF validation studies for the Aimovig PFS and AI, we have determined that additional changes to the IFU are needed to minimize the risk for medication error and to provide clarity. Given that the proposed revisions are editorial in nature and are intended to provide clarity and increase the prominence of the instruction regarding the safe and effective use of the product, these changes can be implemented without requiring additional human factors testing. In addition, we have several recommendations for the PI. We advise our proposed recommendations are implemented prior to approval of this BLA.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. We recommend that the Prescribing Information is updated throughout to include the nonproprietary name suffix ‘aooe’.
   2. We note that the Highlights of Prescribing Information and Section 2.1 Recommended Dosing include the abbreviation “QM” to indicate once monthly dosing. This abbreviation might not be readily understood by users and might increase the risk for incorrect frequency of administration errors. As such, we recommend that all instances of the abbreviation “QM” are deleted.
   3. We recommend that the strength display in Section 3 Dosage Forms and Strengths be revised from “70 mg/1 mL” to “70 mg/mL’ in accordance with USP General Chapter <1>.

5.2 RECOMMENDATIONS FOR AMGEN

Our review of the carton labeling, container labels, Instructions for Use, and HF Validation study results identified areas of concerns that require additional modifications to ensure the safe and

---

\(^d\) Jawidzik, L. Email to Ebony Whaley. Silver Spring (MD): FDA, CDER, ODE I, DNP (US); 2018 FEB 16.
effective use of your product. Given that the proposed revisions are editorial in nature and are intended to provide clarity and increase the prominence of the instruction regarding the safe and effective use of the product these revisions can be implemented without additional human factors validation studies. We recommend the following:

A. Aimovig Prefilled Syringe (PFS) Instructions for Use (IFU)

1. Step 1D informs users that they should not inject the same spot on an injection site that was used for a previous injection. However, subjective feedback from the HF validation studies provides that the IFU does not clearly indicate whether this instruction applies to consecutive injections given on the same day, consecutive injections given one month apart, or both. The IFU also does not indicate whether consecutive injections should be separated by a certain distance (e.g. how many inches apart). We recommend that this IFU step is clarified to mitigate the risk of injection site irritation.

B. Aimovig Autoinjector (AI) Instructions for Use

1. See recommendations A.1. and A.2. above and revise accordingly.

2. Step 3H of the Aimovig AI IFU states “Firmly push the autoinjector down onto skin until it stops moving.” We note failures in the HF validation study included participant performance and subjective feedback regarding confusion with this step. We note that the text can be improved to increase clarity and mitigate the risk of confusion. Revise the statement “Firmly push the autoinjector down onto skin until it stops moving” to “Firmly push the autoinjector down onto skin until the green safety guard stops moving.”

3. Step 3I and 3J of the Aimovig AI IFU includes a graphic depicting the injection process and the word “Click”. We note failures in the HF validation study included subjective feedback regarding confusion about the “click” sounds. We find the IFU does not clearly indicate that they may hear two separate “click” sounds during the injection process (e.g. 1st “click” sound is heard when depressing the purple button [Step I] and the 2nd “click” sound is heard upon
completion of the injection (Step J). We recommend that Step J is clarified to mitigate the risk of underdose due to users incorrectly interpreting the “click” sounds and lifting the AI prior to injection completion.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Aimovig that Amgen submitted on May 17, 2017.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Aimovig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>How Supplied</strong>&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<sup>e</sup> While our review of the submission considered the 140 mg dose, we also note that DNP is considering a 70 mg dose.

<sup>f</sup> While our review of the submission considered the 2-count carton configuration (140 mg dose), we also note that DNP is considering a 70 mg dose.
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 29, 2017, we searched the L:drive and AIMS using the terms, erenumab and AMG 334, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews relevant to this review. In the previous HF protocol review (OSE RCM No: 2015-2510 and 2016-57), we provided recommendations for the HF protocol and labels and labeling for AMG 334 70 mg/mL PFS, and 70 mg/mL AI. However, we note that sponsor did not implement the following recommendations:

1. The sponsor did not revise the HF protocol to allow participants to demonstrate that they can perform injection(s) at the correct injection site without pre-assignment. The HF study protocol states that injection pads were affixed to the participants’ body or body of a mannequin by study moderators. However, we note the knowledge assessment portion of the HF study protocol (Questions 9 and 10) asks users to identify the correct injection sites. Therefore, we find this deficiency does not preclude our ability to interpret the HF validation study results.

2. The sponsor did not revise the HF validation study protocol to allow participants to handle the product during self-training. The HF study protocol states that self-trained participants may look at the device and packaging, but will not handle them. Although not reflective of actual use, this deficiency does not preclude our ability to interpret the HF validation study results.


APPENDIX C. HUMAN FACTORS STUDY

See Human Factors Validation Study results for detailed information on study design and reported results:

\cdsesub1\evsprod\bla761077\0001\m3\32-body-data\32r-reg-info\rpt-025106-device-configuration-pfs.pdf

\cdsesub1\evsprod\bla761077\0001\m3\32-body-data\32r-reg-info\rpt-025417-device-vendor-ai.pdf
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Aimovig labels and labeling submitted by Amgen on May 17, 2017, September 22, 2017, and March 5, 2018.

- Container label
- Carton labeling
- Instructions for Use (Image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

- Container label (prefilled syringe)

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

/s/

EBONY A WHALEY
03/23/2018

LOLITA G WHITE
03/23/2018

QUYNH NHU T NGUYEN
03/23/2018

Reference ID: 4238517
**INTERCENTER CONSULT MEMORANDUM**

<table>
<thead>
<tr>
<th>Date</th>
<th>January 2, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To</strong></td>
<td>Quinou Barry</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Quinou.Barry@fda.hhs.gov">Quinou.Barry@fda.hhs.gov</a></td>
</tr>
<tr>
<td></td>
<td>OMPT/CDER/OPQ/OPRO/DRBPMI/RGBPMI</td>
</tr>
<tr>
<td></td>
<td>240-402-8257</td>
</tr>
<tr>
<td><strong>Requesting Division</strong></td>
<td>CDER</td>
</tr>
<tr>
<td><strong>From</strong></td>
<td>Robert Meyer</td>
</tr>
<tr>
<td></td>
<td>CDRH/ODE/DAGRID/GHDB</td>
</tr>
<tr>
<td><strong>Through (Team Lead)</strong></td>
<td>John McMichael</td>
</tr>
<tr>
<td></td>
<td>CDRH/ODE/DAGRID/GHDB</td>
</tr>
<tr>
<td><strong>Through (Branch Chief)</strong></td>
<td>CDR Alan Stevens</td>
</tr>
<tr>
<td></td>
<td>CDRH/ODE/DAGRID/GHDB</td>
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<tr>
<td><strong>Subject</strong></td>
<td>Consult for Submission # BLA761077</td>
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<tr>
<td><strong>Recommendation</strong></td>
<td>Approval</td>
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## Digital Signature Concurrency Table

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Robert Meyer -A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Team Lead</strong></td>
<td>John C. Mcmichael -S</td>
</tr>
<tr>
<td>Date: 2018.01.10 08:07:13 -05'00'</td>
<td></td>
</tr>
<tr>
<td><strong>Branch Chief</strong></td>
<td>Alan M. Stevens -S</td>
</tr>
<tr>
<td>Date: 2018.01.10 09:16:29 -05'00'</td>
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1. Submission Overview

<table>
<thead>
<tr>
<th>Table 1. Submission Information</th>
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<tbody>
<tr>
<td>ICCR # (Lead)</td>
</tr>
<tr>
<td>ICC tracking # (Lead)</td>
</tr>
<tr>
<td>Submission Number</td>
</tr>
<tr>
<td>Sponsor</td>
</tr>
<tr>
<td>Drug/Biologic</td>
</tr>
<tr>
<td>Indications for Use</td>
</tr>
<tr>
<td>Device Constituent</td>
</tr>
<tr>
<td>Related Files</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Review Team</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below is a list of the Discipline Specific ICCR# and CON#. The CON# are under ICC1700446 in CTS.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discipline Specific Consults</th>
<th>Reviewer Name (Center/Office/Division/Branch)</th>
<th>ICC (Shell)</th>
<th>ICCR #</th>
<th>CON #</th>
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<tbody>
<tr>
<td>N/A</td>
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<table>
<thead>
<tr>
<th>Table 3. Important Dates</th>
</tr>
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<tbody>
<tr>
<td>Information Requests Sent</td>
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<table>
<thead>
<tr>
<th>Review Checkpoints</th>
<th>Meeting / Due Date</th>
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<tbody>
<tr>
<td>Filing</td>
<td>7/14/17</td>
</tr>
<tr>
<td>74-Day Letter</td>
<td>7/28/17</td>
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<tr>
<td>Mid-Cycle</td>
<td>11/17/17</td>
</tr>
<tr>
<td>Primary Review / Lead Device Review</td>
<td>1/17/18 per email on 9/13/17</td>
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<tr>
<td>Internal Meeting</td>
<td>N/A</td>
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<tr>
<td>Safety Meeting</td>
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<tr>
<td>Sponsor Meeting</td>
<td>N/A</td>
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<tr>
<td>Written Responses Due</td>
<td>N/A</td>
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</tbody>
</table>
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   2.2. Indications for Use ................................................................................................................................... 4
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2. PURPOSE/BACKGROUND

2.1. Scope

CDER requests: “Requesting a review for device.”

The Sponsor states [cover letter dated May 17, 2017]: “Amgen is seeking to market erenumab for the indication of prophylaxis of migraine in adults. The proposed dose of 140 mg offers the most clinically meaningful benefit to patients across the entire spectrum of migraine [episodic migraine (EM) and chronic migraine (CM)] coupled with a good safety and tolerability profile. The dosing regimen of 140 mg is to be administered subcutaneously every month by two 70 mg pre-filled syringes or SureClick® autoinjectors.”

2.2. Indications for Use

<table>
<thead>
<tr>
<th>Combination Product</th>
<th>Indications for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erenumab</td>
<td>[TRADENAME] is indicated for prevention of migraine in adults.</td>
</tr>
<tr>
<td>70 mg pre-filled syringes or SureClick® autoinjectors</td>
<td>140 mg once monthly administered as two consecutive subcutaneous injections of 70 mg each using the single-dose prefilled autoinjector or single-dose prefilled syringe.</td>
</tr>
</tbody>
</table>

3. ADMINISTRATIVE

3.1. Documents Reviewed

<table>
<thead>
<tr>
<th>Document Title / Number</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover Letter</td>
<td>GSR - 0001</td>
</tr>
<tr>
<td>draft-labeling-text.pdf</td>
<td>GSR - 0001</td>
</tr>
<tr>
<td>(4x) Instructions for Use documents</td>
<td>GSR - 0001</td>
</tr>
<tr>
<td>container-closure-system-dev-risk-aipen.pdf</td>
<td>GSR – 0001- 3.2.P.7</td>
</tr>
<tr>
<td>rpt-061505-device-commercial-pfs.pdf</td>
<td>Linked to Reviewer Guide</td>
</tr>
<tr>
<td>rpt-057223-device-autoinjector-ai.pdf</td>
<td>Linked to Reviewer Guide</td>
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<tr>
<td>Container-closure-system-dev-val-pfs.pdf</td>
<td>Linked to Reviewer Guide</td>
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<tr>
<td>Container-closure-system-dev-ver-pfs.pdf</td>
<td>Linked to Reviewer Guide</td>
</tr>
<tr>
<td>summary-clin-safety.pdf</td>
<td>Linked to Reviewer Guide</td>
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<tr>
<td>container-closure-system-dev-val-pfs.pdf</td>
<td>Linked to Reviewer Guide</td>
</tr>
<tr>
<td>specifications-pfs.pdf (lot release specs)</td>
<td>Linked to Reviewer Guide</td>
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<tr>
<td>batch-analyses-70mg-pfs.pdf</td>
<td>Linked to Reviewer Guide</td>
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<tr>
<td>container-closure-system-device-ai-pen.pdf</td>
<td>Linked to Reviewer Guide</td>
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</tbody>
</table>
## 4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

<table>
<thead>
<tr>
<th>Device Characteristic</th>
<th>Description / Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injector Name</td>
<td>“Trade Name”</td>
</tr>
<tr>
<td>Injector Platform Name</td>
<td>Sure Click</td>
</tr>
<tr>
<td>Priming Dose / Volume</td>
<td>N/A</td>
</tr>
<tr>
<td>Dose accuracy</td>
<td>[b] (4) mL</td>
</tr>
<tr>
<td>Injection Time</td>
<td>[b] (4) seconds</td>
</tr>
<tr>
<td>Injection Site</td>
<td>Thigh, stomach, upper arm</td>
</tr>
<tr>
<td>Injection tissue and depth of injection</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Audible / visual feedback</td>
<td>Yes</td>
</tr>
<tr>
<td>Cap Removal Force</td>
<td>[b] (4) N</td>
</tr>
<tr>
<td>Activation Force</td>
<td>[b] (4) Kgf</td>
</tr>
<tr>
<td>Visibility of medication container</td>
<td>Yes</td>
</tr>
<tr>
<td>Last Dose Specifications and Safety Features</td>
<td>N/A</td>
</tr>
<tr>
<td>Needle Specifications</td>
<td>27G needle, [b] (4) mm needle extension depth.</td>
</tr>
<tr>
<td>Length(s)</td>
<td></td>
</tr>
<tr>
<td>Gauge(s)</td>
<td></td>
</tr>
<tr>
<td>Connection type</td>
<td>ISO 11608-2:2012</td>
</tr>
<tr>
<td></td>
<td>Prestaked</td>
</tr>
<tr>
<td>Type of Use (e.g. single use, disposable, reusable,</td>
<td>Single use and disposable</td>
</tr>
<tr>
<td>other)</td>
<td></td>
</tr>
<tr>
<td>Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)</td>
<td>Single dose</td>
</tr>
<tr>
<td>Injection mechanism (e.g., manual piston, spring, gas, etc.)</td>
<td>[b] (4)</td>
</tr>
<tr>
<td>Method of actuation</td>
<td>Manual</td>
</tr>
<tr>
<td>Automated Functions</td>
<td>Needle Shield</td>
</tr>
<tr>
<td>Residual Medication</td>
<td>[b] (4) mL</td>
</tr>
<tr>
<td>Delivered Volume (for single dose or selectable volume range for multidose pens)</td>
<td>Single dose - 70 mg/1 mL</td>
</tr>
<tr>
<td>Drug Container Type</td>
<td>Glass</td>
</tr>
<tr>
<td>Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)</td>
<td>1 mL</td>
</tr>
</tbody>
</table>
Environments of use | Non Healthcare or Clinical
---|---
Storage conditions and expiry | Refrigerate from 2 to 8°C
Graduation marks / fill lines | N/A
Preparation and administration (describe all that are applicable) | Warm to room temperature for 30 minutes
- Warm to room temp prior to injection
- Assembling components
- Prime steps
- Setting dose
- Skin preparation steps (e.g., pinch skin, inject through clothing, etc.)
- Changing / disposing needles
- Etc.
Safety Features | Needle Shield
- Needle safety
Electronics / Data transmission | N/A
- Display
- Control functions
- Data transmission technology
- Data being transferred
Material composition of injector | [b (4)] and Glass

The Sponsor is proposing to market a 70 mg/1 mL sterile, clear, colorless solution in a single-dose prefilled syringe and a 70 mg/1 mL sterile, clear, colorless solution in a single-dose prefilled SureClick® autoinjector for subcutaneous administration of Erenumab. The Sponsor states the devices are for self-administration after training from a healthcare provider.

**Prefilled Syringe**

The Sponsor states the PFS is a commercially available syringe assembly with barrel, staked needle and hermetically sealed needle shield (i.e. Primary Container). The components are sourced from [b (4)]. The Sponsor finishes the PFS combination product [b (4)]. The commercial configuration includes a finger flange with a back stop feature.
The PFS (Figure 1) is a single-use, disposable, handheld drug delivery device for patients. The system incorporates the following components:

- Plunger Rod
- Flange Extender
- Plunger-Stopper
- Glass Syringe Barrel
- Needle
- Rigid Needle Shield

![Figure 1. Prefilled Syringe and Components](image)

Table 1. PFS Conditions of Use

<table>
<thead>
<tr>
<th>Item</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic product for injection</td>
<td>AMG 334 only, for subcutaneous injection</td>
</tr>
<tr>
<td>Dosage capability</td>
<td>Single dose: 1.0 ml of 70 mg/mL</td>
</tr>
<tr>
<td>Method of injection</td>
<td>Manual delivery</td>
</tr>
<tr>
<td>Environment of use conditions</td>
<td>Non-Healthcare or Clinical Environments</td>
</tr>
<tr>
<td>Storage</td>
<td>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze.</td>
</tr>
<tr>
<td>Handling</td>
<td>Acclimate to room temperature by setting out at room temperature for 30 minutes. Protect from light. Do not shake.</td>
</tr>
</tbody>
</table>

**Autoinjector (document: container-closure-system-device-ai-pen.pdf)**

The SureClick device is single-use, disposable, handheld, mechanical injection device that administers a fixed dose of drug product into subcutaneous tissue and is intended for patients or caregivers in a non-healthcare environment. The device automatically performs the injection of the drug product within a predetermined period of time after the user has activated the device. The device automatically covers the needle after completion of the injection to reduce the potential for needle-stick injury. It is noted that the prefilled syringe is part of the autoinjector assembly, yet the needle used in the autoinjector is a "

![Figure 1. Autoinjector/Pen (AI/Pen)](image)
5. CLINICAL DEVELOPMENT

The Sponsor states the subject drug was evaluated in 13 clinical studies. This includes 7 phase 1 studies; 4 controlled efficacy and safety studies in subjects with migraine (3 of which include open-label or active treatment extension phases), 1 stand-alone open-label extension study that enrolled eligible CM subjects completing the fourth controlled study; and 1 ongoing phase 2 cardiovascular (stable angina) study.

The Sponsor provides the following Clinical Summary in the “Draft Labeling” document:

Reviewer notes: Multiple clinical studies, including the phase 3 studies, used the to-be-marketed 70 mg/mL PFS, while the to-be-marketed 70 mg/mL AI/pen was used in a bioequivalence study and two clinical home use sub-studies, thus the device validation is acceptable.

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

The Sponsor documents that they have adequately verified and validated the subject prefilled syringes and SureClick autoinjector for subcutaneous administration of Erenumab. In summary the Sponsor validates the design in several clinical studies acceptably; the few failures noted were not due to device failures or misunderstandings. The verification provided demonstrates the devices are able deliver the complete dose after applicable preconditions, such as expiry and shipping, were applied. In addition to the verification, Amgen documents that all lots will be monitored adequately by evaluating acceptable sample sizes from each lot for critical design and functional attributes. In conclusion, it is recommended that the subject devices are approved for use as instructed in the provided labeling.
6.1.1. Design Control Documentation Check

<table>
<thead>
<tr>
<th>Design Control Requirement*</th>
<th>Signed/Dated Document Present</th>
<th>Submission Location</th>
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<tbody>
<tr>
<td>Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer</td>
<td>X</td>
<td>container-closure-system-dev-ver-ai.pdf</td>
</tr>
<tr>
<td>Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.</td>
<td>X</td>
<td>container-closure-system-dev-ver-ai.pdf reviewer-guide.pdf</td>
</tr>
<tr>
<td>Risk Analysis supplied in the NDA / BLA by the Combination Product Developer</td>
<td>X</td>
<td>container-closure-system-dev-risk-pfs.pdf</td>
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</tbody>
</table>
| Validation Data  
|  - Clinical data | X | |
| Traceability Documentation | X | reviewer-guide.pdf |

6.1.2. Design Controls

The Sponsor identifies the intended use, intended user population, clinical requirements, and it is evident these aspects are considered throughout the design process. The Sponsor summarizes how procured components are cleaned and sterilized as well as certified. Essential components of the primary container are noted to conform to applicable standards. In addition, to the in process design controls established by vendors, the process completes lot release testing to verify essential design functions.

Reviewer notes: The documentation adequately demonstrates Amgen applies design controls throughout the entire design, manufacturing and release process.

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

<table>
<thead>
<tr>
<th>Design Verification / Validation Attributes</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation of essential requirements covered by clinical and human factors testing</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To-be-marketed device was used in the pivotal clinical trial</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Verification methods relevant to specific use conditions as described in design documents and labeling  X
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry  X
Traceability demonstrated for specifications to performance data  X

### Discipline Specific Design Verification / Validation*

<table>
<thead>
<tr>
<th>Discipline Specific Design Verification / Validation*</th>
<th>Consult Needed</th>
<th>Consultant</th>
<th>Attributes Acceptable</th>
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</thead>
<tbody>
<tr>
<td>Engineering (Materials, Mechanical, General)</td>
<td>X</td>
<td>N/A</td>
<td>X</td>
</tr>
<tr>
<td>Biocompatibility</td>
<td>X</td>
<td>N/A</td>
<td>X</td>
</tr>
<tr>
<td>Sterility</td>
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</tr>
<tr>
<td>Software / Cybersecurity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical Safety / EMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human Factors</td>
<td>X</td>
<td>N/A</td>
<td>X</td>
</tr>
</tbody>
</table>

### Standards / Guidance Conformance

<table>
<thead>
<tr>
<th>Standards / Guidance Conformance</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 11608-2:2012 – Needles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISO 11608-5:2012 – Automated Functions</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 7.2. Design Validation Review

<table>
<thead>
<tr>
<th>Design Validation Attributes</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I/II/III Study utilized the to-be-marketed device</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Study utilized to-be-marketed device</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Simulated Actual Use Study utilized to-be-marketed device</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Prefilled Syringe Validation**

The Sponsor completed a Summative Human Factors study using the prefilled syringe. They state the study applied the following standards and guidance:

- IEC 62366:2007/(R) 2013, Medical Devices - Application of Usability Engineering to Medical Devices
- AAMI HE75:2009, Human Factors Engineering - Design of Medical Devices

The Sponsor states “The primary objective was to demonstrate that the AMG 334 PFS intended user populations can safely and effectively operate the device to deliver a complete dose without harm to themselves or to others, and without repeatable patterns of use errors resulting in failures, close calls, operational difficulties, and intentional misuse.”

The summative study evaluated 95-individual users which were intended to represent the user population; the study included patients (N=34), caregivers (N=31) and HCPs (N=30). The Sponsor states “the primary objective was to demonstrate that the AMG 334 PFS intended user populations can safely and effectively operate the device to deliver a complete dose without harm to themselves or to others, and without repeatable patterns of use errors resulting in failures, close calls, operational difficulties, and intentional misuse.”

The prefilled syringe summative study results are summarized in the following table:

**Autoinjector Validation**

**Device Design Validation Overview**

The design validation protocol was developed based on the User Needs Requirements and the Validation Plan. The results of the validation testing are recorded in the AMG 334 AI/Pen Usability Engineering File Summary Report. It documents any discrepancies, exceptional conditions, or failures and their resolution. This section summarizes relevant information from the report.
Known Use Problems

The known use problems for this type of device can be summarized as:

• Failure to remove the cap resulting in an inability to insert the needle into the skin and inject (missed dose)

• Holding the device upside down while initiating the injection process, resulting in an inability to start the injection and/or spraying medication toward the user’s face, or injecting into the user’s thumb (needle stick injury potentially resulting in injection and/or missed dose)

• Premature lifting of the autoinjector from the injection site resulting in drug spraying onto skin surface and potential incomplete or missed dose.

Risk Assessment and Task Prioritization

Under Amgen’s risk management program, Device Risk Management Summary [AI/Pen], use-related hazards were identified based on the design inputs and conditions of use. A user Risk Assessment (uRA) was conducted to determine the level of risk associated with particular use errors resulting in failures, close calls, operational difficulties, and intentional misuse with the device and user interface. The (human factors) assessment was based on the intended user population and takes into consideration the device user interface and use environments.

Based on the risk assessment for AMG 334 AI/Pen, the use-related steps were identified as essential (required in order to successfully complete an injection per the device’s intended design), or non-essential, and were assigned with appropriate risk levels. There were no safety-critical steps identified as no hazards identified in the uRA had a risk rating of high or critical, or a severity level of critical (7) or catastrophic (9). These use-related steps were evaluated in the HF summative study to confirm that the risks

Study Samples and populations

<table>
<thead>
<tr>
<th>Table 2. Study Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Count Carton w/ IFU</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Self-Trained</td>
</tr>
<tr>
<td>Moderator-Trained</td>
</tr>
<tr>
<td>Caregivers</td>
</tr>
<tr>
<td>Self-Trained</td>
</tr>
<tr>
<td>Moderator-Trained</td>
</tr>
<tr>
<td>HCPs</td>
</tr>
<tr>
<td>Self-Trained</td>
</tr>
<tr>
<td>Moderator-Trained</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
Reviewer notes: The summative human factors testing for the prefilled syringe and auto injector adequately validates the functions of the device, yet acceptance is ultimately deferred to DMEPA. The testing evaluates an acceptable sample population and sample size, and the critical steps assessed are acceptable.

