CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761077Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
BLA: 761077
Submission date: 5/17/17
Drug: Erenumab, AMG 334 (a calcitonin gene-related peptide receptor antagonist)
Applicant: Amgen
Indication: prophylaxis of migraine in adults

Reviewing Division: Division of Neurology Products

Discussion/Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. Both found the information sufficient to support approval. Questions regarding theoretical cardiovascular safety issues were raised and addressed by the applicant, in a consult review from the Division of Cardiovascular and Renal Products and in the pharmacology/toxicology supervisor memo. I agree with the supervisor memo that that the contribution of CGRP to compensatory vasodilation may be relatively small and that additional nonclinical studies are not likely to provide useful information. I concur that the nonclinical information are adequate to support approval.

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/s/

PAUL C BROWN
05/17/2018

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: May 17, 2018

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: BLA 761077 (Erenumab, AMG 334) for prophylaxis of migraine in adults

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BLA 761077 was submitted on May 17, 2017, by the sponsor (Amgen, in collaboration with Novartis Pharmaceuticals) to support marketing of erenumab (AMG 334) for the prophylaxis of migraine in adults.

Clinical development for the migraine indication was conducted under IND 116098 by Amgen. A battery of nonclinical studies of AMG 334 was conducted under the IND, including pharmacology, safety pharmacology (cardiovascular), PK, toxicity (1- and 3/6-month), and tissue cross-reactivity studies. These studies and the sponsor's request for waiver of carcinogenicity studies were reviewed by Dr. Thompson (Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 26, 2012; Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., February 1, 2016). (b) (4) [redacted] Additional nonclinical studies (in vitro human coronary artery assay and enhanced pre- and postnatal development study in monkey), submitted to IND 116098 and to the BLA, were reviewed by Dr. Nesti (Pharmacology/Toxicology BLA Review and Evaluation, BLA 761077, March 2, 2018).

The nonclinical studies conducted to support clinical development and a BLA for erenumab are consistent with guidance and recommendations of the Division. Upon review of the data from these studies, Dr. Nesti has concluded that they support approval of erenumab for the prophylaxis of migraine in adults. However, concerns remain regarding potential adverse cardiovascular effects, which Dr. Nesti states might be addressed in animals "if a suitable model could be identified."

Summary and Discussion

The sponsor conducted pharmacology, PK, and toxicology studies of AMG 334. The pivotal, GLP-compliant toxicology studies were conducted in cynomolgus monkey, the only biologically relevant species, with CGRP receptor binding potency similar to that of human (IC_{50} of 5.7 nM in monkey [K_i was not given]; K_i values of 20 pM in human; IC_{50} of >10 μM in rat; K_i of 230 nM in rabbit and 260 nM in dog).

Dr. Nesti, based in part on reviews by Dr. Thompson, has concluded that the pivotal (1-mo/acute IV + 4-month recovery; combined 3- and 6-month; enhanced pre- and postnatal development [ePPND]) studies were adequate by design and conduct and were negative for human-relevant drug-related effects. The highest subcutaneous doses tested in the combined 3- and 6-month toxicity (150 mg/kg twice weekly) and the ePPND (50 mg/kg Q2W) studies (both NOAELs) provided serum exposure (AUC) margins >100 and ~17 times that anticipated in humans at the maximum recommended dose of 140 mg QM.

Cardiovascular risk: Because CGRP is known to be involved in regulation of the cardiovascular system and to be a potent vasodilator, concerns were raised regarding potential adverse effects of chronic CGRP antagonism in humans, specifically, the potential for AMG 334 to (1) induce a direct vasoconstrictive effect on coronary arteries and (2) inhibit compensatory vasodilation in coronary vessels that occurs in response to an acute ischemic event (e.g., MaassenVanDenBrink et al., 2016). These effects would be particularly relevant to patients with cardiovascular risk factors. To address these concerns, the sponsor was asked to investigate the cardiovascular effects of AMG 334 by conducting (1) an in vitro human coronary artery study (121150), specifically to assess the potential for AMG 334 to induce vasoconstriction, and (2) a review of the relevant published literature on the biology of CGRP and its role in the cardiovascular system.

The Division requested a consult (Request for Consultation, dated February 27, 2018) from the Division of Cardiovascular and Renal Products (DCaRP) to:

Please comment on the strength and quality of published evidence concerning a theoretical risk with calcitonin gene-related peptide (CGRP) antagonism (via any mechanism – this is a question concerning the mechanistic drug class) of worsened ischemia due to impairment of compensatory vasodilation in the setting of ischemic vascular events.

The following provides a brief summary of the sponsor's review of the literature and DCaRP's evaluation of that information and other relevant published studies. Detailed discussions may be found in the sponsor's Pharmacology Written Summary and DCaRP's consult memo. These documents discuss published animal and human studies conducted with small molecule CGRP antagonists. This memo relies primarily on the data generated by the sponsor and on published studies of $CGRP_{(8-37)}$, identified below. Data on other small molecule antagonists were considered supportive but not necessary for evaluating the question of the cardiovascular risk of AMG 334.

The sponsor assessed the potential for AMG 344 to induce vasoconstriction in Study 121150. AMG 334 was incubated with segments of proximal and