7.3. Design Verification Review

Prefilled Syringe Verification

The Sponsor completed prefilled syringe design verification intended to demonstrate the design output meets the design input requirements and specifications. The design verification testing included evaluation of biocompatibility, functional/performance attributes and the effects of transportation.

Amgen identifies that the plunger rod and flange extender are not part of the primary container and only come into contact with the user, thus they evaluated per ISO 10993-1 with a classification of surface device, intact skin with limited contact duration. Biocompatibility testing performed on the plunger rod and flange extender is summarized in Table 2 and detailed in the following sub-sections.

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Method Description</th>
<th>Acceptance Criteria</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxicity</td>
<td>ISO 10993-5 Tests for Cytotoxicity</td>
<td>according to ISO 10993-5 Section 8.5</td>
<td>Pass</td>
</tr>
<tr>
<td>Sealing</td>
<td>ISO 10993-5 Tests for Seemanship and Intimacy</td>
<td>according to ISO 10993-10 Section 7.6</td>
<td>Pass</td>
</tr>
<tr>
<td>Irritation</td>
<td>ISO 10993-10 Tests for Irritation and Irritation</td>
<td>according to ISO 10993-10 Section 6.5</td>
<td>Pass</td>
</tr>
</tbody>
</table>

Reviewer notes: The biocompatibility test summaries for the extender and plunger rod were reviewed and are in-line with criteria in the 510(k) smart template biocompatibility checklist. Ultimately the biocompatibility acceptance is deferred to CDER; if the drug is stable and compatible after contact with the container, CDRH typically considers the device biocompatible. To further support biocompatibility the components are supplied by a creditable vender are well known biocompatible materials, and are marketed for similar products.

PFS Functional Verification

The Sponsor states the testing tabled below is completed after testing per shipping standard ASTM D4169. In addition to the tabled testing, the Sponsor states Deliverable volume is was verified [From container-closure-system-dev-ver-pfs.pdf].
The following is summarized from “trpt-026802-device-clinical-pfs.pdf”. Amgen completed functional verification testing using 70mg devices which were precondition to temperature limits of 5°C and 40°C (see table 5.3 in the noted document). The break loose force, extrusion force, and needle shield removal forces are summarized in the table provided above (Table 5). The delivered volume accuracy results are tabulated below; all 60 samples delivered the specified dose (10.0±0.4mL).

### Table 5: Summary of Device Functional/Performance Verification Testing for PFS

<table>
<thead>
<tr>
<th>Test Method Description</th>
<th>Acceptance Criteria (AC) &amp; Confidence Interval (CI)</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package Transport Temp.</td>
<td>Functionality: Break Loose</td>
<td>AC: 10 N ± 2 N</td>
</tr>
<tr>
<td>Package Transport Temp.</td>
<td>Needle Shield Removal Force</td>
<td>AC: 10 N ± 2 N</td>
</tr>
</tbody>
</table>

### Table 6: Calculated Deliverable Volume for Drug Configuration (Flow data in Appendix 1)

<table>
<thead>
<tr>
<th>70mg Data (Drug product density)</th>
<th>70mg Data (Drug product density)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Mass (g)</td>
</tr>
<tr>
<td>1</td>
<td>16.5</td>
</tr>
<tr>
<td>2</td>
<td>17.2</td>
</tr>
<tr>
<td>3</td>
<td>18.1</td>
</tr>
<tr>
<td>4</td>
<td>16.9</td>
</tr>
<tr>
<td>5</td>
<td>20.0</td>
</tr>
<tr>
<td>6</td>
<td>21.1</td>
</tr>
<tr>
<td>7</td>
<td>22.2</td>
</tr>
<tr>
<td>8</td>
<td>23.3</td>
</tr>
<tr>
<td>9</td>
<td>24.4</td>
</tr>
<tr>
<td>10</td>
<td>25.5</td>
</tr>
<tr>
<td>11</td>
<td>26.6</td>
</tr>
<tr>
<td>12</td>
<td>27.7</td>
</tr>
<tr>
<td>13</td>
<td>28.8</td>
</tr>
<tr>
<td>14</td>
<td>29.9</td>
</tr>
<tr>
<td>15</td>
<td>30.0</td>
</tr>
</tbody>
</table>

### Auto-injector verification

<table>
<thead>
<tr>
<th>Essential Performance Requirement</th>
<th>Specification</th>
<th>Verification</th>
<th>Validation</th>
<th>Aging/ Stability (Y/N)</th>
<th>Shipping/ Transportation (Y/N)</th>
<th>Lot Release Testing (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
<td>-----------------------------------</td>
<td>-----------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Injection Time</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose Accuracy</td>
<td>mL</td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation Force</td>
<td>Kgf</td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needle Length</td>
<td>mm</td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needle Gauge</td>
<td>27 G</td>
<td>COC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Needle Connection Type</td>
<td></td>
<td>COC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Needle Resistance to Bend / Fracture</td>
<td>Unknown</td>
<td>COC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cap Removal Force</td>
<td>N</td>
<td>(b) (4)</td>
<td></td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From: container-closure-system-dev-ver.ai.pdf

Amgen states “The design verification testing includes evaluation of biocompatibility, functional/performance, physical attributes, and effects of transportation. The testing was performed.
following design verification protocols that were developed based on the approved design input requirements.” The following summarizes the testing completed.

**Biocompatibility**

Amgen identifies the materials tables below as patient contacting, and completed testing per cytotoxicity, sensitization, and irritation requirements within ISO 10993-5 and ISO 10993-10 to demonstrate biocompatibility.

![Image of Table 1](image1.png)

![Image of Table 2](image2.png)

**Reviewer notes:** The biocompatibility study summaries were reviewed per criteria identified in the 510(k) smart template biocompatibility checklist and is considered acceptable.

**Functionality**

In document container-closure-system-dev-ver-ai.pdf Amgen summarizes all of the autoinjector functional verification testing completed using the proposed marketed devices. With different boundary conditions applied, such as temperature boundaries, vibration, free fall, shipping, and accelerated aging, Amgen has completed testing to verify the delivered volume repeatability, shield removal force, needle cover protection pre-injection force, activation force, needle extension length, needle cover override force, and separation force functions/features; the associated reports are with document “trpt-026584-device-d1-system-ai.pdf”, “trpt-026724-device-transportation-ai.pdf”, and [redacted]. In addition to the functional verification, Amgen states all units pass the following visual criteria: All product markings on the DUT are legible (if applicable), no cracks in the body and/or components of the DUT that might impact safe functioning, no compromised assembly bonds, joint and alignments that might impact safe functioning, the drug product in the window is clear and colorless, the needle cap is present and securely attached. The table below is a sample of the summarized tables:
Review notes: The design verification is acceptable. Amgen verified applicable functions and features among an acceptable sample size after foreseeable conditions are applied. The results provided demonstrate the autoinjector functions as intended.

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

N/A

9. RISK ANALYSIS

9.1 Risk Analysis Attributes

<table>
<thead>
<tr>
<th>Risk Analysis Attributes</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk analysis conducted on the combination product</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitigations are adequate to reduce risk to health</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9.2. Summary of Risk Analysis

The Sponsor states their Risk Management Plan applies to each combination product and continues throughout the life of the combination product. The deliverables from the process are archived in the Design History File for each combination product and are listed below.

- Risk Management Plan
- Characterization of Harms Report
- Use Risk Assessment Report
- System Risk Assessment Report
- Design FMEA Report
- Process FMEA Report
- Risk Benefit Analysis
- Risk Management Report
- Risk Management File

The following severity and likelihood ratings were applied to all identified risk to determine the overall safety of the devices to the end users.

<table>
<thead>
<tr>
<th>Severity Rating</th>
<th>Severity Terms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Severe</td>
<td>Catastrophic - Results in patient death</td>
</tr>
<tr>
<td>7</td>
<td>Major</td>
<td>Critical - Results in permanent impairment or life threatening injury</td>
</tr>
<tr>
<td>5</td>
<td>Moderate</td>
<td>Serious - Results in injury or impairment requiring professional medical intervention</td>
</tr>
<tr>
<td>3</td>
<td>Minor</td>
<td>Minor - Results in temporary impairment not requiring professional intervention</td>
</tr>
<tr>
<td>1</td>
<td>Insignificant</td>
<td>Negligible - Results in an inconvenience, annoyance, or temporary discomfort</td>
</tr>
</tbody>
</table>

Prefilled Syringe Risk Management
The table below categorizes risks associated to the PFS which were identified, and assessed using the criteria shown above. The risks identified for the pre-filled syringe are in document “rpt-061505-device-commercial-pfs.pdf”. Risks identified are associated to the device functions, manufacturing, user processes and understandings, and environmental safety.
Autoinjector Risk Management
The risks identified for the Autoinjector are in document “rpt-057223-device-autoinjector-ai.pdf”. Each risk identified was ranked per the aforementioned criteria. The Sponsor states 79 total risks identified (4 medium risks and 75 low risks). Risks identified are associated to the device functions, manufacturing, user processes and understandings, and environmental safety. The high-level hazards associated with the AI are tabulated below.

<table>
<thead>
<tr>
<th>Hazard ID</th>
<th>Hazard</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1</td>
<td>User cannot successfully complete injection</td>
<td>User does not understand how to use the combination product</td>
</tr>
<tr>
<td>1.2.3</td>
<td>User cannot successfully complete injection</td>
<td>User disregards or only reads part of the IFU and delivers wrong number of injections (Applicable for 2 pack)</td>
</tr>
<tr>
<td>1.1.1.4</td>
<td>Patient does not receive the intended dose</td>
<td>User disregards or only reads part of the IFU and delivers wrong number of injections (Applicable for 2 pack)</td>
</tr>
<tr>
<td>1.4.13</td>
<td>Inability to properly unlock and activate the device</td>
<td>User cannot create a firm injection site</td>
</tr>
<tr>
<td>1.4.15</td>
<td>Soft skin does not compress needle cover, leading to inability to unlock/activate device</td>
<td>Skin is soft at injection site and user does not stretch skin taut or use the pinch technique</td>
</tr>
<tr>
<td>1.4.20</td>
<td>User does not receive the intended dose</td>
<td>User does not take two injections as prescribed (applicable to two pack)</td>
</tr>
<tr>
<td>1.5.2</td>
<td>3rd party or user needle stick</td>
<td>Improper disposal of the used device</td>
</tr>
<tr>
<td>1.4.2</td>
<td>User cannot successfully complete injection</td>
<td>User cannot/doesn’t remove needle cap (needle shield remover)</td>
</tr>
<tr>
<td>1.4.23</td>
<td>Incomplete injection</td>
<td>User lifts the device from the injection site prior to injection completion</td>
</tr>
</tbody>
</table>

Reviewer notes: The risk analyses for the prefilled syringe and autoinjector are acceptable. The Sponsor identified risks from applicable perspectives, and considers risks during the development, and after use processes. In addition the Sponsor justifies some of the risks identified by relating them to a product they currently market which uses the same AI device and has a similar user population. The risk tables provided were reviewed and the associated mitigations to risks are acceptable.

10. LABELING

70mg Prefilled Syringe Instructions for Use

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
Storage and Handling [Draft Labeling]
- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use.
- If removed from the refrigerator, [TRADENAME] should be kept at room temperature (up to 25°C [77°F]) in the original carton and must be used within [b] 4 days. Throw away TRADENAME that has been left at room temperature for more than [b] 4 days.
- Do not freeze.
- Do not shake

Reviewer notes: The labeling provides acceptable instructions for device functions, however the adequacy is deferred to CDER.

11. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The Sponsor states “The AI/Pen deliverable volume and injection time are tested as a part of lot release (3.2.P.5.1 Specification [70 mg/mL AI/Pen]) to demonstrate that the assembled AI/Pen is capable of accurately delivering the full dose of drug product as intended. As a function of deliverable volume and injection time testing, the plunger rod extends into the prefilled syringe to expel the drug product. Visual confirmation of complete dose delivery is indicated once the AI/Pen plunger rod has fully extended, expelled the deliverable volume, and changed the AI/Pen viewing window from clear to yellow. The performance of these tests, coupled with the visible color change of the viewing window, demonstrates proper AI/Pen device functionality prior to lot release. Incoming vendor subassemblies intended to be used in the AI/Pen are received per the Certificate of Conformance. Prior to vendor lot release and subsequent shipment from the vendor, AI/Pen subassemblies are assembled with the Erenumab non-rigid needle shield (nRNS) prefilled syringe and undergo functionality testing for needle shield removal force, needle cover pre-injection force, activation force, deliverable volume, injection time, needle extension, needle cover override force, and separation force.

The following Lot Release Specifications for the PFS are provided in document specifications-pfs.pdf various sections of GSR001/3.2.P.5.6. The Sponsor notes 25 units per commercial lot are tested.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Method</th>
<th>Method Type</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Appearance*</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>Color</td>
<td>Color*</td>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>Clarity</td>
<td>Clarity*</td>
<td>Spectrophotometric</td>
<td></td>
</tr>
<tr>
<td>Identity</td>
<td>ELISA</td>
<td>Immunoassay</td>
<td></td>
</tr>
<tr>
<td>Purity and Impurities</td>
<td>CEX-HPLC</td>
<td>Chromatographic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SE-UHPLC</td>
<td>Chromatographic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced CE-SDS</td>
<td>Capillary electrophoresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIC-HPLC</td>
<td>Chromatographic</td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>Bioassay</td>
<td>Cell-based</td>
<td></td>
</tr>
<tr>
<td>Quantity</td>
<td>Protein concentration*</td>
<td>UV Scan</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>Deliverable volume*</td>
<td>Gravimetric</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td>Potentiometric</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osmolality*</td>
<td>Freezing point depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subvisible particles</td>
<td>Light obscuration</td>
<td></td>
</tr>
<tr>
<td>Breakloose and Extrusion</td>
<td></td>
<td>Physical (force)</td>
<td></td>
</tr>
<tr>
<td>Adventitious Agents</td>
<td>Bacterial endotoxins*</td>
<td>LAL</td>
<td></td>
</tr>
<tr>
<td>Sterility</td>
<td></td>
<td>Membrane filtration</td>
<td></td>
</tr>
</tbody>
</table>

For Breakloose and Extrusion verification the Sponsor states: “Mean break-loose force and mean maximum extrusion force are reported from the analysis of at least 10 syringes per reported result. All results are recorded and reported in Newtons (N),” (in document breakloose-extrusion-pfs.pdf - see reviewer guide: link “breakloose-extrusion-pfs.pdf”).

The following summarizes the Deliverable Volume verifications (document - deliverable-volume-pfs.pdf):
The following Lot Release Specifications for the AI are provided in document specifications-ai.pdf, and are in addition to the PFS Lot Release Specifications because the finished AI contains the PFS. It is not clarified how the injection time is measured.

<table>
<thead>
<tr>
<th>Table 1. 70 mg/mL AI/Pen Drug Product Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Device functionality</td>
</tr>
<tr>
<td>Deliverable volume</td>
</tr>
</tbody>
</table>

The Sponsor provides a summary of Batch Analysis records from manufacturing to demonstrate the manufacturing process effectively constructs assemblies per Lot Release Specifications; the image below is a select table from the tables provided (batch-analyses-70mg-pfs.pdf)

<table>
<thead>
<tr>
<th>Table 1. Process 2 (Clinical) AMG 334 Drug Product Batch Analyses (70 mg/mL PFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Method</td>
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<td>Appearance</td>
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<td>Color</td>
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<tr>
<td>Clarity</td>
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<td>Identity by ELISA</td>
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<td>Acidic Peaks (%)</td>
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<tr>
<td>Heavy Chain (% Light Chain)</td>
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<td>Sterility</td>
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<td>Protein concentration (mg/mL)</td>
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<td>Osmolality (mOsm/kg)</td>
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<td>Volume (mL)</td>
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<table>
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<tr>
<th>Table 1. Process 2 (Clinical) AMG 334 Drug Product Batch Analyses (70 mg/mL PFS)</th>
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<tbody>
<tr>
<td>Test Method</td>
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<td>Soluble particles</td>
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<tr>
<td>Break loose (N)</td>
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<tr>
<td>Extrusion (N)</td>
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</table>
Reviewer Notes:

Given the subject intended use does not involve emergency situations the Lot Release Specifications for the PFS and AI are acceptable; they coincide with functional and clinical specifications. In conjunction with the design and manufacturing controls, the specifications verify critical endpoints, thus it is reasonable to believe the released devices will function as intended.

12. RECOMMENDATION

CDRH recommends approval of the subject device constituents.
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Bonner, Kudrow, Ashina, and Rinke were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

There was some evidence of underreporting of non-serious adverse events at Drs. Kudrow’s and Ashina’s sites (please see details in Section III). The frequency of underreported adverse events was low, and most occurred in subjects randomized to placebo or in subjects participating in the open-label phase of a protocol. Therefore, although some underreporting of adverse events was noted, it is considered unlikely to affect the overall safety analyses. There was no evidence of underreporting of serious adverse events at any of the inspected clinical investigator sites.

The final compliance classification of the inspection of Dr. Bonner was No Action Indicated (NAI) and the final compliance classification of the inspection of Dr. Kudrow was Voluntary...
Action Indicated (VAI). The preliminary classification of the inspection of Dr. Rinke was NAI, and the preliminary classification of the inspection of Dr. Ashina was VAI.

II. BACKGROUND

Erenumab injection is a human monoclonal immunoglobulin G2 being developed for the prophylaxis of migraine in adults under BLA 761077. The sponsor has submitted a Phase 2 trial in chronic migraine (Protocol 20120295) and two Phase 3 trials in episodic migraine (Protocols 2010296 and 2010297) to support the efficacy and safety of erenumab for the prophylaxis of migraine in adults.

Protocol 20120295

Title: A Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 [erenumab] in chronic migraine prevention

Subjects: 667 subjects were enrolled

Sites: 67 sites in 10 countries; United States (29 sites), Western Europe (24 sites), Eastern Europe (12 sites), Canada (2 sites)


This was a Phase 2, randomized, double-blind, placebo-controlled, parallel group study in subjects with chronic migraine. Enrolled were subjects 18 to 65 years of age with a history of migraine with or without aura, ≥ 15 headache days per month, ≥ 8 migraine days per month.

Following a 3-week screening phase and a 4-week baseline phase, subjects were randomized in a 3:2:2 ratio to one of three treatment arms:

- Erenumab 70 mg subcutaneously every 4 weeks for 12 weeks
- Erenumab 140 mg subcutaneously every 4 weeks for 12 weeks
- Placebo subcutaneously every 4 weeks for 12 weeks

Clinical assessments were collected by subjects using a handheld electronic diary (DIARYpro). Data was entered into DIARYpro on a daily basis and included: incidence of headache, time of headache onset, time of headache resolution, pain features (for example: pain severity, unilateral, etc.), associated symptoms and severity (nausea, vomiting, photophobia, phonophobia), presence of aura, and use of acute medication. The primary efficacy endpoint was the change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase.
Protocol 20120296

Title: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 [erenumab] in migraine prevention

Subjects: 955 subjects were enrolled

Sites: 121 sites in 13 countries; United States (59 sites), Western Europe (39 sites), Eastern Europe (12 sites), Middle East/Central Asia (6 sites), Canada (5 sites)


This was a Phase 3, randomized, stratified, double-blind, placebo-controlled, parallel group study in subjects with episodic migraine. Enrolled were subjects 18 to 65 years of age with a history of migraine with or without aura for ≥ 12 months, < 15 headache days per month, and ≥ 4 to < 15 migraine days per month.

The study consisted of a 3-week screening phase, a 4-week baseline phase, a 24 week double-blind phase, a 28-week active treatment phase (open-label, dose blinded), and a safety follow-up visit. For the double-blind phase, subjects were randomized in a 1:1:1 ratio to one of three treatment arms:

- Erenumab 70 mg subcutaneously every 4 weeks for 24 weeks
- Erenumab 140 mg subcutaneously every 4 weeks for 24 weeks
- Placebo subcutaneously every 4 weeks for 24 weeks

Similar to Protocol 20120295, assessments were collected by subjects using DIARYpro. The primary efficacy endpoint was the change in mean monthly migraine days from baseline to the last 3 months of the double-blind treatment phase.

Protocol 20120297

Title: A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AMG 334 [erenumab] in migraine prevention

Subjects: 577 subjects were enrolled

Sites: 69 sites in 8 countries; United States (37 sites), Western Europe (28 sites), Eastern Europe (4 sites)

Study Initiation and Completion Dates: 7/20/2015 – 7/11/2016 (data cut-off date)

The study population and design were the same as for Protocol 20120296 except that there were only two treatment arms (placebo and erenumab 70 mg), the duration of the double-blind treatment phase was 12 weeks, and the 28-week active treatment phase was open-label (all subjects received erenumab 70 mg). Similar to Protocols 20120295 and 20120296, assessments were collected by subjects using DIARYpro. The primary efficacy endpoint was the change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase.
Rationale for Site Selection

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

III. RESULTS

<table>
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<tr>
<th>Site #/ Name of CI/ Address</th>
<th>Protocol #/ # of Enrolled Subjects</th>
<th>Inspection Dates</th>
<th>Classification</th>
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| Site #20721  
Jo Bonner, M.D.  
12680 Olive Boulevard  
Suite 200 and  
621 South New Ballas Road  
Suite 419A  
St. Louis, MO 63141 | Protocol 20120295  
Subjects: 17  
Protocol 20120296  
Subjects: 26 | 11-15 Dec 2017 | NAI |
| Site #43996  
David Kudrow, M.D.  
2001 Santa Monica Blvd  
Suite 880W  
Santa Monica, CA 90404 | Protocol 20120295  
Subjects: 26  
Protocol 20120297  
Subjects: 30 | 4-8 Dec 2017 | VAI |
| Site #45744  
Messoud Ashina, M.D.  
Nordre Ringvej 57  
Ringvejsblokken  
Room RB626, 6th Floor  
Enterance 8  
Glostrup, 2600  
Denmark | Protocol 20120295  
Subjects: 24  
Protocol 20120297  
Subjects: 19 | 23-27 Oct 2017 | VAI* |
| Site #30245  
Andrea Rinke, M.D.  
Harmoniestrasse 1  
Bochum 44787  
Germany | Protocol 20120296  
Subjects: 27 | 16-20 Oct 2017 | NAI* |

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.  
VAI = Voluntary Action Indicated, deviation(s) from regulations.  
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.
As discussed in greater detail below, underreporting of non-serious adverse events was an inspectional finding at the clinical sites of Drs. Ashina and Kudrow. For the Kudrow site, there were no underreported adverse events for Protocol 20120295, but there were five unreported adverse events occurring in four of 30 (13%) randomized subjects for Protocol 20120297. Two of the five unreported adverse events occurred in one subject receiving erenumab during the double-blind phase of the study, while the other three adverse events occurred during the open-label phase of the study.

For the Ashina site, there were three unreported adverse events occurring in three of 24 (12%) randomized subjects for Protocol 20120295. One of these adverse events occurred in a subject randomized to erenumab, the other three adverse events occurred in subjects randomized to placebo. There was one unreported adverse event occurring in one of 19 (5%) subject randomized to erenumab during the double-blind phase of Protocol 20120297.

For Protocols 20120295 and 20120297, the sponsor used a central monitoring paradigm that included on-site and remote monitoring of clinical sites. The sponsor was asked to submit the monitoring plans for these studies to the FDA. For on-site monitoring, CROs reviewed source documentation for informed consent and investigational product for all subjects. Data for the 1st, 4th, and 9th subject and every 4th randomized subject thereafter was selected to undergo 100% source document verification (including adverse events). The monitoring plan allowed for source document verification of additional subjects if discrepancies or issues were identified at the clinical site. Clinical investigators were encouraged, via monitoring reports, to enter data into the eCRF within 7 days of a study visit. Remote monitoring could address inconsistencies in reporting; for example, a concomitant medication entry might require a corresponding adverse event entry. Remote monitoring does not verify eCRFs against source documents (progress notes, adverse event logs, etc.).

In order to further evaluate this issue, FDA requested the sponsor to provide information from audits conducted by (or on behalf of) the sponsor for the pivotal trials for this BLA.

- Between February and November 2015, the sponsor audited five clinical sites for Protocol 20120295. The study was conducted from March 2014 to April 2016 and 667 subjects were enrolled. Records were reviewed for a total of 27 subjects. The sponsor noted three adverse events that were not recorded in eCRFs: cold/flu and back pain (2 subjects).

- Between March and December 2016, the sponsor audited 12 clinical sites for Protocol 20120296. The study was conducted from July 2015 to September 2016 and 955 subjects were enrolled. Records were reviewed for a total of 72 subjects. The sponsor noted two adverse events that were not recorded in eCRFs: common cold and toothache.

- Between January and October 2016, the sponsor audited 9 clinical sites for Protocol 20120297. The study was conducted from July 2015 to July 2016 and 577 subjects
were enrolled. Records were reviewed for 50 subjects. The sponsor noted one adverse event of xerostomia that was not recorded in eCRFs.

In total, for all three protocols, the sponsor audited records for 6.8% of subjects and noted a few adverse events (all non-serious) that were not included in eCRFs.

Based on our review of the monitoring plans and audit information for these protocols, OSI is not particularly concerned about any larger, systematic issues regarding the underreporting of adverse events for the pivotal trials for this BLA.

1. **Jo Bonner, M.D.**

For Protocol 20120295, 32 subjects were screened, 17 subjects were randomized, and 17 subjects completed the study. For Protocol 20120296, 32 subjects were screened, 26 subjects were randomized, and 25 subjects completed the double-blind phase and continued into the active treatment phase of the protocol. One subject discontinued the double-blind phase of the study due to subject request. Three subjects discontinued the active treatment phase due to loss to follow-up, withdrawal of consent, and a serious adverse event (suicide attempt).

Signed informed consent forms were present for all subjects who were screened, prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations and primary efficacy endpoint (headache days).

This clinical site printed out the daily diaries between each study visit and these were maintained within each subject binder. Headache data from these print outs were used to verify against sponsor line listings. There were no discrepancies between the line listings and DIARYpro data for either protocol. There was no evidence of underreporting of adverse events in either protocol.

2. **David Kudrow, M.D.**

For Protocol 20120295, 45 subjects were screened, 26 subjects were enrolled, and 26 subjects completed the study. For Protocol 20120297, 39 subjects were screened (one was re-screened), 30 subjects were enrolled, and 28 subjects completed the study. The EIR did not include information for the two subject discontinuations. Per sponsor listings, these subjects discontinued due to loss to follow-up and “protocol specified criteria”.

Signed informed consent forms were present for all subjects who were screened, prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications,
protocol deviations and primary efficacy endpoint (headache days).

For this clinical site, DIARYpro data was available on CDs sent to the site from the sponsor as well as on the web portal to verify against sponsor line listings. There were no discrepancies between the line listings and DIARYpro data for either protocol.

A Form FDA 483 was not issued at the conclusion of the inspection. However, several items were discussed with the clinical investigator, including underreporting of adverse events (AEs) in four of 30 (13%) randomized subjects for Protocol 20120297:

- Subject had “swollen feeling glands” and “fall” noted in progress notes for the (Week 2) phone contact visit. The AEs written in this progress note were dated . These AEs were not transcribed to the subject’s AE log or the eCRF and were not included in the sponsor’s line listing. This subject was randomized to erenumab and these AEs occurred during the double-blind phase of the protocol.

- Subject had “right knee pain and swelling” noted in progress notes for the (Week 16) visit, these AEs started on . The AE log listed right knee pain but not swelling, the latter AE was not included in the sponsor’s line listing. These AEs occurred during the open-label phase of the protocol.

- Subject had “intermittent right flank pain” noted in the AE log. The clinical investigator became aware of this AE on (Week 24), the start date of the AE was . This AE occurred during the open-label phase of the protocol. This subject had also experienced the AE “right lower quadrant pelvic pain” occurring to (overlapping with intermittent right flank pain) that was reported correctly.

- Subject had “possibly edema ankle/hands/feet” noted in progress notes for the visit (Week 20). This AE occurred during the open-label phase of the protocol.

There was no evidence of underreporting of AEs for Protocol 20120295 or SAEs for either protocol.

Reviewer’s comment: Underreporting of adverse events was noted at this clinical site for 13% of randomized subjects for Protocol 20120297, while no underreporting was noted for Protocol 20120295. Two of the unreported adverse events occurred during the double-blind phase of the protocol in a subject receiving erenumab, while the other three adverse events occurred during the open-label phase of the protocol. It is unlikely that these unreported adverse events would significantly impact the overall safety analyses for this application.

3. Messoud Ashina, M.D

For Protocol 20120295, 28 subjects were screened, 24 subjects were randomized, and 24 subjects completed the study. For Protocol 20120297, 19 subjects were randomized and 18
subjects completed the study. One subject discontinued the study due to “subject request”.

Records reviewed included, but were not limited to. source documents, monitoring documents, IRB/sponsor communications, financial disclosure, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations and primary efficacy endpoint (headache days).

For this clinical site, DIARYpro data was available via the web portal to verify against sponsor line listings. There were no discrepancies between the line listings and DIARYpro data for either protocol.

A Form FDA 483 was issued at the conclusion of the inspection for underreporting of adverse events (AEs).

For Protocol 20120295, three adverse events occurring in three of 24 (12.5%) randomized subjects were not reported to the sponsor:

- Subject (b) had “irritated skin (eczema)” in the subject’s AE log and occurred during the double-blind phase of the study. This subject was randomized to the placebo arm.

- Subject (b) had “difficulty to sleep (insomnia)” at Week 8 visit. The AE was recorded on the subject’s AE log and occurred during the double-blind phase of the study. This subject was randomized to the erenumab arm.

- Subject (b) had “heat sensation” from breast toward the neck area lasting 24 hours and starting one hour after investigational product injection reported at the Week 2 visit. The AE was recorded on the subject’s AE log and occurred during the double-blind phase of the study. This subject was randomized to the placebo arm.

For Protocol 20120297, two adverse events occurring in one of 19 (5%) randomized subjects were not reported to the sponsor:

- Subject (b) had “dizziness” at Week 8 and 12 visits. The AE was recorded on the subject’s AE log and occurred during the double-blind phase of the study (Week 8) and the open-label phase of the study (Week 12). This subject was randomized to the erenumab arm.

There was no evidence of underreporting of serious adverse events for either protocol.

Dr. Ashina provided a response to the Form FDA 483 findings. Dr. Ashina acknowledged the inspectional findings and has instituted corrective actions to prevent them from recurring in future clinical trials.

Reviewer’s comment: Underreporting of AEs was noted at this clinical site for 12.5% of randomized subjects in Protocol 20120295 and 5% of randomized subjects in Protocol 20120297. In other words, a total of five AEs occurring in four subjects were not reported to
the sponsor. Although all the AEs were included in the subjects’ AE logs, they were not entered into the eCRF and, therefore, not reported to the sponsor. Three of the AEs occurred in subjects receiving erenumab, while the remaining two AEs occurred in subjects receiving placebo. It is unlikely that these unreported adverse events would significantly impact the overall safety analyses for this application.

4. **Andrea Rinke, M.D.**

For Protocol 20120296, 27 subjects were randomized and 23 subjects completed the study. Four subjects discontinued due to adverse events (erythema, pain in extremities/upper abdominal pain, and headache) and one subject discontinued due to “subject request”.

Records reviewed included but were not limited to source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations and primary efficacy endpoint (headache days).

For this clinical site, ePRO data was available via the web portal to verify against sponsor line listings. There were no significant discrepancies between the line listings and DIARYpro data. There was no evidence of underreporting of adverse events.

*See appended electronic signature page*

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

*See appended electronic signature page*

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Document Room/BLA #761077
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Heather Fitter
DNP/Medical Officer/Laura Jawidzik
DNP/Project Manager/Lana Chen
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters
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/s/

CARA L ALFARO
03/15/2018

PHILLIP D KRONSTEIN
03/15/2018
Inspection summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of study 20140477 for BLA 761077 at Antidrug antibody (ADA) and neutralizing antibody (NAb) assays for AMG-334 under study 20140477 were audited.

No significant deficiencies were observed that impacted study 20140477. However, Form FDA 483 was issued at the inspection close-out for an observation related to studies submitted under other FDA applications that are NOT covered in this EIR review. The inspection classification is Voluntary Action Indicated (VAI). This VAI classification does not impact study 20140477.
After reviewing the inspectional findings, we conclude that there are no data integrity issues for the ADA and NAb assays for study 20140477 and the data is acceptable. However, the review div

**Inspected study**

**Study No.:** 20140477  
**Study title:** An Open Label Randomized Parallel Group Study in Healthy Volunteers to Assess the Relative Bioavailability of 3 Different AMG 334 Treatments

**Dates of study sample analysis:**
- ADA assay (U-16006):  
- NAb assay (U-16014):  

**Analytical site:**  
OSIS scientists Melkamu Getie-Kebtie, R.Ph., Ph.D. and Makini Cobourne-Duval 77 at  

The inspection included a thorough examination of the facility, equipment, records for method validation and sample analysis, SOPs, sample shipment, handling, and storage, software audit trails, and interviews and discussions with management and staff.

At the conclusion of the inspection, we did not find any objectionable findings that impact study 20140477. However, the following Form FDA 483 observation was issued for objectionable findings pertaining to studies submitted under other FDA applications that are not covered in this EIR view. These studies were also audited by OSIS during the analytical inspection.
Form FDA 483 observation

This observation has no impact on study 20140477 because 

Stability assessment for study 20140477 was conducted sponsor (Amgen) and OSIS did not audit Amgen’s data. This 483 observation will be discussed in a separate review.

However, for study 20140477, the following items were discussed with the firm’s management:
**Conclusion**

After reviewing the inspectional findings, we conclude that there are no data integrity issues for the immunogenicity data from the audited study. Based on this finding, the immunogenicity data is acceptable. However, OSIS recommends that the relevance of

**Classification:**

VAI: 

CC:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswa/Ayala

Reference ID: 4222847
OTS/OSIS/DGDBE/Cho/Kadavil/Skelly/Choi/Au/Cobourne-Duval/Getie-Kebtie

Draft: MG 2/7/2018; 2/09/2018; 2/12/2018; 2/16/2018
Edit: SA 02/07/2018, 02/09/18, 2/12/18; JK 2/15/2018

ECMS: Cabinets/CDER OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/BLA 761077

OSI fil
FACTS:

Reference ID: 4222847
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

________________________
/s/
________________________
MELKAMU GETIE KEBTIE
02/16/2018

MAKINI COBOURNE-DUVAL
02/16/2018

STANLEY AU
02/16/2018
Acting Team Lead

JOHN A KADAVIL
02/16/2018

Reference ID: 4222847
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 5, 2018
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: BLA 761077
Product Name and Strength: Aimovig (erenumab-xxxx) Injection, 70 mg/mL auto-injector and prefilled syringe
Applicant/Sponsor Name: Amgen
Submission Date: December 1, 2017; January 23, 2018
OSE RCM #: 2017-993-1
DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO
The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Aimovig (Appendix A) to determine if the labels and labeling are acceptable from a medication error perspective. The revisions are in response to recommendations the Agency communicated to the sponsor via email correspondence on November 20, 2017. We note the sponsor also requests feedback on their proposal to include:

- two sponsor logos (e.g. Amgen and Novartis) on the carton labeling
- a toll-free number for product complaints and a training website address on the Aimovig labeling (e.g. carton labeling, Instructions for Use, and Prescribing Information)

The sponsor states they intend to submit the final labeling in February 2018 for Agency review.

---

a The proper name for Aimovig has not yet been determined; therefore, “erenumab-xxxx” is used throughout this review as the proper name for this product.
b Labeling PMR/PMC Discussion Comments for Aimovig BLA 761077. Silver Spring (MD): FDA, CDER, OND, ODE I, DNP (US); 2017 NOV 20.
2 CONCLUSION
The revised container labels for Aimovig are acceptable from a medication error perspective. However, the revised carton labeling for Aimovig is unacceptable from a medication error perspective.

3 RECOMMENDATIONS FOR AMGEN
We recommend the following be implemented prior to approval of this BLA 761077:

A. Carton labeling

1. We previously recommended that for cartons that contain two autoinjectors or two pre-filled syringes, revise the statement from (b)(4) to read “2 x 70 mg/mL prefilled autoinjectors” or “2 x 70 mg/mL prefilled syringes” (as appropriate for the delivery device). Your response indicated that this revision was incorporated but it does not appear in the revised labeling. We recommend you submit revised carton labeling to reflect this change accordingly.

2. We find the presentation of the logos (e.g. Amgen and Novartis) compete for prominence with key prescribing information (e.g. the proprietary name, strength, proper name). We recommend that you reduce the prominence of the logos to ensure that they do not take readers’ attention away from important product information. We note you indicate the location of the Novartis logo represents the final intended labeling version but the font and size depicted does not represent the final version of the logo. Please note upon Agency review of your final intended carton labeling, additional recommendations may be provided.

3. We find the proposal to include a toll-free number and training website address in the labeling (e.g. carton labeling, Instructions for Use, and Prescribing Information) appears acceptable. However, we note that draft labeling that incorporates the proposed addition of the toll-free number and training website will be submitted in February 2018. As such, the acceptability of the final product labeling is subject to review.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EBONY A WHALEY
02/05/2018

LOLITA G WHITE
02/05/2018
# CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

**Full Review Template version:** December 26, 2017

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<td>Clinical Reviewer/Clinical Team Leader (CTL)</td>
<td>Laura Jawidzik, MD/Heather Fitter, MD</td>
</tr>
<tr>
<td>Review Division PM</td>
<td>Lana Chen</td>
</tr>
<tr>
<td>COA Reviewer</td>
<td>Sarrit M. Kovacs, PhD</td>
</tr>
<tr>
<td>COA TL/Secondary Reviewer</td>
<td>N/A</td>
</tr>
<tr>
<td>COA Associate Director</td>
<td>Elektra Papadopoulos, MD, MPH</td>
</tr>
<tr>
<td>Instrument 1</td>
<td>Migraine Physical Function Impact Diary (MPFID)</td>
</tr>
<tr>
<td>COA Type 1 and Endpoint Concepts</td>
<td>Patient-reported outcome (PRO) assessing the impact of migraines on physical functioning (everyday activities and physical impairment)</td>
</tr>
<tr>
<td>Intended Population</td>
<td>Adults (18 to 65 years of age) experiencing episodic migraine (EM) with history of migraine with or without aura for ≥ 12 months</td>
</tr>
</tbody>
</table>

*Please check all that apply:*
- Rare Disease/Orphan Designation
- Pediatric
A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Neurology Products (DNP) regarding BLA 761077. The applicant is currently post-phase 3 in their drug development program and awaiting an approval decision from the FDA. The proposed indication is prophylaxis of migraine in adults.

The applicant has developed a novel patient-reported outcome (PRO) instrument – the Migraine Physical Function Impact Diary (MPFID) – to assess the impact of migraines on physical impairment and everyday activities. The applicant included the MPFID to support two secondary endpoints in two completed phase 3 clinical trials (Studies 20120296 and 20120297) in adult patients (18 to 65 years of age) experiencing episodic migraine (EM) with a history of migraine with or without aura for ≥12 months.

The targeted MPFID-related labeling claims are included in Section C.1.1.4 below. It is important to note that the MPFID results were not statistically significant in Study 20120297 (only the 70 mg. dose was studied); the applicant only reported MPFID results for Study 20120296 (both the 70 mg. and 140 mg. doses were studied).

The evidence submitted by the applicant demonstrates that the MPFID’s content validity, domain structure, and psychometric properties and performance (i.e., internal consistency reliability, test-retest reliability, convergent validity, known-groups validity, and ability to detect change over time) exceeded the applicant’s pre-specified criteria for acceptability and was in line with their expectations.

The applicant’s rationale for item retention and reduction appears acceptable based on the qualitative research they conducted with migraine patients; however, it is unclear why the applicant retained items with high floor effects that were found during their quantitative analyses performed on both the observational study and phase 3 clinical trial 20120297 data.

In conclusion, we suggest the MPFID (version 2.0) would benefit from modification prior to use in future drug development programs as it has been shown to have high floor effects for more than half of the items, reducing its sensitivity to detect treatment effects.

B. BACKGROUND

During the phase 3 clinical trials, erenumab (AMG 334) was dosed monthly, subcutaneously using pre-filled syringes in the upper arm, upper thigh, or abdomen.
Materials reviewed:
- Previous COA Reviews completed by this reviewer during the IND 116098 phase:
  - C2017003 (finalized in DARRTS on February 10, 2017; Reference ID: 4053508)
  - AT 2016-261 (finalized in DARRTS on January 13, 2017; Reference ID: 4039683)
  - AT 2016-208 (finalized in DARRTS on January 13, 2017; Reference ID: 4039646)
  - AT 2016-167 (finalized in DARRTS on November 23, 2016; Reference ID: 4010151)
  - AT 2016-016 (finalized in DARRTS on April 23, 2016; Reference ID: 3916449)
  - AT 2015-079 (finalized in DARRTS on August 16, 2015; Reference ID: 3802788)
  - AT 2015-005 (finalized in DARRTS on April 16, 2015; Reference ID: 3726223)
  - AT 2014-041 (finalized in DARRTS on June 13, 2014; Reference ID: 3524831)
- MPFID version 2.0 evidence dossier (dated March 31, 2017)
- Applicant’s clinical trial protocols, clinical study reports, statistical analysis plans, integrated summary of efficacy, clinical efficacy summary and overview, proposed labeling language, etc.
- Minutes from January 31, 2017 meeting with sponsor (finalized in DARRTS on February 28, 2017; Reference ID: 4062281)

The following items are appended:
- Appendix A: Definitions of Migraine Day and Headache Day
- Appendix B: Screenshots of MPFID Version 2.0
- Appendix C: Previous Version of MPFID (Version 1.0)
- Appendix D: CDF Figures (Impact on Everyday Activities Domain) Submitted by Applicant during IND Phase (Observational Study 20140136)
- Appendix E: CDF Figures (Physical Impairment Domain) Submitted by Applicant during IND Phase (Observational Study 20140136)
- Appendix F: CDF Figures (Impact on Everyday Activities Domain) Submitted by Applicant during IND Phase (Phase 3 Trial 20120297)
- Appendix G: CDF Figures (Physical Impairment Domain) Submitted by Applicant during IND Phase (Phase 3 Trial 20120297)
- Appendix H: ________________________________
- Appendix I: ________________________________
- Appendix J: CDF Figure (Change From Baseline to Mean of Months 4, 5, 6 on Impact on Everyday Activities Domain Score by Treatment Group in Efficacy Analysis Set for Study 20120296)
C. CLINICAL OUTCOME ASSESSMENT REVIEW

The review concludes that the evidence submitted by the applicant demonstrates that the MPFID’s content validity, domain structure, and psychometric properties and performance (i.e., internal consistency reliability, test-retest reliability, convergent validity, known-groups validity, and ability to detect change over time) exceeded the applicant’s pre-specified criteria for acceptability.

However, we caution against use of the MPFID (version 2.0), without modification, in future drug development programs as it may continue to have high floor effects for more than half of the items, leading to its insensitivity in detecting treatment effects.

1 CONTEXT OF USE

1.1 Clinical Trial Population

The two completed phase 3 clinical trials (Studies 20120296 and 20120297; refer to Section 1.2 Clinical Trial Design) included adults ≥18 to ≤65 years of age upon entry into screening with history of migraine (with or without aura) for ≥12 months prior to screening according to the IHS Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or patient self-report. Adults experienced episodic migraine (EM; ≥4 and <15 migraine days per month on average across the 3 months prior to screening) and headache (i.e., migraine and non-migraine headache) frequency of < 15 headache days per month on average across the 3 months prior to screening. Refer to Appendix A for the definitions for migraine day and headache day.

1.2 Clinical Trial Design

Two phase 3 pivotal clinical trials were completed by the applicant in adults with episodic migraine:

- **Study 20120296**: A phase 3, multicenter, randomized, stratified, double-blind, placebo-controlled, parallel-group study of subjects with EM. 955 subjects were randomized 1:1:1 to placebo, AMG 334 70 mg, or AMG 334 140 mg; 858 subjects completed the double-blind treatment phase (DBTP) of the study. The randomization was stratified by region (North America vs Other) and treatment status with migraine prophylactic medication (a. current migraine prophylactic medication treatment; b. prior migraine prophylactic medication treatment only; c. no prior or current migraine prophylactic medication treatment.)
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Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

* 16 weeks after last dose of investigational product.
Note: Active treatment was also double-blind as to the actual dose of AMG 334 received.
QM = monthly; SC = subcutaneous
### Table 1. Schedule of Assessments - Study Visits Through Double-blind Treatment Phase

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening Phase (up to 7 wks)</th>
<th>Baseline Phase (4 wks)</th>
<th>Double-blind Treatment Phase (24 wks)</th>
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<tr>
<td>Study Visit</td>
<td>X</td>
<td>X</td>
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</tr>
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<td>Phone Call to Subject</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Informed Consent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calls to IVR/IRM System</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Entry into the Baseline Phase</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Randomization into the Double-blind Treatment Phase</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical and Medication History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis Sample Collection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIDS</td>
<td>X</td>
<td></td>
<td>Testing as needed throughout study based on investigator’s clinical suspicion</td>
</tr>
<tr>
<td>Pregnancy Testing: Serum</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Testing: Urine</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chemistry, Hematology</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
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<td>ECG</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
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<td>PK Sampling</td>
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<td>X</td>
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<td>PK Substudy Sampling (~171 subjects)</td>
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<td>Day 8 and Day 91</td>
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<td>Biomarker Development; Blood</td>
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</tr>
<tr>
<td>Pharmacogenetic Studies (Optional)</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Anti-AMG 334 Antibodies; Serum</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CGAs</td>
<td></td>
<td></td>
<td>X (Daily)</td>
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<td>Site Assigns eDiary to Subject</td>
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<tr>
<td>Subject Brings eDiary to Site for Use during Study Visit</td>
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<td>MSQ</td>
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<td>Menses Start Date</td>
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<td>IP Administration</td>
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</tr>
<tr>
<td>Adverse Event Recording</td>
<td></td>
<td>X (SAEs only)</td>
<td>X</td>
</tr>
<tr>
<td>Product Complaints Recording</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
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BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

- **Study 20120297**: A phase 3, multicenter, randomized, stratified, double-blind, placebo-controlled, parallel-group study of subjects with EM. 577 subjects were randomized 1:1 to placebo or AMG 334 70 mg; 546 subjects completed the DBTP of the study. The randomization was stratified by region (North America vs Other) and treatment status with migraine prophylactic medication (a. current migraine prophylactic medication treatment; b. prior migraine prophylactic medication treatment only; c. no prior or current migraine prophylactic medication treatment).
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Migraine Physical Function Impact Diary (MPFID)

**Diagram Description:**
- **Screening Phase** (up to 7 weeks)
  - Initial Screening Phase (up to 3 weeks)
  - Baseline Phase (4 weeks)
- **Double-blind Treatment Phase** (12 weeks)
  - Placebo QM SC n ~ 270
  - AMG 334 70 mg QM SC n ~ 270
- **Open-label Treatment Phase** (28 weeks)
  - AMG 334 70 mg QM SC
  - Safety Follow-up (8 weeks*)

* 12 weeks after last dose of investigational product
QM = monthly; SC = subcutaneous

Reference ID: 4210510
Table 1. Schedule of Assessments - Study Visits Through Double-blind Treatment Phase

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening Phase (up to 7 wks)</th>
<th>Baseline Phase (4 wks)</th>
<th>Double-blind Treatment Phase (12 wks)</th>
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<td>Initial Screening (up to 3 wks)</td>
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<td>D 1 (post-</td>
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<td>Randomization into the Double-blind Treatment Phase</td>
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<td>Hepatitis Sample Collection</td>
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<td>UDS</td>
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<td>Testing as needed throughout study based on investigator’s clinical suspicion</td>
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<tr>
<td>Pharmacogenetic Studies (Optional)</td>
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<td>CQAs 15</td>
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</tr>
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<td>Menses Start Date</td>
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<tr>
<td>Product Complaints Recording</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
1.3 Endpoint Hierarchy and Definition

The figure below was reproduced from the applicant’s Study 20120296 protocol and represents the endpoint testing hierarchy for the pre-specified primary and secondary endpoints included in the Study 20120296 phase 3 clinical trial. The change from baseline endpoints were analyzed as change from baseline to months 4, 5, and 6 (last 3 months of trial).
The figure below was reproduced from the applicant’s Study 20120297 protocol and represents the endpoint testing hierarchy for the pre-specified primary and secondary endpoints included in the Study 20120297 phase 3 clinical trial. The change from baseline endpoints were analyzed as change from baseline to the last month of the 12-week DBTP.
Reviewer’s comments: During the IND phase, the applicant asked the Review Division if they could revise the endpoint testing hierarchy for Study 20120296 (i.e., pre-specifying a “change from baseline in mean monthly average” MPFID domain scores as secondary endpoints instead of “in each MPFID domain score) based on the MPFID findings from Study 20120297, without completely invalidating the second trial (Study 20120296). At the time of this request, the trial 20120296 database was still blinded per the applicant’s assertion. The applicant’s rationale for this change was because the applicant reviewed results of the unblinded MPFID data for their completed EM trial (20120297). The Review Division asked the applicant to provide a copy of the new statistical analysis plan (SAP) for Agency review in order to provide feedback regarding the acceptability of this proposed change.

We find the newly proposed “change from baseline” endpoints proposed by the applicant to be preferable; however, the COA Staff defer to the Review Division and the Office of Biostatistics (OB) regarding suitability of the change from baseline MPFID domain endpoints (as well as plans for handling of missing data, multiplicity adjustment, endpoint analysis, etc.).

1.4 Labeling or promotional claim(s) based on the COA

An adapted representation of the content of the applicant’s proposed labeling claims related to the MPFID results from Study 20120296 (Note: The MPFID results were not statistically significant in Study 20120297.) is as follows:
Reviewer’s comments: The MPFID endpoints did not yield statistically significant results in the Study 20120297 phase 3 clinical trial. It is possible that this is due to the retention of items that had high floor effects, which could have led to the insensitivity of the instrument to detect a treatment effect on the impact of migraines on everyday activity and physical impairment. If the 70 mg dose will be approved (in addition to, or instead of, the 140 mg dose), we recommend that the applicant include the nonsignificant MPFID results for “Study 3” (Study 20120297) in Section 14 of the labeling.

We recommend the following edits to the two paragraphs in the labeling that are related to the MPFID (see strikethrough text for proposed deletions and proposed added text in italicized bolded font):

We recommend deleting “Instead, the MPFID domain names should be used. In addition, we believe that the global item should be described as assessing the overall difficulty doing usual activities in
line with the item being administered to subjects. Finally, we believe that the labeling should include the number of days that are averaged in a monthly score (i.e., 28 days). The reviewer recommends against stating “statistically significant” or “” in the labeling and rather to include only the words “demonstrated improvements.”

With regard to the data included in Table 4 above, the COA Staff defers to the Review Division and the OB statistical reviewer regarding whether the applicant should include the MPFID data that is currently included.

2 CONCEPTS OF INTEREST AND CONCEPTUAL FRAMEWORK

In order to develop the conceptual framework of the MPFID, the applicant performed both exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) using data from a prospective observational study (Study 20130136) on a random day and a migraine day (see Section 6 for more information regarding the observational study). The applicant stated that the EFA results provided evidence supporting both a one-factor and two-factor structure for the MPFID. They asserted that although the unidimensional (one-factor) model had good fit, the two-factor solution had a relatively better model fit, and two factors were readily interpretable as domains reflecting impact on everyday activities and physical impairment. Feedback from clinical experts supported the relevance of two separate factors/domains. Subsequently, the applicant conducted CFA on the 12 core items of the final MPFID version 2.0 (excluding the one global item assessing the overall difficulty doing usual activities). CFA conducted on the first half of the observational study sample (n=264) supported the two factor/domain model on both a random day and a migraine day. All items showed strong loadings to their respective domains, indicating that all items contributed to the measurement of the underlying concept in their respective domains. A repeated CFA was repeated in the second half of subjects (n=300) and also on the final full dataset (n=562) and confirmed the two factor/domain solution.

The conceptual framework diagram in the figure below was reproduced from the applicant’s MPFID evidence dossier (page 22) and illustrates that the MPFID has two domains – impact of migraines on everyday activities and impact of migraines on physical impairment. It also includes a stand-alone global question (item 8).
Reviewer’s comments: This reviewer conveyed to the applicant during the IND phase that their original proposed [removed] is not reasonable given that there are items in the “every day activities” domain that do not represent an impact on physical function (e.g., difficulty concentrating, avoiding interactions with people). Therefore, this reviewer recommended [removed] that the applicant keep the “physical ability” (previous label; now called “physical impairment”) and “every day activities” domain scores separate.

This reviewer agreed that the exploratory and confirmatory factor analyses conducted by the applicant appeared reasonable to support a two-factor solution and their item response theory (IRT) analysis results appeared reasonable to support the final 12 core items (in addition to the global item) and two domains of the MPFID. However, the following comments were conveyed to the applicant:

- The concept of “walking” appears conceptually relevant and important to migraine patients. Therefore, this reviewer recommended that the applicant include either original [removed] or both in the CFA and IRT analyses to see if either one of them fits the model, and if one fits better than the other.
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Migraine Physical Function Impact Diary (MPFID)

The applicant stated that Clinical experts suggested removing items as these impacts were covered by the “difficulty moving head,” “difficulty moving body,” and “difficulty bending over” items. CFA and IRT analyses were performed and they supported the final 12 core items (in addition to the global item) and two domains of the MPFID.

- Given that the applicant’s (currently Item #13 in their conceptual framework) “double-loaded” on both MPFID domains, this reviewer asked the applicant for their rationale for rationale for choosing to include it in the “physical impairment” domain rather than the “impact on everyday activities” domain.
- The applicant replied that the double-loading was seen only on a random day. In the EFA, using data from a migraine day, item clearly loaded on the physical impairment domain (0.6) rather than on the impact on everyday activity domain (0.3). CFA confirmed this. The Agency found this acceptable.

3 CLINICAL OUTCOME ASSESSMENT

The MPFID is a 13-item PRO instrument that assesses the daily impact of migraines on physical functioning during the previous 24 hours on days with or without a headache/migraine. The MPFID includes two domains – impact on everyday activities (7 items) and impact on physical impairment (5 items) – and a global question (see conceptual framework diagram in Section C2 [Concepts of Interest and Conceptual Framework]). Subjects respond to items using a 5-point scale, with difficulty items ranging from “without any difficulty” to “unable to do” and frequency items ranging from “none of the time” to “all of the time.” These are assigned scores from 1 to 5, with 5 representing the greatest burden. Subjects in the phase 3 clinical trials completed the MPFID electronic diary (eDiary) daily using a handheld electronic device.

The MPFID was developed for use in adults with either EM or chronic migraine (CM); however, the two phase 3 clinical trials included only adults with EM. Appendix B contains screen shots of the MPFID version 2.0.

- Prior versions: An early version (version 0.1) was included in round 1 of patient cognitive
interviews, then a second version (version 0.2) was tested in round 2 of patient cognitive interviews. Revisions based on the cognitive interview study resulted in the MPFID version 1.0 (see Appendix C), which was subsequently migrated for administration on an electronic device. The applicant subsequently removed MPFID version 1.0 and made further modifications, which yielded the final 13-item MPFID version 2.0.

- **User manual:** The applicant submitted a user manual and scoring guide for the MPFID version 2.0 (dated March 22, 2017).
- **Timing, data collection method, and mode of administration:**
  - Daily eDiary on a handheld electronic device
  - Self-administered at the end of each day, every day during baseline (4 weeks) and the DBTP of both phase 3 clinical trials (20120296, 24-weeks; and 20120297, 12-weeks).
- **Training method/materials:** Study staff were trained on the importance of collecting patient-reported data and on administration of the MPFID; and subjects were trained to use the electronic device and on how to respond to the MPFID items. The applicant submitted the training materials as part of the MPFID evidence dossier. In addition, usability testing of the electronic device was conducted prior to the MPFID’s inclusion in the clinical trials.

**Reviewer’s comments:** The training materials submitted appear adequate and appropriate.

During the IND phase, this reviewer asked the applicant to walk the Agency through their question branching document (received by the Agency on July 31, 2015 in response to the information request), because it was still unclear whether patients are asked the questions regarding their pain and symptoms (e.g., nausea, vomiting, etc.) regardless of whether or not the patients reported experiencing a headache/migraine in those past 24 hours. The applicant confirmed that all subjects complete the MPFID daily regardless of whether or not they experienced a headache/migraine in the past 24 hours.

During the IND phase, the applicant stated that the patients would complete the instrument in evenings; however, it was unclear to this reviewer whether patients will complete the instrument only on evenings when they experienced migraines during the 24-hour reporting period, but skip filling out the instrument on evenings when they do not experience a migraine. If this is the case, this reviewer suggested including a “not applicable” (i.e., skip) option for patients who did not experience migraine in the “past 24 hours.” The applicant confirmed that patients would complete the instrument daily, regardless of whether they experienced a migraine on that day, to fully capture the patients’ experience. Therefore, they did not consider a “not applicable” option necessary. The Agency agreed that this is acceptable.
4 SCORING ALGORITHM

The following scoring and missing data imputation information was reproduced from the applicant’s MPFID user manual and scoring guide found in the MPFID evidence dossier (pages 108-109).
Reviewer’s comments: The MPFID scoring algorithm appears reasonable, but the COA Staff ultimately defers to the OB statistical reviewer to review the scoring algorithm for the endpoint score calculation. The Agency conveyed to the applicant during the IND phase that an assessment using a mean 28-day score is likely more meaningful. The COA Staff also defers to the OB statistical reviewer to review the adequacy of the applicant’s plans for handling missing form-level and item-level data, and to make a determination related to the acceptability of using raw or transformed MPFID scores. The OB statistical reviewer conveyed the following to the applicant during the IND phase: “The raw score metric would be useful for both the psychometric evaluation of the MPFID and for assessing the treatment effect. The rationale for providing the raw score metrics rather than using the transformed score is to improve the interpretability and transparency of the scale.”

The MPFID items are scored on a scale from 1 to 5, yielding a range of scores for each domain of 7-35 and 5-25, respectively. This reviewer suggested that the Review Division consider asking the sponsor to rescore the items to be on a scale of 0 to 4 (rather than 1-5) so the domain scores would range from 0-28 and 0-20, respectively, for ease of interpretation. The OB statistical reviewer agreed that the rescaling (0 to 4 instead of 1 to 5) would result in a more intuitive total
score range, especially since it appears that the Review Division is more interested in the raw total scores rather than the transformed 0 – 100 total scores.

5 CONTENT VALIDITY

The applicant developed the MPFID to measure the daily impact of migraines on physical functioning (everyday activities and physical impairment) in order to evaluate the benefit of their prophylaxis migraine treatment. The applicant conducted research using both qualitative and quantitative methods to develop the MPFID and for establishing its measurement properties and defining clinically meaningful within-patient changes in scores.

To date, the following information has been submitted:

☑ Literature review and/or publications
☑ Documentation of expert input
☑ Qualitative study protocols and interview guides for focus group or patient interviews
☑ Chronology of events for item generation, modification, and finalization (item tracking matrix)
☑ Qualitative study summary with evidence to support item relevance, item stems and response options, and recall period
☑ Qualitative support for meaningful change
☑ Quantitative study summary with evidence to support item retention and scoring
☑ Transcripts (if available)

The figure below was reproduced from the applicant’s MPFID evidence dossier (page 17) and represents an overview of the applicant’s work in development of the MPFID.
Systematic review of the extant literature was conducted to understand patients' experience with migraines and to review existing PRO instruments used in migraine studies in order to identify symptoms and impacts of migraines. The migraine/headache impact concepts identified were
related to 1) performing everyday activities; 2) participating in social and leisure activities; 3) emotional responses; and 4) cognitive difficulties. The applicant used these to develop the probing questions in the concept elicitation interview guide (following the open-ended questions). The applicant included expert input when developing the MPFID comprising five PRO measurement experts with extensive experience in PRO instrument development and psychometric evaluation, as well as three clinical expert interviews with extensive experience in migraine (2 neurologists with expertise in treating migraine patients and 1 clinical psychologist with expertise in headache and pain management). These experts provided feedback on the preliminary concept list developed from the literature review, and to ensure clinical relevance of the impacts identified.

Qualitative concept elicitation semi-structured interviews were conducted with 32 adults with migraine (21 with EM and 11 with CM; Study 20130172) by five trained and experienced interviewers. Interviews included open-ended questions followed by probes (that were based on literature and PRO instrument content reviews and interviews with migraine clinician experts) to understand the subjects’ experiences. Qualitative data from the concept elicitation interviews were systematically analyzed to inform the development of the concepts of interest and conceptual framework (see Section 2) and generate items for the MPFID. The table below was reproduced from the applicant’s MPFID evidence dossier (page 34) and represents the concepts endorsed as well as the saturation grid:

<table>
<thead>
<tr>
<th>Concept</th>
<th>EM Subjects (N = 21)</th>
<th>CM Subjects (N = 11)</th>
<th>Total Number of Subjects Mentioning the Concept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (N = 5)</td>
<td>Group 2 (N = 5)</td>
<td>Group 3 (N = 5)</td>
</tr>
<tr>
<td>Ability to move head/limiting body movements/difficulty walking/standing</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Energy level need to rest/exhaustion/fatigue/tiredness</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Abnormality, leaving early, making up at other time (school or work)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Difficulty doing household chores</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Unable to look after others/caregiver for family</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Difficulty with school or work (performance)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Difficulty looking after self/appointments/driving</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Need to avoid bright light, limiting activity</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Need to avoid loud noises, isolating oneself, avoiding activity</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ability to do activities that require concentration</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unable to keep to a schedule</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
</tr>
</tbody>
</table>

CM = chronic migraine; EM = episodic migraine; NA = not applicable

Subjects interviews in the concept elicitation study resulted in variability regarding subjects’ experience related to the frequency, duration, and severity of migraines. Subjects also reported that migraines impacted their lives during the nonmigraine days. In order to capture the day-to-day variability in the experience of impacts of migraine on daily life, a recall period of the
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preceding 24 hours was selected by the applicant (i.e., daily diary), which would also allow for capture of the impact migraine on days with and without migraine.

Cognitive interviews of prior versions of the MPFID were conducted with 17 adults with migraine (12 with EM and 5 with CM; Study 20130375) in two rounds and confirmed the content validity of the MPFID ensuring that the wording of the items is relevant and appropriate, and that subjects understood the instructions, item stems, and response options as intended. The applicant submitted an item tracking matrix as an appendix to the MPFID evidence dossier providing detail related to modifications made during the development process of the instrument.

In addition, the applicant conducted exit interviews with three subject who completed phase 3 clinical trial 20120296 (see Section 7 Interpretation of Scores for more detail on the exit interviews). One subject was on placebo, one was on the 140 mg dose, and one was on the 70 mg dose. The former two subjects (placebo and 140 mg dose) both reported that the MPFID items related to “moving their head” and “bending over” were not applicable, and the first subject (placebo) also reported that the items related to “moving the body” and “avoiding interactions with people” were also not applicable to them. All of these items also yielded high floor effects in both the observational study and the phase 3 clinical trial 20120297 (with the exception of “moving the head” which nearly exceeded the 30% floor effect threshold pre-specified by the applicant in the observational study [28.2%], but did exceed the 30% threshold in Trial 20120297 [32.5%]). Refer to Section 6 (Other Measurement Properties) for more information related to the floor effects seen in both studies.

The applicant conducted usability testing of the electronic version of the MPFID (previous version 1.0; [version]) with one-on-one cognitive interviews, as well as evaluated the conceptual equivalence between electronic and pen-and-paper modes of administration (non-randomized; pen-and-paper version was completed first and then the electronic version), with 10 adults with migraine (Study 20140252). Feedback on the usability of the electronic device was positive. The majority of subjects rated different aspects of the device usability as a four or higher (on a scale of 1 to 5, where 1=poor and 5=excellent) with no one giving a rating of 1 across any of the domains. Among those subjects providing low ratings (2 or 3), no subjects showed an inability or severe impediment in using the device. Regarding issues related to loading speed/time on the Instructions screen, the applicant recommends this issue be addressed during device training sessions to have subjects get accustomed to using the device including its loading times. The applicant does not recommend any changes regarding the usability of the device based on the results of their study.

Conceptual equivalence was met for all subjects (n=10; 100%) for all but one of the items (17 out of 18 total items). Conceptual equivalence was ‘not evaluable’ in one item because of one subject (n=1, 10% for Item 9). The subject did not understand the item (Item 9, “In the past 24 hours, overall, how difficult was it to do your usual activities?”) while completing it on pen and paper (“Just cause I didn’t understand, I didn’t understand this”).

Reference ID: 4210510
Reviewer's comments: The exploratory and confirmatory factor analyses conducted by the applicant appear reasonable to support a two-factor solution. The IRT analyses appear reasonable to support the two domains of the MPFID.

This reviewer conveyed to the applicant during the IND phase that their qualitative research appears adequate and all concepts appear to have been endorsed by either EM or CM patients. From the saturation of concepts data provided by the applicant during the IND phase, it appeared that saturation had been reached for the EM group, but there was no evidence shown that saturation has been reached for the CM group. This reviewer requested a detailed saturation grid including all of the concepts endorsed by both EM and CM patients (specifying to which group the endorser belonged) as well as whether the concepts endorsed were spontaneous or probed. This reviewer stated that given that they plan to use this PRO instrument in both EM and CM patient groups, it is necessary to ensure that every item in the instrument is relevant to both EM and CM patients, not just to one of the two patient populations. The applicant asserted that based on their review of the cognitive interview quotes across EM and CM subjects, all items were determined to be relevant across both populations. The Agency agreed that, based on their assertion, the items may be used in both EM and CM patient populations. The applicant provided the detailed saturation grid with the BLA submission.

During the IND phase, this reviewer stated that the “household chores” item may not be applicable to all patients on each day, and that perhaps it would be preferable to include a response option of “not applicable” to this item and to other relevant items in case patients did not have an opportunity to complete some of the activities during the 24-hour period. The applicant expressed concern that including a “not applicable” response option for “household chores” would create missing data and change the scoring algorithm. The sponsor claimed that based on the patient interviews, patients interpreted the item “household chores” in their own ways. Some interpreted it as cooking, cleaning, and repairs. Some explained that they are things that you need to do everyday. The Agency suggested possibly combining items 1 (“household chores”) and 2 (“usual activities outside the home”) into one item, as well as possibly combining other potentially redundant items (e.g., items 3 and 6, 4 and 5). The sponsor stated that item redundancy would be captured in the prospective observational psychometric evaluation study where they would look at items’ discriminant values. For example, items 4 (activities requiring concentration) and 5 ( ) were found to be redundant and item 5 was removed from the MPFID.

We found the applicant’s rationale for item retention and reduction acceptable based on the qualitative research they conducted; however, it is unclear why the applicant retained items with high floor effects based on their quantitative analyses performed on both the observational study and phase 3 clinical trial 20120297 data (see Section 6 for more detail on the high floor effects).
During the IND phase, this reviewer reviewed the applicant’s PRO evidence dossier outline and recommended the applicant consider the following:

1. Include a section for “Interpretation of meaningful change in MPFID scores.”
2. Include a timeline (chart or table) for all of the qualitative work (i.e., literature review, expert input, patient concept elicitation interviews, item generation, patient cognitive interviews, item modification, etc.).
3. With regard to ePRO migration, in addition to inclusion of the study report, add an appendix for the study protocol.
4. If the PRO dossier will be used as an independent document, consider including the phase 3 study 20120297 protocol as an appendix.
5. Include a copy of the MPFID version 1.0 as an appendix.
6. Include exact screenshots of the final MPFID version 2.0 that were administered to patients in the phase 3 trials in an appendix.
7. Consider including item tracking matrices from each round of patient cognitive debriefing interviews.
8. In addition to patient qualitative transcripts, add an appendix for the qualitative interviewer scripts.
9. Include sample sizes for analyses, table columns or rows as appropriate, and for categories defined in the legends of each graph.

In conclusion, we believe that the MPFID evidence dossier is adequate and comprehensive. The evidence from the applicant’s qualitative research (literature review; concept elicitation and cognitive interviews with adults experiencing EM or CM; expert input) demonstrated that the MPFID is content valid and measures the concepts of interest (impact of migraine on everyday activities and physical impairment) including support that the items and domains of the instrument are clinically important, important to patients, appropriate, and comprehensive in its intended context of use.

6 Other Measurement Properties (Reliability, Construct Validity, Ability to Detect Change)

The sponsor explored the reliability, validity, and ability to detect change of the 13-item version (v2.0) of the MPFID using data from the observational study (Study 20140136). Statistical analyses were conducted in 3 distinct stages. The first 2 stages focused on item selection and evaluating the cross-sectional psychometric properties of MPFID scores. The third stage examined the ability of the MPFID to detect change over time in EM subjects and to develop methods to interpret the clinical meaningfulness of MPFID change scores. The applicant used transformed MPFID domain scores (0-100 point scale) in all analyses included in the MPFID evidence dossier, but also submitted results based on raw, untransformed scores in an appendix as requested by the Agency.
The applicant conducted analyses on the MPFID (previous version 1.0; [8.4]) using data from a multicenter, prospective, observational study (Study 20140136) in subjects with EM and CM who were receiving standard migraine care in clinics in the US. Study subjects attended two visits over the study timeframe and completed PRO instruments in the form of daily diaries each day between study visits, and questionnaires at pre-specified study time points on an electronic device. Enrolled subjects represented patients taking no daily preventative migraine medication, patients stable on one or more preventative migraine medications, and patients newly initiating a migraine medication or increasing their current dose. The study design schema is shown below in a figure reproduced from the applicant’s submission.

The observational study 20140136 included adults 18 to 65 years of age with EM (≥4 and ≤14 headache days per month) or CM (≥15 headache days per month, of which ≥8 were migraine days), in each of the 3 months prior to screening. Subjects were receiving usual standard of care as migraine treatment. Individuals were excluded if they were older than 50 years of age at
migraine onset, had more than one migraine with duration longer than 72 hours during 3 months prior to screening (in subjects with EM), continuous pain without any pain-free periods during the one month prior to screening (in subjects with CM), history of cluster headache or hemiplegic migraine headache, history or evidence of fibromyalgia or chronic pelvic pain syndrome, opioid use greater than 6 days during 3 months prior to screening, or history of a major psychiatric disorder.

The observational study was conducted with a large sample of EM and CM subjects (n=569). The sample used for item reduction, scoring, and psychometric testing of the MPFID appeared to be consistent with the intended context of use (for clinical trials of prophylactic migraine medications) and representative of the targeted patient population.

Analyses evaluating MPFID item performance were based on available data for subjects who had completed week 1 (n=264) at the time of the interim data cut in the observational study. In order to examine the differences in item performance on days with migraine versus non-migraine day experiences, analyses were conducted using:

- One randomly-selected diary day per subject from week 1 (which can be a day with or without a headache or migraine; see Appendix A for definitions of migraine day and headache day); and
- One migraine day per subject was randomly selected from week 1, since migraines are episodic in nature and impacts may vary by type of headache experienced.

Item performance was evaluated and items were flagged as potentially problematic if they exhibited large floor or ceiling effects (defined \( a \text{ priori} \) as >30%), very high or very low inter-item correlations (defined \( a \text{ priori} \) as greater than 0.80 or less than 0.20), low factor loading or loading on more than one factor in the EFA, or a poor fit within the domain in IRT analyses based on a graded response model (GRM). The sponsor concluded that that their IRT analyses supported the two unidimensional domains of the MPFID. All items were discussed in detail with the applicant’s PRO development team and external experts (clinicians and psychometricians). The discussions also included consideration of the qualitative data from the concept elicitation and cognitive interview studies (Studies 20130172 and 20130375) and clinical relevance of the concept for evaluating the benefit of a migraine prophylaxis treatment. Final decisions to revise or remove items were based on these mixed methods and consensus agreement among the PRO development team and external experts. The mixed methods of analyses resulted in retaining 13 items and the removal of 4 items included in version 1.0 of the MPFID.

The applicant conducted psychometric analyses on the MPFID using data from the observational study 20140136. The two tables below were reproduced from the applicant’s submission and provide a summary of the psychometric analyses and data sets used.
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BLA 761077  
Erenumab; AMG 334/Aimovig  
Migraine Physical Function Impact Diary (MPFID)

<table>
<thead>
<tr>
<th>Stage 1: Item Evaluation and Scoring</th>
<th>Analytical Data Set</th>
<th>Sample Size</th>
<th>Study Time Points of Interest</th>
</tr>
</thead>
</table>
| Item analysis (descriptive characteristics; item-item correlations) | Interim data cut: 21Jan2015 | Total sample, N=264 (181 EM subjects; 83 CM subjects) | Cross-sectional analyses in combined Cohort 1 and 2 samples on a random day and a migraine day from Week 1  
Data pooled across EM and CM subjects |
| Exploratory and initial confirmatory factor analyses | | | |
| Item response theory | | | |
| Item retention and scoring algorithm | | | |

<table>
<thead>
<tr>
<th>Stage 2: Evaluation of Measurement Properties</th>
<th>Analytical Data Set</th>
<th>Sample Size</th>
<th>Study Time Points of Interest</th>
</tr>
</thead>
</table>
| Item descriptive characteristics | Interim data cut: 31Mar2015 | Total sample, N=569 (323 EM subjects; 246 CM subjects) | Cross-sectional analyses in combined Cohort 1 and 2 samples (where possible) using data from the first 4 weeks of the study  
Using pooled data and analyzed separately for EM and CM subjects |
| Confirmatory factor analysis | | | |
| Reliability (internal consistency; test-retest) | Final data cut: 03Oct2016 | | |
| Validity (construct; known-groups) | | | |

<table>
<thead>
<tr>
<th>Stage 3: Responsiveness</th>
<th>Analytical Data Set</th>
<th>Sample Size</th>
<th>Study Time Points of Interest</th>
</tr>
</thead>
</table>
| Ability to detect change | Interim data cut: 1Sep2015 | Cohort 2 sample, N=80 EM subjects | Longitudinal analyses in Cohort 2 sample at Study visit 1 to Final Visit (Week 16)  
Analyzed separately for EM and CM subjects |
| Interpretation of change scores | | | |
| o Responder definition | | | |
| o Between-groups | | | |
| o Impairment day | | | |
| Interim data cut: 3Oct2016 | Total Cohort 2 sample, N=279 (167 EM subjects; 112 CM subjects) | | |

* MSQ, HIT-6™ and PROMIS-PF data for convergent and known-group validity testing were based only on Cohort 1 data, as these instruments were not completed at Week 4 in the Cohort 2 sample based on study assessment schedule.

Reference ID: 4210510
<table>
<thead>
<tr>
<th>Analysis Objective</th>
<th>Interim Data Sets</th>
<th>Final Data</th>
<th>Dossier Section Reporting Results</th>
<th>Documents Previously Submitted to FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate item performance; Item reduction; EFA; IRT</td>
<td>January 2015</td>
<td>March 2015</td>
<td>September 2015</td>
<td>October 2016</td>
</tr>
<tr>
<td></td>
<td>n = 264&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pooled</td>
<td>Pooled EM/CM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EM/CM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Develop scoring algorithm; preliminary CFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 264&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sample 1</td>
<td>Pooled EM/CM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm domains and scoring; final CFA</td>
<td></td>
<td></td>
<td>n = 300</td>
<td>N = 562&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sample 2 from an N = 562</td>
<td>Pooled EM/CM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pooled EM/CM</td>
<td></td>
</tr>
<tr>
<td>Evaluate measurement properties; reliability and validity</td>
<td>n = 342&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pooled</td>
<td>Pooled EM/CM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EM/CM</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Evaluate responsiveness; ability to detect change</td>
<td></td>
<td></td>
<td>n = 78&lt;sup&gt;c&lt;/sup&gt;</td>
<td>EM only</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>n = 279&lt;sup&gt;e&lt;/sup&gt;</td>
<td>EM and CM separately</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Note: A supplemental analysis was conducted using an interim sample of blinded clinical trial data to evaluate response among EM subjects in a sample with a true treatment-free baseline period from Study 20120297.

CFA = confirmatory factor analysis; CM = chronic migraine; EFA = exploratory factor analysis; EM = episodic migraine; FDA = Food and Drug Administration; IRT = item response theory; MPFID = Migraine Physical Function Impact Diary; SN = serial number.

<sup>a</sup> Available week 1 completers
<sup>b</sup> Available week 4 completers
<sup>c</sup> Available week 16 (Cohort 2 EM) completers
The applicant conducted an item analysis to examine the descriptive statistics for the MPFID items on a migraine day during week 1 of the observational study (total sample; \( n=472 \)). Below is a table reproduced from the applicant’s MPFID observational study 20140136 validation report (page 118 of the report found as an appendix to the MPFID evidence dossier) and shows that more than half of the MPFID items exceeded the applicant’s pre-specified floor effects threshold of 30% during a migraine day. The applicant provided rationale for inclusion of those items with high floor effects asserting that most of the participants included in the concept elicitation interview study endorsed those concepts and that the clinical expert feedback indicated that inclusion of those concepts provided a more comprehensive picture of the impact of migraine on various types of daily activities.

<table>
<thead>
<tr>
<th>Item</th>
<th>( N )</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>Floor (N,%)</th>
<th>Ceiling (N,%)</th>
</tr>
</thead>
</table>

The applicant performed a supplemental analysis using an interim sample of blinded and pooled clinical trial data (Study 20120297) to evaluate the MPFID domains’ psychometric properties and performance among EM subjects in a sample with a true treatment-free baseline period (which was not possible in the observational study).

The applicant conducted another item analysis to examine the descriptive statistics for the MPFID items using a randomly-selected migraine day at baseline in the Study 20120297 study \( (n=569) \). Below is a table reproduced from the applicant’s MPFID evidence dossier (page 1421)
and shows that more than half of the MPFID items exceeded the applicant’s pre-specified floor effects threshold of 30%, just as was seen in the observational study data described above:

<table>
<thead>
<tr>
<th>Item</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Minimum-Maximum</th>
<th>Floor (N,%)</th>
<th>Ceiling (N,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to do Household Chores</td>
<td>569</td>
<td>2.3 (1.09)</td>
<td>2.00</td>
<td>1.5</td>
<td>145 (25.5%)</td>
<td>21 (3.7%)</td>
</tr>
<tr>
<td>Ability to do Activities Outside Home</td>
<td>569</td>
<td>2.4 (1.16)</td>
<td>2.00</td>
<td>1.5</td>
<td>138 (24.3%)</td>
<td>41 (7.2%)</td>
</tr>
<tr>
<td>Ability to Keep Daily Routine</td>
<td>569</td>
<td>2.4 (1.16)</td>
<td>2.00</td>
<td>1.5</td>
<td>138 (24.3%)</td>
<td>34 (6.0%)</td>
</tr>
<tr>
<td>Ability to Concentrate on Activities</td>
<td>569</td>
<td>2.6 (1.17)</td>
<td>3.00</td>
<td>1.5</td>
<td>117 (20.6%)</td>
<td>38 (6.7%)</td>
</tr>
<tr>
<td>Ability to Get Ready for the Day</td>
<td>569</td>
<td>2.0 (1.14)</td>
<td>2.00</td>
<td>1.5</td>
<td>245 (43.3%)</td>
<td>17 (3.0%)</td>
</tr>
<tr>
<td>Time Avoided Interacting with Others</td>
<td>569</td>
<td>2.1 (1.17)</td>
<td>2.00</td>
<td>1.5</td>
<td>223 (39.2%)</td>
<td>22 (3.9%)</td>
</tr>
<tr>
<td>Time to Rest during Normal Waking Hours</td>
<td>569</td>
<td>2.3 (1.12)</td>
<td>2.00</td>
<td>1.5</td>
<td>173 (30.4%)</td>
<td>17 (3.0%)</td>
</tr>
<tr>
<td>Overall Difficulty with Usual Activities</td>
<td>569</td>
<td>2.4 (1.07)</td>
<td>2.00</td>
<td>1.5</td>
<td>126 (22.3%)</td>
<td>21 (3.7%)</td>
</tr>
<tr>
<td>Time with Difficulty Moving Your Head</td>
<td>569</td>
<td>2.2 (1.10)</td>
<td>2.00</td>
<td>1.5</td>
<td>185 (32.5%)</td>
<td>17 (3.0%)</td>
</tr>
<tr>
<td>Time with Difficulty Moving Your Body</td>
<td>569</td>
<td>1.9 (1.04)</td>
<td>1.00</td>
<td>1.5</td>
<td>285 (50.3%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Ability to Get Out of Bed</td>
<td>569</td>
<td>2.0 (1.06)</td>
<td>2.00</td>
<td>1.5</td>
<td>253 (44.5%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Ability to Bend Over</td>
<td>569</td>
<td>2.1 (1.13)</td>
<td>2.00</td>
<td>1.5</td>
<td>229 (40.2%)</td>
<td>15 (2.6%)</td>
</tr>
<tr>
<td>Ability to do Usual Physical Activities</td>
<td>569</td>
<td>2.4 (1.21)</td>
<td>2.00</td>
<td>1.5</td>
<td>147 (25.8%)</td>
<td>45 (7.9%)</td>
</tr>
</tbody>
</table>

The applicant examined the MPFID domain scores’ ability to detect change in subjects known to have changed in clinical or health status, using a pre-defined PRO anchor scale, and controlling for age, sex, and baseline MPFID scores in the analysis. The PRO anchor threshold anchor used in the analysis was based on a previously established criterion that represented meaningful between-group differences in other datasets and publications cited by the applicant:

- \(\geq 1.2\) or \(< 1.2\) monthly migraine days

The applicant also conducted post-hoc exploratory analyses using the final, pooled data from clinical trial 20120297 to provide additional evidence establishing what constitutes clinically meaningful changes in MPFID domain scores to examine the results from the 20120296 phase 3 clinical trial and to inform labeling claims.

The following two tables and figures were reproduced from the applicant’s submission and represent the results from the analyses conducted to examine the MPFID domains’ ability to detect change:
Clinical Outcome Assessment Review
Sarrit M. Kovacs, PhD
BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

Ability to Detect Change: MPFID Score Change from Baseline to Month 3 (Weeks 9 to 12) by Reduction in Migraine Days Groups in Study 20120297 (N=164)

<table>
<thead>
<tr>
<th>Change Score</th>
<th>Change from Baseline in Monthly Migraine Days at Month 3</th>
<th>LS Mean Difference (95% CI)</th>
<th>Overall F-value (P-value)</th>
<th>P-value for Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.2 Days n LS Mean (SE)</td>
<td>&lt;1.2 Days n LS Mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domain 1: Impact on Everyday Activities</td>
<td>118 (-7.92 (0.79))</td>
<td>46 (1.19 (1.07))</td>
<td>-9.11 (-11.29, -6.94)</td>
<td>25.3 (&lt;0.0001)</td>
</tr>
<tr>
<td>Domain 2: Physical Impairment</td>
<td>118 (-6.22 (0.82))</td>
<td>46 (2.02 (1.10))</td>
<td>-8.23 (-10.49, -5.98)</td>
<td>24.0 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Anchor-Based Estimates for MPFID Domain Scores from Baseline to Month 3 (Weeks 9 to 12) in Study 20120297 (N=164)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly Migraine Days=50% Reduction</td>
<td>Primary Anchors</td>
<td>Exploratory Anchors</td>
<td>Exploratory Anchors</td>
<td>Exploratory Anchors</td>
</tr>
<tr>
<td>Monthly Migraine Days=50% to 70% Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Item from MPFID=≥20% Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSQ, RF-R Domain=5 to 10 point Increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT-6=5 to 10 Point Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly Migraine Days with Severe Pain=1 Day Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT-6=3 to 5 Point Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impact on Everyday Activities</th>
<th>N</th>
<th>Mean, (SD)</th>
<th>Mean, (SD)</th>
<th>Mean, (SD)</th>
<th>Mean, (SD)</th>
<th>Mean, (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>74</td>
<td>-9.1 (6.5)</td>
<td>-9.1 (5.9)</td>
<td>-7.5 (7.0)</td>
<td>-6.5 (5.4)</td>
<td>-2.2 (8.8)</td>
</tr>
<tr>
<td>Mean, (SD)</td>
<td>-7.4</td>
<td>-6.0</td>
<td>-7.4</td>
<td>-3.8</td>
<td>-7.3</td>
<td>-6.8</td>
</tr>
<tr>
<td>Physical Impairment</td>
<td>N</td>
<td>-7.6 (7.0)</td>
<td>-7.3 (6.6)</td>
<td>-5.5 (6.8)</td>
<td>-5.2 (5.3)</td>
<td>-1.1 (9.6)</td>
</tr>
<tr>
<td>Median</td>
<td>-5.8</td>
<td>-5.0</td>
<td>-5.7</td>
<td>-1.8</td>
<td>-5.3</td>
<td>-4.9</td>
</tr>
</tbody>
</table>

Reference ID: 4210510
Summary of Anchor- and Distribution-based Estimates for Change in MPFID Impact on Everyday Activities Domain Score from Baseline to Month 3 (Weeks 9-12) Based on Data from Study 20120297 (N=164)

*Exploratory anchor

Note: Reference line denotes proposed 5-point within-subjects change proposed based on blinded analysis of clinical trial 20120297 data.
Reviewer’s comments: During the IND phase, this reviewer asked the applicant to clarify whether the MPFID scores used in each of the reliability and validity analyses using the observational study (Study 20140136) were the average 28-day scores or the single day scores. The applicant replied that the analyses of convergent and known groups validity were conducted on the average of the 28 day scores on the MPFID and scores from the relevant measures completed at week 4; test-retest analysis was evaluated in a subgroup of stable patients using an average of the 7 day scores (between week 1 and week 4) and internal consistency was assessed using data from one random day.

During the IND phase, this reviewer requested that the applicant provide the Agency with the following data:

1. Descriptive statistics for the MPFID domain scores and overall impact global item.
2. **Baseline MPFID scores, item distribution by categories of response for each MPFID item; and floor and ceiling effects for each MPFID item.**

In general, the MPFID domains’ psychometric properties and performance (internal consistency, test-retest reliability, convergent validity, known-groups validity, and ability to detect change (using the blinded, pooled clinical trial data from Study 20120297) exceeded the applicant’s pre-specified criteria for acceptability and was in line with their expectations. However, the floor effects seen for more than half of the MPFID items exceeded the applicant’s pre-specified threshold of 30%. It is unclear why the applicant did not choose to remove those MPFID items with high floor effects before finalizing the instrument, given that floor effects indicate that a significant proportion of the patients are not experiencing those particular impacts of migraine and, therefore, would not be able to show improvement on those impacts. Although the applicant provided rationale for inclusion of those items with high floor effects based on the clinical expert input, those items may be suitable for use in clinical practice to obtain a more comprehensive picture of the impact of migraine on various types of daily activities, some of the concepts may not have regulatory utility for inclusion in a clinical outcome assessment intended to support an endpoint in a pivotal clinical trial for drug approval purposes. Therefore, while the MPFID’s measurement properties exceeded the applicant’s pre-specified criteria for acceptability, we caution against future use of the MPFID (version 2.0), without modification, in future drug development programs as it may continue to have floor effects for more than half of the items, leading to its insensitivity in detecting treatment effects.

7 **INTERPRETATION OF SCORES**

Interim analyses of longitudinal data from the observational study (Stage 3 of Study 20140136) and blinded, pooled data from one of the phase 3 clinical trials (Study 20120297) were used to interpret what constitutes a clinically meaningful within-subject improvement in MPFID domain scores.

For a within-subject improvement thresholds, two primary anchor scales were used by the applicant:

- ≥30% or ≥50% reduction from baseline in monthly migraine days
- ≥20% or ≥50% reduction from baseline in the monthly MPFID global question (item 8) score

The applicant provided rationale, based on their and other programs’ investigational prophylaxis migraine treatment trials, for using a 50% or greater reduction in monthly migraine days as a clinically meaningful anchor scale to interpret clinically meaningful improvement in MPFID domain scores. Furthermore, they included this responder definition as a pre-specified secondary endpoint in their phase 3 clinical trials. The applicant also provided rationale for using percent change in the MPFID global item (item 8) as a PRO anchor scale given that it represents the
subjects’ global impression of the overall impact of migraine (i.e., difficulty) related to performing their usual activities.

The table below was reproduced from the applicant’s MPFID evidence dossier (pages 72-73) and represents a summary of the anchor- and distribution-based estimates for point change in monthly MPFID domain scores (within-subject improvement thresholds).

<table>
<thead>
<tr>
<th>Study</th>
<th>Observational Study 20140136</th>
<th>Clinical Trial 20120297</th>
<th>Proposed Range of Thresholds for Within-subject Change in MPFID Domain Score (Responder Definition)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 1 to Month 4</td>
<td>Baseline Month to Month 3</td>
<td></td>
</tr>
<tr>
<td>Final Data (n = 167 EM)</td>
<td>Final, Pooled Data (n = 538 EM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point change</td>
<td>Point change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Mean</td>
<td>Median</td>
<td>N</td>
</tr>
<tr>
<td>MPFID EA domain Anchor-based estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly migraine days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30% reduction</td>
<td>94</td>
<td>-3.9</td>
<td>-3.4</td>
</tr>
<tr>
<td>≥ 50% reduction</td>
<td>76</td>
<td>-3.4</td>
<td>-3.4</td>
</tr>
<tr>
<td>Monthly MPFID G-EA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 20% reduction</td>
<td>91</td>
<td>-5.6</td>
<td>-4.1</td>
</tr>
<tr>
<td>≥ 50% reduction</td>
<td>51</td>
<td>-6.7</td>
<td>-5.2</td>
</tr>
<tr>
<td>HIT-6™ score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 point reduction</td>
<td>64</td>
<td>-2.6</td>
<td>-2.3</td>
</tr>
<tr>
<td>MSQ RF-R score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 point increase</td>
<td>111</td>
<td>-2.8</td>
<td>-2.4</td>
</tr>
<tr>
<td>Distribution-based estimates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50 SD at baseline</td>
<td>167</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>0.50 SD at final month</td>
<td>167</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>1 SEM (baseline to final month)</td>
<td>167</td>
<td>5.1</td>
<td></td>
</tr>
</tbody>
</table>
The applicant concluded that, based on the anchor-based analyses, a within-subject improvement of at least 5 points in the mean monthly MPFID domain scores (on a 0-100 point transformed scale) is clinically meaningful.
The applicant submitted CDF figures showing MPFID domain change score data from baseline to the mean of months 4, 5, 6 by treatment group in the efficacy analysis set for Study 20120296 (see appendices J and K).

After contacting 30 United States clinic sites, the applicant conducted three exit interviews with subject who completed the DBTP of phase 3 clinical trial 20120296 in order to collect qualitative data to understand the meaningfulness of changed in the MPFID scores from the patient perspective. Of the ten interested clinic sites, seven were sent study materials, completed a web-based training and received IRB approval. Five subjects were recruited and signed an informed consent form but ultimately three subjects were interviewed. All three of the subjects were women, White, and two were Not Hispanic or Latino and one was Hispanic or Latino. Their ages were: 52, 57, and 63 years. The subject characteristics table below was reproduced from the applicant's Exit Interview Study Report 20160343 (found as an appendix to the MPFID evidence dossier):

<table>
<thead>
<tr>
<th>Subject Characteristic</th>
<th>Female</th>
<th>Female</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>52</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>White</td>
<td>White</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic or Latino</td>
<td>Not Hispanic or Latino</td>
<td>Not Hispanic or Latino</td>
</tr>
<tr>
<td>Treatment Assignment during Double-blind Phase</td>
<td>AMG 334 140mg</td>
<td>AMG 334 70mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>Treatment Assignment during Active Treatment Phase</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mean Monthly Migraine Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening Phase$^1$</td>
<td>7.4</td>
<td>5.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Double-blind phase$^2$</td>
<td>1.3</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Active Treatment Phase$^4$</td>
<td>1.0</td>
<td>1.6</td>
<td>6.1</td>
</tr>
</tbody>
</table>

1 Mean monthly migraine days during screening period
2 Mean monthly migraine days from each of the last three DBTP months; months 4, 5, and 6
3 MMD during ATP up until the last full month prior to the subject’s interview during ATP

The table below represents the three exit interview subjects’ scores on the MPFID domains and were reproduced from the applicant’s Exit Interview Study Report.
Clinical Outcome Assessment Review
Sarrit M. Kovacs, PhD
BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

(Change scores from baseline that met the responder threshold of ≥5 points are shaded)

<table>
<thead>
<tr>
<th>MPFID Everyday Activities</th>
<th>Baseline</th>
<th>DBTP</th>
<th>ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject (140mg in DBTP)</td>
<td>20.1</td>
<td>4.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Subject (70mg in DBTP)</td>
<td>8.6</td>
<td>6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Subject (PBO in DBTP)</td>
<td>13.7</td>
<td>5.1</td>
<td>9.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MPFID Physical Impairment</th>
<th>Baseline</th>
<th>DBTP</th>
<th>ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject (140mg in DBTP)</td>
<td>13.8</td>
<td>2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Subject (70mg in DBTP)</td>
<td>6.8</td>
<td>5.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Subject (PBO in DBTP)</td>
<td>7.8</td>
<td>3.2</td>
<td>6.3</td>
</tr>
</tbody>
</table>

* DBTP MPFID scores are from the mean monthly average MPFID domain scores of the last 3 months of the DBTP, months 4-6 of the DBTP, MPFID scores from the ATP were each subject’s average month score from the last full month prior to their interview.

The subject who was on the 140 mg dose reported a meaningful benefit in all MPFID domain items and also showed an improvement in MPFID domain scores that exceeded the applicant’s pre-defined 5-point improvement threshold for each domain. The subject who was on the 70 mg dose also reported meaningful benefits in all MPFID domain items, but did not show improvement that met the applicant’s pre-defined 5-point improvement threshold for each domain. The subject who was on placebo reported noticing a “mild” change in her migraines during the DBTP and then reported feeling “markedly improved” when moving from the DBTP to the active treatment period. Her MPFID Impact on Everyday Activities domain improvement in scores met the applicant’s pre-defined 5-point improvement threshold, but her MPFID Physical Impairment domain improvement did not.

Reviewer’s comments: During the IND phase, this reviewer agreed that the applicant’s proposed strategy to develop preliminary responder definitions for both domains of the MPFID using the longitudinal data from the observational study (Study 20140136) appeared reasonable. Regarding using the clinically meaningful within-patient change from baseline in mean monthly migraine or headache days as anchor items, this reviewer asked the applicant to establish a priori what number of mean monthly migraine or headache days is considered clinically meaningful. This reviewer also recommended that the applicant examine the change in baseline in the MPFID global question (overall difficulty doing usual activities) as an exploratory anchor item in their observational study, as well the other anchor items that they included, including examining both “minimally improved” and “much improved”... The applicant confirmed that they plan to do use multiple anchors to explore the responder definitions.

During the IND phase, the applicant proposed... in either MPFID average (28-day) domain score as a clinically meaningful within-subject improvement threshold; however, the Agency did not agree that there was enough evidence submitted to support that this improvement threshold is clinically meaningful with regard to how patients feel and function in daily life. The Agency discouraged the applicant from using data from one of the...
two phase 3 trials (Study 20120297) to develop a within-subject improvement threshold for the MPFID, and rather to rely on data that will not be used to evaluate efficacy for approval. The applicant agreed with the Agency in not applying a threshold developed from a set of data to the same set of data. They clarified that their exploratory analyses to determine clinically meaningful within-subject change in MPFID domain scores are being conducted on pooled 20120297 data (and in observational study 20140136) and results will be included in the MPFID evidence dossier for Agency review, in addition to their rationale for selected anchors. The applicant asserted that they made no changes to the MPFID instrument or scoring algorithm based on results from their blinded analysis of the MPFID data from the 20120297 trial.

During the IND phase, this reviewer recommended the following to the applicant:
Submit cumulative distribution function (CDF) curves separately for all of the anchor scales included in the phase 3 trial (Study 20120297) as well as the observational study (Study 20140136). The x-axis would be the score change from baseline to month 3 (or month 1 to month 4 for the observational study) for each MPFID domain score (plot each domain score in a separate graph). The y-axis is the cumulative proportion of the patients (treatment and placebo arms pooled and blinded) in each of the corresponding anchor scale categories that reach the score change on the x-axis. A variety of responder definitions or thresholds can be examined simultaneously along the cumulative distribution of response curve for each anchor scale. More specifically, submit the following CDFs for the phase 3 trial and observational study, in addition to CDFs for the included only in the observational study (see Appendices H and I for copies of these scales):

- A CDF figure for MPFID “Impact on Everyday Activities” domain change scores from baseline to month 3 (or month 4 for the observational study) for all patients (treatment and placebo arms pooled and blinded) with separate curves for ≥50% reduction from baseline in mean monthly migraine days at month 3 (or month 4 for the observational study) versus <50% reduction from baseline in mean monthly migraine days at month 3 (or month 4 for the observational study). A similar CDF figure should be created for the “Physical Impairment” domain separately.

- A CDF figure for MPFID “Impact on Everyday Activities” domain change scores from baseline to month 3 (or month 4 for the observational study) for all patients (treatment and placebo arms pooled and blinded) with separate curves for ≥20% change versus <20% change from baseline in MPFID Overall Impact Global Item at month 3 (or month 4 for the observational study). A similar CDF figure should be created for the “Physical Impairment” domain separately.

- A CDF figure for MPFID “Impact on Everyday Activities” domain change scores from baseline to month 3 (or month 4 for the observational study) for all patients (treatment and placebo arms pooled and blinded) with separate curves for the different score point changes (e.g., 1-point, 2-point, 3-point, etc.) from baseline in
MPFID Overall Impact Global Item at month 3 (or month 4 for the observational study). A similar CDF figure should be created for the “Physical Impairment” domain separately.

- A similar CDF figure for the [BLA 761077] included only in the observational study
- Other CDF figures were requested but are not included in this review document.

During the IND phase, this reviewer recommended that the applicant consider having trained interviewers conduct patient interviews at study exit in both of the phase 3 clinical trials to assess their perception of what constitutes a clinically meaningful change from baseline in MPFID domain items and scores, as well as in reduction in mean monthly migraine days. And ensure that the patient population for the exit interviews includes patients with a range of migraine severity and other relevant demographics to provide robust data to help supplement the anchor-based and CDF methods to determine a clinically meaningful threshold and generate a responder definition. Optimally, patients would be interviewed at the beginning, middle and end of the trial. The applicant conducted some exit interviews at the end of the DBTP of Trial 20120296. We do not believe that there were enough subjects in the exit interview study to draw concrete conclusions regarding the clinical meaningfulness of changes in MPFID domain scores; however, the data obtained from the three subjects appears to be consistent with the rest of the applicant’s MPFID content validity and psychometric evaluation data.

After this reviewer examined the aforementioned CDF figures subsequently submitted by the applicant for Agency review (refer to Appendices D-G of the present document for a reproduced copy of the MPFID within-subject improvement threshold data and CDF figures submitted by the applicant during the IND phase), the following was conveyed to the applicant in a Written Response Only letter dated April 11, 2016:

“Regarding the anchor-based approaches to deriving a responder definition provided in your current submission, at this time, it is premature to agree that the confirmatory responder definition analyses (Phase 3 study 20120297) based on the 50% migraine reduction anchor supports [BLA 761077] that you propose as a responder definition for both MPFID domain scores. Using the anchor-based analyses and the medians obtained from the evaluation of cumulative distribution function (CDF) displays, the responder definitions obtained from the Phase 3 interim blinded data for both the Impact on Everyday Activities domain and the Physical Impairment domain appear to be higher than the [BLA 761077] threshold found using the observational data. Note that the clinical meaningfulness of the MPFID Phase 3 data will be reviewed with the BLA submission, along with the MPFID evidence dossier, anchor scale screen shots, patient and investigator training materials, and translation report.”

The following was conveyed to the applicant during the IND phase in minutes from the January 31, 2017 meeting with the Agency:
“Determination of the clinical meaningfulness of the MPFID will be evaluated during the review of your BLA and the complete MPFID evidence dossier. We suggest that you provide your rationale for using the anchor scales that you have proposed for determining within-patient change in your BLA submission. When doing so, we suggest that you use data from your existing qualitative research with migraine patients and observational psychometric evaluation study. We also suggest that you establish thresholds using the MPFID domain point change, rather than percent change, in line with the endpoint definition given that percent change can be affected by the baseline score.”

This reviewer expressed the following concerns to the Review Division regarding the applicant’s proposed approaches to support the clinical meaningfulness of change in MPFID domain scores:

- The applicant should clarify their rationale for using the following anchor scales categories for determining within-patient change based on their existing qualitative research with migraine patients and quantitative data from the observational psychometric evaluation study (Study 20140136):
  - “1, 2 day reduction in monthly acute migraine-specific medication treatment days”
  - “20%, 50% reduction or 1, 2 point reduction in MPFID global item score"

The applicant provided rationale for the clinical meaningfulness of their selected PRO anchors.

The COA Staff deferred to the Review Division and the OB statistical reviewer regarding the adequacy of the applicant’s plans to evaluate between-group differences as COA Staff do not review separation between study arms, but rather the clinical meaningfulness of within-patient improvement in scores.

With regard to our conclusion regarding the applicant’s proposed threshold for clinically meaningful within-subject improvement in MPFID domain scores, we still believe that the improvement thresholds More specifically, based on the data provided in appendices D-G in the present review document, we have the following comments:

- For the Impact on Everyday Activities domain:
  - The observational study data showed a 4.1-point improvement (reduction) in score (from the baseline month to month 4) for 50% of subjects reporting at least a 50% reduction in migraine days (results obtained from the CDF figure located in Appendix D, but the applicant’s new table included above in this section shows a 3.4-point median improvement for EM subjects), but a mean improvement of 4.7 points for all subjects reporting at least a 50% reduction in migraine days (results based on data table submitted by the applicant during the IND phase, but the
applicant’s new table included above in this section shows a 3.4-point mean improvement for EM subjects).

- We do not agree with the applicant that a 3% improvement anchor threshold for the MPFID global item is clinically meaningful because a 20% improvement in MPFID global item score does not correspond with a full category change in item score except for patients who move in response categories from “extremely difficult” at baseline to “very difficult” at month 4, which is likely not a clinically meaningful improvement in categories from the patient perspective. Therefore, we believe that a clinically meaningful improvement threshold for the MPFID Impact on Everyday Activities domain should exceed the 4.4-point improvement (reduction) seen for 50% of subjects experiencing at least a 20% improvement in MPFID global item score. The new table from the applicant included above in this section shows mean and median improvements (reductions) of 6.7 points and 5.2 points respectively using a 50% or greater MPFID global item improvement threshold.

- Looking at the CDF figure to be helpful because the applicant pooled the response categories with the respective anchor, 50% of subjects reporting at least a 3-point improvement in score (which may be clinically meaningful depending on the subject’s baseline score) showed an improvement (reduction) of 5.9 points.

- We do not find the CDF figure to be helpful because the applicant pooled the response categories with the respective anchor, 50% of subjects reporting at least a 3-point improvement in score (which may be clinically meaningful depending on the subject’s baseline score) showed an improvement (reduction) of 5.9 points.

- The phase 3 clinical trial (Study 20120297) data showed higher improvement thresholds than the observational study likely because the observational study did not include a true treatment-free baseline.

- A mean improvement of 9.1 points was seen for all subjects reporting at least a 50% reduction in migraine days and a 7.4-point improvement (reduction) in score for 50% of subjects reporting at least a 50% reduction in migraine days (results based on a data table submitted by the applicant during the IND phase and a CDF figure included in Appendix F, but the applicant’s new table included above in this section shows mean and median improvements (reductions) of 9.0 points and 7.6 points respectively).

- The CDF figure displaying the results for the MPFID global item improvement anchor shows that 50% of subjects experiencing at least a 20% improvement in MPFID global item score had a 7.4-point improvement (reduction) in their MPFID Impact on Everyday Activities domain score. As mentioned above, we do not agree that a
improvement in MPFID global item score is clinically meaningful. The new table from the applicant included above in this section shows mean and median improvements (reductions) of 9.3 points and 7.8 points respectively using a 50% or greater MPFID global item improvement threshold.

- In conclusion, we believe that the threshold for clinically meaningful improvement in the MPFID Impact on Everyday Activities domain should be and probably in the range of 8 or 9 points, although we do not have the data necessary to determine a more concrete improvement threshold. Around a threshold range of about 8 to 9 points improvement in domain score, there is about a 10% to 7% magnitude of separation between the treatment and placebo arm curves, respectively, in the CDF Figure appended as Appendix J (Study 20120296 clinical trial).

- For the Physical Impairment domain:
  - The observational study data submitted by the applicant during the IND phase showed a very small point improvement (reduction) in score (from the baseline month to month 4) for 50% of subjects reporting at least a 50% reduction in migraine day; the reduction was likely less than 3 points but the legend containing the median score under the CDF figure submitted by the applicant was cut off. The new table from the applicant included above in this section shows a median improvement (reductions) of 1.1 points. The applicant reported a mean improvement of 3.1 points for all subjects reporting at least a 50% reduction in migraine days in a data table submitted during the IND phase, but a 1.6-point mean improvement (reduction) in the new table included above in this section.
    - As mentioned above, we do not agree with the applicant that a % improvement anchor threshold for the MPFID global item and the are clinically meaningful anchors. However, in the new table included above in this section, the applicant showed mean and median improvements (reductions) of 7.4 and 6.0 points using a 50% or greater MPFID global item improvement threshold.
    - Looking at the as an anchor, 50% of subjects reporting at least a 3-point improvement in score (which may be clinically meaningful depending on the subject’s baseline score) showed an improvement.
  - The phase 3 clinical trial (Study 20120297) data showed higher improvement thresholds than the observational study likely because the observational study did not include a true treatment-free baseline.
    - A mean improvement of 7.6 points was seen for all subjects reporting at least a 50% reduction in migraine days and a 5.9-point improvement (reduction) in score for 50% of subjects reporting at least a 50% reduction in migraine days.
The CDF figure displaying the results for the MPFID global item improvement anchor shows that 50% of subjects experiencing at least a \( \frac{80}{(80)} \)% improvement in MPFID global item score had a 5.7-point improvement (reduction) in their MPFID Impact on Everyday Activities domain score. As mentioned above, we do not agree that a \( \frac{80}{(80)} \)% improvement in MPFID global item score is clinically meaningful.

In conclusion, we believe that the threshold for clinically meaningful improvement in the MPFID Physical Impairment domain should be \( \frac{6}{(6)} \) and probably in the range of 6 or 7 points, although we do not have the data necessary to determine a more concrete improvement threshold. Around a threshold range of about 6 to 7 points improvement in domain score, there is about a 12% to 10% magnitude of separation between the treatment and placebo arm curves, respectively, in the CDF Figure appended as Appendix K (Study 20120296 clinical trial).

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Both phase 3 clinical trials (Study 20120296 and 20120297) included sites across North America and Europe, and potentially other regions. The MPFID was translated into 20 languages and culturally adapted for 25 countries. All translated versions of the MPFID were confirmed to be conceptually equivalent and well understood in the 25 countries evaluated.

Two forward translations by native translators, a reconciliation of forward translations, back-translation by one English-speaker fluent in the target language, and a final review by a native-speaking language coordinator were conducted for each non-English language. Comparison between languages for consistent interpretation was performed to ensure conceptual equivalence across languages. The content of the translated versions was tested using cognitive interviews with at least 5 native-speaking migraine subjects for each language/country combination \( (n=146) \). Interview data were analyzed qualitatively to assess linguistic and cultural validity in each language, and to confirm conceptual equivalence. The applicant provided a report of the translation and cross-cultural adaptation work, and documented minor revisions to items resulting from this process in the item tracking matrix also submitted in their MPFID evidence dossier.

Reviewer’s comments: We believe that the translation and cultural adaptation processes used by the applicant appear acceptable.

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

The applicant evaluated the conceptual equivalence between electronic and pen-and-paper modes of administration (non-randomized; pen-and-paper version was completed first and then the electronic version) with 10 adults with migraine (Study 20140252). Conceptual equivalence was
met for all subjects (n=10; 100%) for all but one of the items. Conceptual equivalence was ‘not evaluable’ in one item because of one subject (n=1, 10% for Item 9). The subject did not understand the item (Item 9, “In the past 24 hours, overall, how difficult was it to do your usual activities?”) while completing it on pen and paper (“Just cause I didn’t understand, I didn’t understand this”).

*Reviewer’s comments: The applicant’s mode equivalence testing appears acceptable.*

10 REVIEW USER MANUAL

The applicant submitted a user manual and scoring guide for the MPFID version 2.0 (dated March 22, 2017). The user manual is consistent with the applicant’s context of use.

*Reviewer’s comments: The applicant’s MPFID user manual appears acceptable.*
D. APPENDICES

Appendix A – Definitions of Migraine Day and Headache Day

[The definitions included below were copied from the applicant’s phase 3 clinical trial protocol.]

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as 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 pain features:
   - Unilateral
   - Throbbing
   - Moderate to severe
   - Exacerbated with exercise/physical activity

b) ≥ 1 of the following associated symptoms:
   - Nausea and/or vomiting
   - Photophobia and phonophobia

If the subject took a migraine-specific medication (i.e., triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

Headache Day: Any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered
Appendix B – Screenshots of MPFID Version 2.0

The Migraine Physical Function Impact Diary (MPFID)
(Version 2.0)

The following questions are about your ability to function in the past 24 hours.

We would like to understand how a migraine affects your ability to do day-to-day activities.

Symptoms of migraine can include headache pain, nausea, vomiting, or sensitivity to light or noise.

We want you to think about the symptoms that you experience and how they impact your day-to-day activities.

Please answer all questions by selecting the one option that best describes your experience.

1. In the past 24 hours, were you able to do your usual household chores?

   - Without any difficulty
   - With a little difficulty
   - With some difficulty
   - With much difficulty
   - Unable to do

2. In the past 24 hours, were you able to do your usual activities outside your home? (For example, shopping or running errands)

   - Without any difficulty
   - With a little difficulty
   - With some difficulty
   - With much difficulty
   - Unable to do

3. In the past 24 hours, were you able to keep to your daily routine or schedule?

   - Without any difficulty
   - With a little difficulty
   - With some difficulty
   - With much difficulty
   - Unable to do
4. In the past 24 hours, were you able to do activities that required you to concentrate?

- Without any difficulty
- With a little difficulty
- With some difficulty
- With much difficulty
- Unable to do

5. In the past 24 hours, were you able to get yourself ready for the day?

- Without any difficulty
- With a little difficulty
- With some difficulty
- With much difficulty
- Unable to do

6. In the past 24 hours, how much of the time did you avoid interacting with other people?

- None of the time
- A little of the time
- Some of the time
- Most of the time
- All of the time

7. In the past 24 hours, how much of the time did you need to rest or lie down during your normal waking hours?

- None of the time
- A little of the time
- Some of the time
- Most of the time
- All of the time
8. In the past 24 hours, overall, how difficult was it to do your usual activities?

- Not difficult
- A little difficult
- Moderately difficult
- Very difficult
- Extremely difficult

9. In the past 24 hours, how much of the time did you have difficulty moving your head?

- None of the time
- A little of the time
- Some of the time
- Most of the time
- All of the time

10. In the past 24 hours, how much of the time did you have difficulty moving your body?

- None of the time
- A little of the time
- Some of the time
- Most of the time
- All of the time

11. In the past 24 hours, were you able to get out of bed?

- Without any difficulty
- With a little difficulty
- With some difficulty
- With much difficulty
- Unable to do
12. In the past 24 hours, were you able to bend over?

- Without any difficulty
- With a little difficulty
- With some difficulty
- With much difficulty
- Unable to do

13. In the past 24 hours, were you able to do usual activities that required physical effort?

- Without any difficulty
- With a little difficulty
- With some difficulty
- With much difficulty
- Unable to do
Appendix C – Previous Version of MPFID (MPFID; Version 1.0)
Appendix D – CDF Figures (Impact on Everyday Activities Domain)
Submitted by Applicant during IND Phase (Observational Study 20140136)
Clinical Outcome Assessment Review
Sarrit M. Kovacs, PhD
BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

Figure A5. CDF Plot – Domain 1: Impact on Everyday Activities Change by MPFID Global Point Change at Baseline Month (Weeks 1-4) to Month 4 (Weeks 13-16), Study 156 (Cohort 2 EM, N=78)
Clinical Outcome Assessment Review
Sarrit M. Kovacs, PhD
BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)
Appendix E – CDF Figures (Physical Impairment Domain) Submitted by Applicant during IND Phase (Observational Study 20140136)

Figure 1b. CDF Plot – Physical Impairment Change by 50% Migraine Reduction at Baseline Month (Weeks 1-4) to Month 4 (Weeks 13-16), Study 20130136 (Cohort 2 EM, N=78)
Appendix F – CDF Figures (Impact on Everyday Activities Domain) Submitted by Applicant during IND Phase (Phase 3 Trial 20120297)

Figure 2a. CDF Plot – Impact on Everyday Activities Change by 50% Migraine Reduction at Baseline Month (Weeks -4 to 0) to Month 3 (Weeks 9-12), Study 20120297 (N=164)
Clinical Outcome Assessment Review
Sarrit M. Kovacs, PhD
BLA 761077
Erenumab; AMG 334/Aimovig
Migraine Physical Function Impact Diary (MPFID)

Figure A6. CDF Plot – Domain 1: Impact on Everyday Activities Change by MPFID Global Point Change at Baseline Month (Weeks -4 to 0) to Month 3 (Weeks 9-12), Study 297 (N=154)
Appendix G – CDF Figures (Physical Impairment Domain) Submitted by Applicant during IND Phase (Phase 3 Trial 20120297)

Figure 2b. CDF Plot – Physical Impairment Change by 50% Migraine Reduction at Baseline Month (Weeks -4 to 0) to Month 3 (Weeks 9-12), Study 20120297 (N=164)
Figure A8. CDF Plot – Domain 2: Physical Impairment Change by MPFID Global Point Change at Baseline Month (Weeks -4 to 0) to Month 3 (Weeks 9-12), Study 297 (N=164)
Appendix J – CDF Figure (Change From Baseline to Mean of Months 4, 5, 6 on Impact on Everyday Activities Domain Score by Treatment Group in Efficacy Analysis Set for Study 20120296)
Appendix K - CDF Figure (Change From Baseline to Mean of Months 4, 5, 6 on Physical Impairment Domain Score by Treatment Group in Efficacy Analysis Set for Study 20120296)
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/s/

SARRIT M KOVACS
01/22/2018

ELEKTRA J PAPADOPOULOS
01/23/2018
We have the following comments regarding your proposed container labels and carton labeling submitted on May 17, 2017.

A. General Comments
1. The container label and carton labeling do not include the proprietary name Aimovig (found conditionally acceptable August 21, 2017) or the proper name (erenumab-xxxx). Remove the term “(b)(4)” and replace it with the proper name “erenumab-xxxx”. We recommend that the label and labeling are revised throughout to include this key prescribing information.

B. PFS and Autoinjector Container Label
1. Consider relocating “Rx Only” to appear in the upper right corner of the prefilled autoinjector container label to allow for prominence of other critical information on the principal display panel such as dosage form and discard statement.
2. Add the dosage form “injection” to appear underneath the proper name in the identical font size and color as the proper name as follows:
   
   Trade name
   (proper name)
   Injection

You may accommodate this change by removing the licensed manufacturer address (Thousand Oaks, CA 91320) and listing only the licensed manufacturer name and U.S. license number as follows: “Amgen Inc. U.S. License No. 1080”. We consider this to be a partial label and the licensed manufacturer address is not required information on partial labels. Revise the order of appearance of the licensed manufacturer name so that the U.S. License No. 1080 appears after the licensed manufacturer name.

3. The appropriate package-type term for this product is “single-dose”. A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/infusion. Use of the term “single-dose” container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials/PFS may be needed to obtain a single dose. Revise the term “(b)(4)” to read “single-dose” and include a statement of “Discard unused portion” as follows: “Single-dose. Discard unused portion”. To accommodate this important information, you may consider removing the container closure statement from the container label.
4. The storage information is not required for a partial label. Consider removing to reduce clutter or revise the storage statement from “Store at 2°C to 8°C (36°F to 46 ºF)” per USP definitions (see USP chapter <659> Packaging and Storage Requirements).

5. Clarify the difference between the container label and the white container label provided in the submission.

C. PFS and Autoinjector Carton Labeling

1. Add the dosage form “injection” to appear underneath the proper name in the identical font size and color as the proper name as follows:

   Trade name
   (proper name)
   Injection

2. To comply with 21 CFR 610.61(b), ensure that the U.S. license number appears after the licensed manufacturer name and address as follows: “Manufactured by Amgen Inc. Address US License No. 1080”

3. To reduce clutter and redundancy, remove the statement “Sterile, preservative-free solution” from the principal display panel. This information is already in the quantitative and qualitative ingredient list on the side panel.

4. Revise the strength statement in the colored circles to the appropriate strength presentation for this dosage form: “70 mg/mL”. Per USP General Chapters <7> Labeling, strength per single mL should be expressed as mg/mL. For cartons that contain two autoinjectors or two prefilled syringes, revise the strength statement in the colored circles to read “70 mg/mL”.

5. For cartons that contain two autoinjectors or two pre-filled syringes, revise the statement from “2 x 70 mg/mL prefilled autoinjectors” or “2 x 70 mg/mL prefilled syringes” (as appropriate for the delivery device).

6. The strength statement appearing on the principal display panel of the carton labeling is not prominent and may be overlooked. We recommend that the prominence (e.g. font size) is increased to mitigate the risk of user confusion regarding the product strength per 21 CFR 201.15(a)(6).

7. For consistency with the prescribing information, provide complete storage information for the end user, and space for documentation of date removed from the refrigeration. Add the storage statement “Storage: Refrigerate at 2°C to 8°C (36°F to 46 ºF) in the original carton to protect from light. Do Not Freeze. Do Not Shake. If needed, patients/caregivers may store Aimovig at room temperature up to 25°C (77°F) for up to 42 days. Once stored at room temperature, do not place back in the refrigerator. Discard after 42 days. Write the date removed from the refrigerator ___/___/___.”
8. Revise the storage statement on the principal display panel to read “Store at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do Not Freeze. Do Not Shake. Discard Any Unused Portion.”

9. Revise the package type term in the qualitative and quantitative ingredient list to “single-dose” and the proper name from “(b) (4)” to “erenumab”.

10. Revise the term “(b) (4)” to read “single-dose” throughout carton labeling.

11. Unbold the Rx only statement as it competes with other important information and relocate the Rx only statement to the upper portion of principal display panel near the NDC number.
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/s/

LANA Y CHEN
11/20/2017
with concurrence from Tracy Peters, ADL and Heather Fitter, MD, CDTL
DATE: November 15, 2017

TO: Billy Dunn, M.D.
Director
Division of Neurology Products (DNP)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Routine inspection of QPS-Miami Research Associates (QPS-MRA), LLC, Miami, FL.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of Study 20140477 (BLA 761077) conducted at QPS-MRA, LLC, Miami, FL.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited study (Study 20140477) are reliable. Thus, I recommend that the data from Study 20140477 and other studies of similar design be accepted for further Agency review.

Inspected Study:

Study Number: 20140477
Study Title: “An open Label Randomized Parallel Group Study in Healthy Volunteers to Assess the Relative Bioavailability of 3 Different AMG 334 Treatments”
**Dates of study:** 1/31/2016 - 8/24/2016

* Data snapshot

**Clinical Site:** QPS-MRA, LLC  
6141 Sunset Drive, Suite 301  
Miami, FL 33143-5026

ORA investigator Craig A. Garmendia (DBIMO-I) inspected QPS-MRA, LLC, Miami, FL from October 2 - 10, 2017.

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

At the conclusion of the inspection, investigator Garmendia did not observe any objectionable conditions and did not issue Form FDA 483 to QPS-MRA.

**Conclusion:**

After reviewing the inspectional findings, I conclude the data from the audited study are reliable. Therefore, I recommend that the data from **Study 20140477 (BLA 761077)** be accepted for further review. In addition, the data from studies of similar design submitted to pending applications (**Attachment 1**) should be accepted for further Agency review.

Based on the inspectional findings, studies of similar design conducted between the previous inspection (Sep 2013) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection.

Yiyue Zhang, Ph.D.  
DNDBE, OSIS

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**Attachment 1**

**Study submitted in Support of Pending Application**

<table>
<thead>
<tr>
<th>Application #</th>
<th>Study #</th>
<th>Drug Name</th>
<th>Dates of conduct</th>
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<tr>
<td>BLA 761077</td>
<td>20140477</td>
<td>AMG 334</td>
<td>1/31/2016 - 8/24/2016</td>
</tr>
</tbody>
</table>
Final Classification:

Clinical Site
NAI - QPS-MRA, LLC, Miami, FL (FEI: 3010409481)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au
ORA/OMPTO/OBIMO,DBIMOI/Garmendia

Draft: YZ 11/9/2017, 11/14/2017
Edit: RCA 11/9/2017; 11/15/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES/QPS-MRA, LLC, Miami, FL, USA/BLA 761077_Prefilled Syringe Prefilled Auto-Injector Syringe Vial

OSIS File#: BE 7560
FACTS: 11763265
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/s/

YIYUE ZHANG
11/15/2017

RUBEN C AYALA
11/16/2017

ARINDAM DASGUPTA
11/16/2017
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products  
DCRP Consult BLA 761077

DATE:  
Date of Document: June 9, 2017  
Date of Consult: 6/26/17  
Desired Completion Date: Jan 17, 2018  
Date of Completion: November 9, 2017

FROM:  
Preston M. Dummmon, M.D., M.B.A., Medical Officer  
Division of Cardiovascular and Renal Products, HFD-110

THROUGH:  
Shari L. Targum, M.D., M.P.H., Medical Team Leader  
Division of Cardiovascular and Renal Products, HFD-110  
Norman Stockbridge, M.D., Ph.D., Division Director  
Division of Cardiovascular and Renal Products, HFD-110

TO:  
Heather Fitter, MD, CDTL, DNP

PRODUCT NAME:  
Aimovig (erenumab, AMG 334)

FORMULATION/DOSE:  
140 mg IV, single dose

PRODUCT CLASS:  
IgG2 mAb antagonist for calcitonin gene-related peptide (CGRP)

SPONSOR:  
Amgen

INVESTIGATIONAL INDICATION:  
for the prophylaxis of migraine

REASON FOR CONSULT AND CONSULT QUESTIONS:

CGRP is known to be a potent vasodilator and thought to play a role in cardiovascular homeostasis. The sponsor has conducted study 20140254, a small study of patients with stable angina who were administered a single dose of erenumab and who then underwent treadmill testing.
The Review Division requests that DCRP review this study, and then answer the following questions:

- Is the study designed appropriately to meet the primary objective and safety objectives?
- Is the stratification by time of ETT (exercise treadmill test) appropriate?
- The sponsor has used a change of 90 seconds from baseline as the non-inferiority margin. Is the change Reference ID: 4116582 from baseline of 90?
- Is this the appropriate margin to use for both stratification groups?
- Does this study adequately

Following the submission of this consult, the Review Division also requested that DCRP review two cardiac deaths that have occurred in the development program (these did not occur in the treadmill study 20140254). DCRP has also been asked to comment on what appears to be a dose related increase in the occurrence of supraventricular arrhythmias in the Phase 3 trials.

DOCUMENTS REVIEWED:

- 04/04/2016 SAP for Study 20140254
- 01/07/2017 SAP for Study 20140254
- 04/13/2017 Study 20140254 Clinical Study Report
- 05/17/2017 ISS
- 06/26/2017 DPP consult to DCRP


- CGRP is localized to sensory nerves innervating multiple organs, including the heart, allowing into act in a sensory-efferent manner to local (tissue level stimuli)
- CGRP is a microvascular vasodilator, potency that is ~10-fold higher than the most potent prostaglandins and 10–100 times greater than other vasodilators such as ACh and neuropeptide substance P (SP). It is thus the most potent microvascular vasodilator known as of the writing of the October 2014 of the physiology and pathophysiology review by Russell et al (Physiol Rev 94: 1099–1142, 2014. doi:10.1152/physrev.00034.2013)
- Shown to act as a vasodilator in healthy human volunteers and in cardiovascular patients
- Raises intracellular adenylate cyclase (AC) activity and cAMP
- Positive inotropic and chronotropic responses in the heart, in addition to vasodilator effects, are observed after intravenous CGRP administration

BLA 761077

Reference ID: 4180099
• Data from CGRP antagonists appears to confirm that antagonism of CGRP receptors does not particularly affect BP, though CGRP knockouts in the ANG II model has shown that CGRP deletion not only leads to increased hypertension, but enhances loss of eNOS.
• ET-1-induced arterial contractions are sensitive to relaxation by CGRP, and this effect is independent of NO, cyclic nucleotides, and K⁺ channels
• CGRP-immunoreactive fibers have been reported to innervate the heart vasculature, in a diffuse, but comprehensive manner throughout the myocardium and coronary vessels, thus are positioned to act in a sensory-efferent manner
• A cardioprotective role for CGRP has been suggested, but as for hypertension, knowledge of the exact mechanisms involved is limited. The following observations are relevant to this consult regarding the role of this pathway in ischemia:
  o CGRP as a cardiac signaling molecule has been shown to be a very potent endogenous mediator of preconditioning (the phenomenon whereby preexposure of the heart to a preconditioning agent can attenuate subsequent damage incurred by an ischemic episode)
  o In humans following acute myocardial infarction, immunoreactive CGRP is raised in plasma, as well as in nerves, implicating its release in response to either the stressed metabolic environment that occurs after ischemia, or to the decreased vasodilatation
  o CGRP is also implicated in coronary artery disease (CAD) patients where serum levels were reduced compared with normal healthy individuals
• Russell et al diagram the potential local and systemic mechanisms involving CGRP in cardiovascular regulation as follows:

**STUDY 20140254: (report date 13 April 2017):**

**Title**

BLA 761077
A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 34 on (Standard Bruce) Exercise Time During a Treadmill Test in Subjects with Stable Angina

Study Initiation Date:

23 November 2015 (first subject enrolled)

Study Completion Date:

- Last subject enrolled: 19 January 2017
- Primary analysis (complete), data cutoff date: 23 January 2017
- Safety follow-up is ongoing

Objectives

- Primary: To evaluate the effect of AMG 334 compared to placebo on exercise capacity in subjects with stable angina as measured by total exercise time during an exercise treadmill test.

- Secondary: To evaluate the effect of AMG 334 compared to placebo during an exercise treadmill test on the time to the onset of:
  - Exercise-induced angina
  - \( \geq 1 \) mm ST-segment depression

Study Design and Schematic (from sponsor CSR)

This was a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. At least 54 subjects were randomized in a 1:1 ratio to receive either a single dose of AMG 334 140 mg or placebo intravenously (IV) prior to completing an exercise treadmill test (using the standard Bruce protocol, per the figure below):
Randomization was stratified by the total exercise time average (≤ 7 minutes or ≥ 7 minutes) of the 2 qualifying exercise treadmill tests performed during screening. Treatment groups were blinded to the investigators, subjects, and the Amgen study team. The study duration for an individual subject was approximately 18 weeks, consisting of a period up to 6 weeks for screening and a 12-week safety follow-up period that followed the single dose of investigational product.

Reviewer’s Comment: The original plan was for 120 enrolled subjects. This was reduced to “at least 54” by study amendment 4. The SAP revision was dated 7 January 2017, which was 12 days following the last subject’s enrollment and 16 days before the primary analysis data cutoff date. This amendment 4 also modified the primary hypotheses, specifically to change the non-inferiority margin from -60 seconds to -90 seconds.

Study Centers
Trial Oversight

An independent DMC oversaw subject safety for this study.

Key Inclusion Criteria

- Age ≥ 18 to ≤ 85 at the time of screening
- History of chronic stable angina for at least 3 months prior to screening, with at least 1 angina episode/month, on average over that period
- Ischemic heart disease documented by any one or more of the following:
  - A history of myocardial infarction (MI) with elevated Creatine kinase - myocardial band (CK-MB), troponin I or T, or the presence of electrocardiogram (ECG) changes consistent with an MI, or
  - Coronary angiography demonstrating at least 1 major epicardial coronary artery (e.g., left anterior descending, left circumflex, or right coronary artery) with a stenosis of at least 50% diameter or greater but excluding > 50% or flow-limiting stenosis of the left main coronary artery unless revascularized by coronary artery bypass grafting, or
  - Revascularization procedure (e.g., cardiac bypass graft, angioplasty) ≥ 3 months prior to screening
- Receiving stable doses of cardiac medications (e.g., beta blockers, calcium channel blockers, antianginals, etc.) for at least 30 days prior to randomization and that are not expected to change during the study
- Completes 2 qualifying ETTs during screening period (as described for Screening in Section 7.3.7 and Section 7.3.8). The following ETT qualifications are required:
  - Limitation of exercise due to symptoms related to myocardial ischemia (such as angina pectoris, chest pain/discomfort, dyspnea, shortness of breath), or ≥ 3 mm ST-segment depression
Key Exclusion Criteria

- Inability to refrain from use of caffeine or nicotine products within 2 hours prior to a scheduled ETT
- Unable to refrain from unaccustomed strenuous physical activity from the date of consent through their completion of the trial
- History of cardiovascular conditions (including but not limited to severe aortic or mitral stenosis, heart failure New York Heart Association (NYHA) class 3 or 4, Brugada or long QT syndrome) that may interfere with the conduct or interpretation of the study or may constitute a safety risk per the investigator
- Systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure (DBP) > 90 mmHg (determined by the mean of 3 consecutive measurements at least 5 minutes apart during screening)
- Within the 3 months prior to or during screening
  - Unstable angina or acute coronary syndrome
  - Transient ischemic attack (TIA) or stroke
  - Revascularization procedure
  - d. Instability in ST-segment depression between screening ETTs, as assessed by the core ECG laboratory
- ECG findings that preclude analysis of the ETT, including but not limited to:
  - Any right or left bundle branch block
  - Pacemaker
  - Resting ST-segment depression ≥ 1.0 mm
  - Left ventricular hypertrophy with repolarization changes
  - Wolf-Parkinson White
- Digitalis or Implantable defibrillator use

Amendment 4

AMENDMENT 4
28 October 2016
(38 subjects enrolled)

- Change in primary hypotheses, specifically to change the non-inferiority margin from -60 seconds to -90 seconds
- Sample size was changed from 120 subjects to at least 54 subjects

Analysis Set Definitions
• The Full Analysis Set (FAS) includes all randomized subjects. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received.

• The Efficacy Analysis Set (EAS) utilizes the FAS and includes subjects who received IP and completed the exercise treadmill test post-randomization (ETTr). Subjects will be grouped according to their randomized treatment, regardless of the treatment received.

Efficacy Endpoints and Analysis Methods (from the SAP)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Primary and Secondary Analysis Methods (EAS)</th>
<th>Sensitivity Analysis Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in TET (seconds)</td>
<td>• Primary analysis: Two-Way ANOVA model with terms of treatment group and randomization strata (&lt; 7 or ≥ 7 minutes)</td>
<td>• Analysis of covariance (ANCOVA) model with terms of treatment group and baseline TET as a continuous measure</td>
</tr>
<tr>
<td>Time to onset of exercise-induced angina* (seconds)</td>
<td></td>
<td>• Repeat primary analysis by subgroups, including baseline TET randomization strata, age group and sex (if sample size permits)</td>
</tr>
<tr>
<td>Time to onset of ≥ 1 mm ST-segment depression (seconds)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*includes angina-related symptoms

Missing Data (from SAP)

Missing assessment at baseline or on-study will not be imputed.

BLA 761077
Reviewer’s Comment: According to the SAP, as amended shortly before database lock, (the primary analysis was a “non-inferiority study” with the following hypotheses:

- **Null Hypothesis:** In subjects with angina, AMG 334 does significantly decrease exercise capacity (by at least 90 seconds), as measured by change from baseline in total exercise time, compared to placebo, and that the true treatment difference in change from baseline in TET is -90 seconds or more (worse).

- **Alternative Hypothesis:** In subjects with angina, AMG334 does not decrease exercise capacity, as measured by change from baseline in total exercise time, compared to placebo, and that the difference in change from baseline in TET if any, is less than a 90 second decrease.

The sponsor rationalizes this change by stating the following:

Assuming between-subject standard deviation for change from baseline in exercise duration of 130 seconds, with a planned study size of at least 27 subjects in each group and a difference in change from baseline in exercise duration of 0 seconds between AMG 334 group and placebo group, there is an 80% probability (power) that the lower bound of the 90% confidence interval (CI) will exceed -90 seconds. A margin larger than -60 seconds between groups was required to accommodate the possibility of more than 60 second (up to 20%) difference allowed in qualifying TETs for individual subjects. Because of this within-subject TET variation, a maximum TET difference of 90 seconds between the AMG 334 group and placebo group was considered reasonable in this study. A margin of -90 seconds was selected, which corresponds to the margin used in previous study testing a comparable hypothesis (Patterson, et.al 2005). Twenty-nine subjects are needed in each group if considering 5% dropout.

The sponsor’s decision to cut the sample size after 14 months appears to have driven the decision to expand the “non-inferiority margin”, though in the end, that did not appear necessary assuming that a 90% confidence interval for the placebo-corrected change from baseline is sufficient for this small/truncated study to support a regulatory claim.

Of note, the reference by Patterson et al (used by Amgen to support their analytical approach (Br J Clin Pharmacol. 2005, 60: 459-468) was a study funded by Lilly that tested the ETT effects of Tadalafil on ETT performance. In that randomized, placebo-controlled, doubleblind, two-period crossover study in 23 subjects, the difference of mean exercise duration of the groups (tadalafil minus placebo) was 3 seconds with the lower 95% CI for the mean least squares difference (tadalafil minus placebo) being -14 s which did not exceed the
predefined limit of -60 s of a Modified Bruce Protocol. This information is indeed included in the Tadalafil label as a claim that tadalafil was non-inferior to placebo with respect to time to ischemia.

Disposition of Subjects

Table 9-1. Subject Disposition: Full Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 44</th>
<th>AMG 334 140 mg N = 45</th>
<th>Total N = 89</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Investigational product accounting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects who never received investigational product</td>
<td>0 (0.0)</td>
<td>1 (2.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Subjects who received investigational product</td>
<td>44 (100.0)</td>
<td>44 (97.8)</td>
<td>88 (98.9)</td>
</tr>
<tr>
<td>Subjects who completed investigational product</td>
<td>44 (100.0)</td>
<td>44 (97.8)</td>
<td>88 (98.9)</td>
</tr>
<tr>
<td>Subjects who discontinued investigational product</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Decision by sponsor</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Subject request</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Study completion accounting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects who completed study</td>
<td>19 (43.2)</td>
<td>19 (42.2)</td>
<td>38 (42.7)</td>
</tr>
<tr>
<td>Subjects who discontinued study</td>
<td>0 (0.0)</td>
<td>1 (2.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Withdrawal of consent from study</td>
<td>0 (0.0)</td>
<td>1 (2.2) a</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Decision by sponsor</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Number of subjects screened: 255 subjects
N = Number of subjects in the analysis set.
n = Number of subjects with non-missing values.
% = n/N * 100
First subject enrolled: 23 November 2015; Last subject enrolled: 19 January 2017
a This subject withdrew consent before receiving investigational product

Source: Table 14-1.1

Reviewer’s Comment: over half the subjects in both treatment arms have not complete the study. However, A total of 88 subjects are included in the efficacy analysis set, which includes subjects who received investigational product and completed the post-randomization exercise treadmill test; 44 subjects from the AMG 334 140-mg group and 44 subjects from the placebo group. Safety follow-up in the study is ongoing.
Primary Efficacy Analysis

The primary efficacy analysis as performed by the sponsor is shown in the following table:

### Table 10-1. Analysis of Variance for Change of Total Exercise Time:

<table>
<thead>
<tr>
<th>Efficacy Analysis Set</th>
<th>Placebo</th>
<th>AMG 334 140 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>N = 44</td>
<td>N = 44</td>
</tr>
<tr>
<td>Baseline, total exercise time (seconds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Mean</td>
<td>474.8</td>
<td>486.0</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(436.9, 512.7)</td>
<td>(447.5, 524.5)</td>
</tr>
<tr>
<td>SD</td>
<td>149.5</td>
<td>148.2</td>
</tr>
<tr>
<td>Median</td>
<td>478.5</td>
<td>446.3</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>368.5, 594.8</td>
<td>385.0, 563.5</td>
</tr>
<tr>
<td>Min, Max</td>
<td>223, 845</td>
<td>261, 969</td>
</tr>
<tr>
<td>Day 1 (post investigational product), total exercise time (seconds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Mean</td>
<td>483.0</td>
<td>488.9</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(438.5, 527.6)</td>
<td>(446.4, 531.4)</td>
</tr>
<tr>
<td>SD</td>
<td>175.7</td>
<td>167.7</td>
</tr>
<tr>
<td>Median</td>
<td>474.0</td>
<td>472.5</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>351.5, 586.0</td>
<td>380.0, 601.5</td>
</tr>
<tr>
<td>Min, Max</td>
<td>172, 1083</td>
<td>144, 1070</td>
</tr>
<tr>
<td>Change from baseline in total exercise time (seconds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Mean</td>
<td>8.2</td>
<td>-2.7</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(-8.3, 24.8)</td>
<td>(-33.0, 27.5)</td>
</tr>
<tr>
<td>SD</td>
<td>65.4</td>
<td>116.5</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>-0.3</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>-8.0, 39.3</td>
<td>-16.0, 20.0</td>
</tr>
<tr>
<td>Min, max</td>
<td>172, 1083</td>
<td>144, 1070</td>
</tr>
</tbody>
</table>

**ANOVA – unadjusted analysis**

- **LS Mean**
- **SE**
- **(90% CI)**

**ANOVA – adjusted analysis**

- **LS Mean**
- **SE**
- **(90% CI)**

---

ANOVA = Analysis of variance, N = Number of subjects in the analysis set, n = Number of subjects with observed data.

*a* ANOVA model includes treatment and randomization strata (<7 or ≥7 minutes) as covariates.

*b* ANOVA model includes treatment, randomization strata (<7 or ≥7 minutes), age group (<65, ≥65) and sex as covariates.

Source: Table 14-4.1.1
The sponsor claims success regarding the primary efficacy analysis as follows:

There was no clinically meaningful difference in total exercise time between subjects who received AMG 334 140 mg and those received placebo based on a regression analysis using an analysis of variance (ANOVA) model adjusting for treatment group and baseline total exercise time (<7 minutes or ≥ 7 minutes) randomization strata (Table 10-1). The lower limit of the 90% CI of the difference in total exercise time did not reach the non-inferiority margin of -90 seconds (adjusted least squares mean [90% CI] of -11.0 [-44.9, 22.9]), supporting the hypothesis that AMG 334 does not decrease exercise capacity compared to placebo.

Reviewer’s comments:

- 90% CI instead of 95% CI with threshold for success lowered to -90 msec 12 days after the last subject was enrolled. This lowers our confidence that knowledge of the study’s outcomes did not influence the analytical plan modifications.
- 2/44(4.5%) of subjects in the AMG 334 treatment arm did not have baseline exercise test results. It is not clear how the change from baseline exercise time was calculated for these subjects, and how this mathematical manipulation may have impacted the ANOVA analysis of placebo adjusted change from baseline results.

There were no significant differences between the treatment groups on the secondary endpoints of Time to Exercise-induced Angina or Time to ≥ 1 mm ST-segment Depression, though the hazard ratio for these outcomes using the pre-specified, stratified (< 7 or ≥ 7 minute randomization strata) Cox proportional hazards regression model for both of these outcomes leaned negatively, as shown in the tabular results and K-M curves for these two endpoints, as follows, respectively (from the sponsor CRS):
### Table 10-2. Time to Exercise-induced Angina: Efficacy Analysis Set

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 44</th>
<th>AMG 334 140 mg N = 44</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>44 (n)</td>
<td>44 (n)</td>
<td></td>
</tr>
<tr>
<td>Events - n (%)</td>
<td>29 (65.9)</td>
<td>33 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Censored - n (%)</td>
<td>15 (34.1)</td>
<td>11 (25.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Stratified log-rank test</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal score&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>1.55</td>
</tr>
<tr>
<td>p-value</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time to exercise-induced angina (KM) (seconds)</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>506.0</td>
<td>500.0</td>
<td></td>
</tr>
<tr>
<td>90% CI of the median</td>
<td>(405.0, 572.0)</td>
<td>(420.0, 540.0)</td>
<td></td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>381.0, 664.0</td>
<td>380.0, 603.0</td>
<td></td>
</tr>
<tr>
<td>Adjusted hazard by stratified baseline total exercise time strata</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 7 or ≥ 7 minutes)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>1.11</td>
</tr>
<tr>
<td>90% CI</td>
<td>(0.73, 1.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted hazard by continuous baseline total exercise time&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(0.52, 1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted hazard&lt;sup&gt;d,e&lt;/sup&gt; (90% CI)</td>
<td></td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>(0.52, 1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = Number of subjects in the analysis set. KM = Kaplan-Meier. Percent based on N. The analysis includes only those endpoints that occurred while subjects were on investigational product.

<sup>a</sup> Stratification factor is baseline total exercise time strata (< 7 minutes or ≥ 7 minutes).

<sup>b</sup> A normal score < 0 indicates fewer than expected events for AMG 334 140 mg relative to placebo and therefore a longer survival time.

<sup>d</sup> Time to exercise-induced angina is calculated as the number of seconds from subject received investigational product to onset of exercise-induced angina.

<sup>e</sup> The hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced angina free survival for AMG 334 140 mg relative to placebo.

<sup>f</sup> Stratification factors are: baseline total exercise time strata (< 7 or ≥ 7 minutes), age group (< 65, ≥ 65), and sex.

Source: Table 14-4.2.1

Reference ID: 4180099
Figure 10-1. Kaplan-Meier Estimates of Time to Onset of Exercise-induced Angina: Efficacy Analysis Set

Product-limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

Event Free Time in Seconds

1: Group = AMG 334
2: Group = Placebo
### Table 10.3. Time to ≥ 1 mm ST-segment Depression: Efficacy Analysis Set

<table>
<thead>
<tr>
<th>Subject Status</th>
<th>Placebo</th>
<th>AMG 334 140 mg</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 44</td>
<td>N = 44</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>44</td>
<td>44</td>
<td>0.59</td>
</tr>
<tr>
<td>Events - n (%)</td>
<td>36 (81.8)</td>
<td>35 (79.5)</td>
<td></td>
</tr>
<tr>
<td>Censored - n (%)</td>
<td>8 (18.2)</td>
<td>9 (20.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Stratified log-rank test**

<table>
<thead>
<tr>
<th>Normal score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**Time to ≥ 1 mm ST-segment depression (KM) (seconds)**

<table>
<thead>
<tr>
<th>n</th>
<th>Median</th>
<th>90% CI of the median</th>
<th>Q1, Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>420.0</td>
<td>(409.0, 480.0)</td>
<td>349.0, 540.0</td>
</tr>
<tr>
<td>44</td>
<td>407.0</td>
<td>(380.0, 443.0)</td>
<td>299.0, 539.0</td>
</tr>
</tbody>
</table>

**Adjusted hazard by stratified baseline total exercise time strata (<7 or ≥ 7 minutes)**

| 1.14 | (0.75, 1.69) |

**Adjusted hazard by continuous baseline total exercise time**

| 1.08 | (0.73, 1.60) |

**Adjusted hazard**

| 1.24 | (0.82, 1.87) |

---

N = Number of subjects in the analysis set. KM = Kaplan-Meier. Percent based on N.
The analysis includes only those endpoints that occurred while subjects were on investigational product.

a Stratification factor is baseline total exercise time on exercise treadmill test (<7 minutes or ≥ 7 minutes).

b A normal score < 0 indicates fewer than expected events for AMG 334 140 mg relative to placebo and therefore a longer survival time.

c Time to ≥ 1 mm ST-segment depression is calculated as the number of seconds from subject starting the exercise treadmill test post-randomization to onset of ≥ 1 mm ST-segment depression.

d The hazard ratio estimates are obtained from the Cox Proportional Hazard Model. A hazard ratio < 1.0 indicates a lower average event rate and a longer exercise-induced angina free survival for AMG 334 140 mg relative to placebo.

e Stratification factors are: baseline total exercise time strata (<7 or ≥ 7 minutes), age group (< 65, ≥ 65), and sex.

Source: Table 14-4.3.1
Reviewer’s comment: For both the time to exercise-induced angina and time to ≥ 1mm ST-segment depression secondary endpoints, the Normal Score of the stratified log-rank test was > 0, suggesting a higher than expected number of events for AMG 334 140 mg relative to placebo and therefore a shorter “survival time” (see sponsor footnotes b in the above tables).

REVIEW OF CV DEATHS:

From the N=2682 subjects who were randomized to AMG 334 across trials integrated for safety, two deaths occurred, both cardiovascular (CV) deaths. There were no deaths among the N=1056 subjects from the ISS who were randomized to placebo. The two CV deaths from the active treatment arms are summarized as follows:
1. **Subject**: This 43-year-old male died while participating in the active treatment phase of Phase 3 Trial 20120296. While this subject had a medical history of hypercholesterolemia, he had no personal or family history of sudden cardiac death, premature atherosclerosis, coronary artery disease, peripheral artery disease, thromboembolism, or genetic diseases. He was described as an active man and during physical exertion he was completely asymptomatic and without any limitations. It is noted that a echocardiogram showed only minor mitral insufficiency. The subject received the first dose of investigational product (IP) on . On , the subject began the active treatment phase. On , the subject was found dead at home. He had also taken sumatriptan within 30 days of death. Post mortem examination demonstrated the following findings:

- Ahythmogenic cardiomyopathy and general arteriosclerosis of the first degree
- Fat infiltration of the right heart chamber musculature
- Hypertrophy of the left cardiac musculature
- Dilation of both cardiac chambers
- Pulmonary edema and brain edema

The direct cause of death was reported as heart failure due to arrhythmogenic cardiomyopathy. Post mortem genetic testing found the subject was heterozygous for a frameshift variant that was likely pathogenic in the SCN5A gene, likely consistent with a genetic form of arrhythmia cardiomyopathy. A cardiologist who had previously seen the subject reported that this subject’s electrocardiogram (ECG) records were abnormal (however in long term follow-up without any changes) and in the differential diagnosis had considered Brugada syndrome in the past. The investigator and the sponsor concluded that study drug was unlikely to have contributed to this subject’s death.

2. **Subject**: Subject was a 54-year-old white male who was participating in the open-label treatment phase of Phase 2 Study 20120178. His medical history included migraine with aura, hypertension, osteoarthritis, myopia, season allergy, insomnia and obesity. The subject also had an electrocardiogram on which showed left anterior hemiblock. The subject’s family history included hypertension, heart attack and “Etoh” (father died at age 39). The subject received the first dose of investigational product (IP) in the double-blind phase on and the first dose in the open-label treatment phase on . On , the subject was found dead in his apartment in a state of decomposition. On , the subject’s autopsy demonstrated advanced putrefactive decomposition and severe coronary atherosclerosis. The subject’s postmortem toxicology screen was positive for ethanol, phenylpropanolamine and norpseudoephedrine in the liver tissue. No adverse events occurred within a +/- 7-day window of the onset of the SAE. The sponsor and the investigator agreed that this case was likely a natural death due to
atherosclerotic and hypertensive cardiovascular disease, potentially exacerbated by ingestion of cardiac stimulants, and unlikely to be related to study drug.

**REVIEW OF SURPRVENTRICULAR ARRHYTHMIAS**

The sponsor has reported an imbalance between placebo and treatment groups in ectopic supraventricular rhythms (0.3% for placebo, 1.3% for 70mg, and 2.2% for 140mg group). Ectopic supraventricular rhythms were defined to include the following:

- Premature atrial complex (PAC)
- Premature Junctional Complex (PJC)
- Ectopic Atrial tachycardia (EAT)
- Multifocal Atrial Tachycardia (MAT)
- Paroxysmal Supraventricular Tachycardia (PSVT)
- Junctional Escapes.

Reviewer’s note: The sponsor states in an IR from 14 September 2017 that a supraventricular rhythm classification required three or more consecutive non-sinus P waves with atrial rate < 100 bpm, which is not consistent with the diagnosis of the abovementioned tachycardias. The sponsor also stated the following in that IR response:

*ECG tracings of all 39 subjects with a classification of ectopic supraventricular rhythm were reviewed by an Amgen cardiologist in a blinded manner for potential clinical relevance (Summary of Clinical Safety Section 4.2). In this review, the majority of tracings were classified as normal, or showed sinus bradycardia or a right bundle branch block. Only 3 cases of PJC (2 on placebo in Study 20120296 and 1 on AMG 334 70 mg in Study 20120178) and 1 case of PAC (2 events occurring in the same subject in Study 20120178, 1 on placebo and 1 on AMG 334 70 mg) were diagnosed. The classification criteria for supraventricular rhythm applied by the external central facility can include many non-specific electric abnormalities. Considering the high prevalence and clinical benignity of PAC and PJC, these findings were not considered clinically relevant.*

From this response, it is evident that the sponsor is mixing elements of conduction system abnormalities (node firing rates and AV nodal conduction times) with elements of supraventricular complexes (not tachycardia) and elements of supraventricular rhythms resulting in tachycardia. To sort this out further, another IR was sent to the sponsor on October 17, 2017 as follows (the response to which has not yet been submitted):

*In the ISS, you reported an imbalance between placebo and treatment groups in ectopic supraventricular rhythms (0.3% for placebo, 1.3% for 70mg, and 2.2% for 140mg group). You have also stated in a prior IR response that all 39 events...*
of ectopic supraventricular rhythm classified by the external central facility were included in the ISS analysis. In order to comprehensively evaluate this finding, we request that you provide us the following information about all occurrences of ectopic supraventricular rhythms from these 39 subjects:

1. Vital sign data if available at the time of the abnormal ECG
2. Duration of the arrhythmia (number of consecutive beats, or minutes if sustained)
3. Rate of the arrhythmia
4. The associated tracings documenting the arrhythmia
5. Duration of treatment with study drug at the time of the abnormal ECG
6. Requirement for medical intervention to terminate the arrhythmia
7. Any cardiac biomarker data obtained around the time of the event
8. Whether the noted arrhythmia was an adverse event itself, or associated with an adverse event that occurred the same day. If yes, please provide us with the narrative of the adverse event(s).
9. Whether the noted arrhythmia occurred in a subject who experienced an adverse event of dizziness, presyncope, or syncope at any time during the study.
10. Whether long-term cardiac rhythm monitoring was performed at any time on any of these 39 subjects.

DCRP will review this information when it is submitted.

RESPONSES TO CONSULT QUESTIONS:

1. Regarding treadmill study Treadmill Study 20140254

   a. Is the study designed appropriately to meet the primary objective and safety objectives?

   **DCRP Response:** The study as it was originally designed would likely have met the needs of our Division to assess its results. The original plan was to enroll 120 subjects, although this sponsor was using the lower 90% CI of the difference from change from baseline treadmill time. Approximately one year into the study, this sponsor submitted amendment 4 which reduced the study sample size from 120 to 88 and arbitrarily extended the threshold for harm from 60 sec to 90 sec of a Standard Bruce Protocol. Note that the Patterson study also used a 60 sec deterioration of exercise time as the threshold for harm, but applied this difference threshold to results from the Modified Bruce Protocol. Trial 20140254 extended the time to clinically meaningful harm from 60 sec
to 90 sec using a Standard Bruce Protocol, which represents a longer than 30 sec extension under the Modified Bruce Protocol.

b. Is the stratification by time of ETT (exercise treadmill test) appropriate?

DCRP Response: The stratification based on baseline treadmill time was reasonable to prevent inadvertent asymmetry in the functional severity of the underlying coronary artery disease between the two treatment arms.

c. The sponsor has used a change of 90 seconds from baseline as the non-inferiority margin. Is the change from baseline of 90 seconds clinically relevant?

DCRP Response: Yes, but the much lower threshold for harm used in the Patterson study of 60 sec on a Modified Bruce Protocol was also clinically significant. A 60 second deterioration on a Standard Bruce ETT, which was the original threshold of harm for study 20140254, was a larger deterioration threshold compared to the 60 second deterioration threshold on the Modified Bruce ramp protocol that was used in the Patterson study of Cialis. When they increased their margin for harm to 90 seconds of a Standard Bruce Protocol, the margin became even larger. Using this large margin along with a 90% CI biased their trial toward nominal success.

d. Is this the appropriate margin to use for both stratification groups?

DCRP Response: 90 seconds of deterioration on a Standard Bruce ramp protocol is clinically significant for either stratum but likely too large for both (see response to item c above), particularly the stratum exercising less than 7 minutes total at baseline.

e. Does this study adequately

DCRP Response: No.

Given that there is a potential mechanism for harm with CGRP-r blockade in the setting of active myocardial ischemia, we do not believe that the negative leans of all outcomes
2. Are the two CV deaths that occurred in the active treatment groups of the registration studies representative of a safety problem with AMG 334 that would impact approvability or labeling?

**DCRP Response:** Both of these deaths have confirmed non-drug related explanations at post-mortem exam (SCN5A mutation and extensive coronary artery disease), neither of which appear to be related to drug therapy. We do not think that either of these occurrences should impact approvability of labeling decisions.

3. What is DCRP’s assessment of the apparently dose-responsive occurrence of ectopic supraventricular rhythms that occurred in the late phase studies of the development program?

**DCRP Response:** The sponsor’s explanation for these events from a September 2017 IR was insufficient, and thus a repeat IR was issued Oct 17, 2017 to the sponsor as follows:

In the ISS, you reported an imbalance between placebo and treatment groups in ectopic supraventricular rhythms (0.3% for placebo, 1.3% for 70mg, and 2.2% for 140mg group). You have also stated in a prior IR response that all 39 events of ectopic supraventricular rhythm classified by the external central facility were included in the ISS analysis. In order to comprehensively evaluate this finding, we request that you provide us the following information about all occurrences of ectopic supraventricular rhythms from these 39 subjects:

1. Vital sign data if available at the time of the abnormal ECG
2. Duration of the arrhythmia (number of consecutive beats, or minutes if sustained)
3. Rate of the arrhythmia
4. The associated tracings documenting the arrhythmia
5. Duration of treatment with study drug at the time of the abnormal ECG
6. Requirement for medical intervention to terminate the arrhythmia
7. Any cardiac biomarker data obtained around the time of the event
8. Whether the noted arrhythmia was an adverse event itself, or associated with an adverse event that occurred the same day. If yes, please provide us with the narrative of the adverse event(s).

9. Whether the noted arrhythmia occurred in a subject who experienced an adverse event of dizziness, presyncope, or syncope at any time during the study.

10. Whether long-term cardiac rhythm monitoring was performed at any time on any of these 39 subjects.

DCRP will review this information when it is submitted.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
11/12/2017

SHARI L TARGUM
11/13/2017

NORMAN L STOCKBRIDGE
11/13/2017
Date: October 24, 2017

To: Oumou Barry, CDER/OPQ/OPRO
Oumou.Barry@fda.hhs.gov

Hamet Toure, CDER/OPQ/OPRO
Hamet.Toure@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: Nazia Rahman, DMQ, OC, CDRH

From: Daniel Ramsey, POND, DMQ, OC, CDRH

Applicant: Amgen Inc.
One Amgen Center Drive
Thousand Oaks CA, 91320
FEI# 2026154

Application # BLA761077
Consult # ICC1700444

Product Name: Erenumab

Combination
Product Intended Use: Prophylaxis of Migraine

Pre-Approval Inspection: Yes

Documentation Review: No Additional Information Required

Final Recommendation: Approve

The Office of Compliance at CDRH received a consult request from CDRH to evaluate the applicant’s compliance with applicable Quality System Requirements for the approvability of BLA761077.

PRODUCT DESCRIPTION

Prefilled Syringe

The subject device is a 1ml Type I glass syringe with a 27-gauge stainless steel needle, a plunger-stopper with a natural rubber needle shield, rigid needle shield, plunger rod, and flange.
The prefilled syringe is available in standalone and autoinjector configurations, with the autoinjector syringe having a "(b)(4)" needle design.

**Autoinjector**

The subject device is a single use delivery device consisting of a front assembly, rear assembly, and pre-filled syringe.

**REGULATORY HISTORY**

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Amgen Manufacturing Limited
   
   Address Rd 31 Km 24.6
   
   Juncos, Puerto Rico 00777, US
   
   FEI #1000110364
Responsibility – Drug Product manufacture, autoinjector assembly, primary labeling, and packaging. This includes management responsibility.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection conducted on April 26-May 10, 2017. The inspection covered drug GMP, and was classified VAI. The last inspection to cover device QSR was conducted July 24-August 15, 2013 and was classified NAI. A recent inspection was conducted ending on June 4-17, 2013. No 483 was issued at the conclusion. The initial recommendation was for an inspection of this facility. The firm was inspected between August 14, 2017 and August 21, 2017 with a baseline medical device inspection which was classified as NAI.

Inspection Recommendation:

An inspection is not required because:

- A recent medical device inspection of the firm was acceptable

2. Amgen Inc.

    One Amgen Center Drive

    Thousand Oaks, California

    FEI #2026154

Responsibility – This firm is responsible for management controls design controls, purchasing controls, and CAPA.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed an inspection conducted on April 11-19, 2017. The inspection covered drug GMP, and was classified VAI. The last inspection to cover device QSR was conducted August 12-27, 2014 and was classified NAI. The inspection was a compliance follow-up to a medical device OAI inspection conducted June 4-17, 2013. The initial recommendation was for an inspection of this facility. The firm was inspected between August 14, 2017 and August 21, 2017 with a baseline medical device inspection which was classified as NAI.

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable

**DOCUMENTATION REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

**Management Control, 21 CFR 820.20**

In section 3.2.P.3.3, the firm states that Amgen has established procedures for management responsibility per 21CFR 820.20 for the combination product, including management reviews and designation of appropriate management personnel. The firm states in their July 17, 2017 response, that the management responsibility and establishment of the quality system is done at the Amgen Thousand Oaks facility.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

**Design Control, General, 21 CFR 820.30**

In section 3.2.P.3.3, the firm provides a summary of how design controls are incorporated, including discussion of requirements of 21CFR 820.30, discussion of design changes, and the location of the DHF (Amgen, Thousand Oaks, California).

They state that Amgen is responsible for combination product design controls. They state that the design control for the autoinjector components is maintained by [b] (4) Amgen DHF.

They finally state that design control responsibilities are specified in the Design and Development Plans (DDP) maintained at Amgen and in their agreements with suppliers. They note that the Amgen DHF identifies the location of all design control documentation for the device components.
In section 3.2.P.7, the firm provides information on its design development of the device, design verification, design validation, and risk management.

Verification included evaluating biocompatibility, shelf-life, distribution testing, and component. Validation testing includes human factors and simulated use testing to evaluate potential misuse, as well as a risk analysis and a DFMEA table.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

**Purchasing Controls, 21 CFR 820.50**

In section 3.2.P.3.3, the firm notes that they have established procedures for purchasing controls with suppliers which include quality agreements for suppliers and designers of device components. They state that Amgen will be notified of any changes to components per these agreements. Finally, they note that all suppliers are appropriately qualified commensurate with the potential to impact the design, function, and GMP operations.

In section 3.2.P.7, the firm describes their suppliers for device constituent parts, including needles, syringes, stoppers, and needle caps. They state that components are received, sampled, quarantined, tested and accepted/rejected based on specific procedures involving sampling of incoming devices, or acceptance of a manufacturer’s certificate.

The submission references a masterfile for the autoinjector component (MAF) which includes information on the supplier testing of critical dimensions and functional requirements. In section 3.2.P.5.1, the firm also notes that prior to release, the device functionality is assessed.

**Reviewer Comment:** The firm has provided adequate information on supplier controls, including agreements with suppliers, change control, purchasing data, and balancing purchasing data and acceptance activities.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

**Corrective and Preventive Action (CAPA), 21 CFR 820.100**
In section 3.2.P.3.3, the firm states that they have established CAPA procedures based on inputs from non-conformances, complaints, returned product, risk assessments, audits, inspections, and trend. They state that issues are identified to allow an evaluation of root causes and effect on product quality. Changes are evaluated within the change control process, and if necessary the CAPA is evaluated to verify effectiveness.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

**Installation, 21 CFR 820.170**

Installation is not required for this combination product.

**Servicing, 21 CFR 820.200**

Servicing is not required for this combination product.

**MANUFACTURING**

**Production Flow**

*Prefilled Syringe*
**Reviewer Comment:** In section 2.3.P, the sponsor confirmed that all drug product manufacturing, including filling is conducted at the Amgen Manufacturing Limited facility.

**RECOMMENDATION**

The submission should be approved.

Daniel S. Ramsey -A
2017.10.24 15:01:47 -04'00'
Prepared: DSRamsey: 10/24/17

Reviewed:

CTS No.: ICC170444
BLA761077
Questions regarding this consult should be referred to one of the following individuals:

**Primary Contact**

Daniel Ramsey  
Consumer Safety Officer  
Physical Medicine, Orthopedic, Neurology & Dental Device Branch  
Division of Manufacturing and Quality  
Office of Compliance, WO66 RM  
Phone: 301-796-6451

**Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Matthew Krueger  
Chief  
Physical Medicine, Orthopedic, Neurology & Dental Device Branch  
Division of Manufacturing and Quality  
Office of Compliance, WO66 RM 3448  
Phone: 301-796-5585

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION**
DATE: 8/16/2017

TO: Office of New Drugs
   Division of Neurology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
      Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without on-site inspection

RE: BLA 761077

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale
OSIS recently inspected the sites listed below. The inspctional outcome from the inspections was classified as No Action Indicated (NAI).

inspection Sites

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<td>West Coast Clinical Trials (WCCT) Global</td>
<td>5630 Cerritos Avenue, Cypress, CA</td>
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<td>1000 Westgate Drive, Suite 149, St. Paul, MN</td>
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<td>1085 North Harbor Boulevard, Anaheim, CA</td>
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</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANGEL S JOHNSON
08/22/2017

Reference ID: 4142356
Date: July 31, 2017

To: Oumou Barry, CDER/OPQ/OPRO
   Oumou.Barry@fda.hhs.gov

   Hamet Toure, CDER/OPQ/OPRO
   Hamet.Toure@fda.hhs.gov

   Office of combination products at combination@fda.gov

Through: Matthew Krueger Chief, POND, DMQ, OC, CDRH

From: Daniel Ramsey, POND, DMQ, OC, CDRH

Applicant: Amgen Inc.

One Amgen Center Drive
The Office of Compliance at CDRH received a consult request from CDRH to evaluate the applicant’s compliance with applicable Quality System Requirements for the approvability of BLA761077.

**PRODUCT DESCRIPTION**

**Prefilled Syringe**

The subject device is a 1ml Type I glass syringe with a 27-gauge stainless steel needle, a plunger-stopper with a natural rubber needle shield, rigid needle shield, plunger rod, and flange.
The prefilled syringe is available in standalone and autoinjector configurations, with the autoinjector syringe having a "(b)(4)" needle design.

**Autoinjector**

The subject device is a single use delivery device consisting of a front assembly, rear assembly, and pre-filled syringe.

**REGULATORY HISTORY**

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Amgen Manufacturing Limited
   
   Address Rd 31 Km 24.6
   
   Juncos, Puerto Rico 00777, US
   
   FEI #1000110364
Responsibility – Drug Product manufacture, autoinjector assembly, primary labeling, and packaging. This includes management responsibility.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed that an inspection conducted on April 26-May 10, 2017. The inspection covered drug GMP, and was classified VAI. The last inspection to cover device QSR was conducted July 24-August 15, 2013 and was classified NAI. A recent inspection was conducted ending on [date]. This inspection covered device QSR and was conducted for [date]. No 483 was issued at the conclusion.

**Inspection Recommendation:**

An inspection is not required because:

- A recent medical device inspection of the firm was acceptable

2. Amgen Inc.

   One Amgen Center Drive
   Thousand Oaks, California
   FEI #2026154

Responsibility – This firm is responsible for management controls design controls, purchasing controls, and CAPA.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years showed an inspection conducted on April 11-19, 2017. The inspection covered drug GMP, and was classified VAI. The last inspection to cover device QSR was conducted August 12-27, 2014 and was classified NAI. The inspection was a compliance follow-up to a medical device OAI inspection conducted June 4-17, 2013.

**Inspection Recommendation:**

An inspection is required because:

- The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
• A recent medical device inspection of the firm has not been performed.

**DOCUMENTATION REVIEW**

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

**Management Control, 21 CFR 820.20**

In section 3.2.P.3.3, the firm states that Amgen has established procedures for management responsibility per 21 CFR 820.20 for the combination product, including management reviews and designation of appropriate management personnel. The firm states in their July 17, 2017 response, that the management responsibility and establishment of the quality system is done at the Amgen Thousand Oaks facility.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

**Design Control, General, 21 CFR 820.30**

In section 3.2.P.3.3, the firm provides a summary of how design controls are incorporated, including discussion of requirements of 21 CFR 820.30, discussion of design changes, and the location of the DHF (Amgen, Thousand Oaks, California).

They state that Amgen is responsible for combination product design controls. They state that the design control for the autoinjector components is maintained by [b] [4]

They finally state that design control responsibilities are specified in the Design and Development Plans (DDP) maintained at Amgen and in their agreements with suppliers. They note that the Amgen DHF identifies the location of all design control documentation for the device components.

In section 3.2.P.7, the firm provides information on its design development of the device, design verification, design validation, and risk management. [b] [4]
Verification included evaluating biocompatibility, shelf-life, distribution testing, and component. Validation testing includes human factors and simulated use testing to evaluate potential misuse, as well as a risk analysis and a DFMEA table.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

**Purchasing Controls, 21 CFR 820.50**

In section 3.2.P.3.3, the firm notes that they have established procedures for purchasing controls with suppliers which include quality agreements for suppliers and designers of device components. They state that Amgen will be notified of any changes to components per these agreements. Finally, they note that all suppliers are appropriately qualified commensurate with the potential to impact the design, function, and GMP operations.

In section 3.2.P.7, the firm describes their suppliers for device constituent parts, including needles, syringes, stoppers, and needle caps. They state that components are received, sampled, quarantined, tested and accepted/rejected based on specific procedures involving sampling of incoming devices, or acceptance of a manufacturer’s certificate.

The submission references a masterfile for the autoinjector component (MAF) which includes information on the supplier testing of critical dimensions and functional requirements. In section 3.2.P.5.1, the firm also notes that prior to release, the device functionality is assessed.

**Reviewer Comment:** The firm has provided adequate information on supplier controls, including agreements with suppliers, change control, purchasing data, and balancing purchasing data and acceptance activities.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

**Corrective and Preventive Action (CAPA), 21 CFR 820.100**

In section 3.2.P.3.3, the firm states that they have established CAPA procedures based on inputs from non-conformances, complaints, returned product, risk assessments, audits, inspections,
and trend. They state that issues are identified to allow an evaluation of root causes and effect on product quality. Changes are evaluated within the change control process, and if necessary the CAPA is evaluated to verify effectiveness.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

**Installation, 21 CFR 820.170**

Installation is not required for this combination product.

**Servicing, 21 CFR 820.200**

Servicing is not required for this combination product.

**MANUFACTURING**

**Production Flow**

*Prefilled Syringe*

*Autoinjector*
Reviewer Comment: In section 2.3.P, the sponsor confirmed that all drug product manufacturing, including filling is conducted at the Amgen Manufacturing Limited facility.

RECOMMENDATION

The approvability of application for Erenumab – BLA761077 should be delayed for the following reasons:

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies. However, a pre-approval inspection is recommended for:

   Amgen Inc.

   One Amgen Center Drive

   Thousand Oaks, California

   FEI #2026154

________________________________________
Daniel Ramsey
Prepared: DSRamsey: 7/13/17

Reviewed: KRBittleman: 7/28/2017

CTS No.: ICC170444

BLA761077
Inspectional Guidance

Firms to be inspected:

1. Amgen Inc.
   
   One Amgen Center Drive
   
   Thousand Oaks, California
   
   FEI #2026154

   CDRH recommends the inspection under the applicable Medical Device Regulations of Amgen Inc., located in Thousand Oaks, California (FEI # 2026154).

   A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

   Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.
**REGULATORY STRATEGY**

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

**Primary Contact**

Daniel Ramsey  
Consumer Safety Officer  
Physical Medicine, Orthopedic, Neurology & Dental Device Branch  
Division of Manufacturing and Quality  
Office of Compliance, WO66 RM  
Phone: 301-796-6451

**Secondary Contacts (if Primary is unavailable and a timely answer is required)**

Matthew Krueger  
Chief  
Physical Medicine, Orthopedic, Neurology & Dental Device Branch  
Division of Manufacturing and Quality  
Office of Compliance, WO66 RM 3448  
Phone: 301-796-5585

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION**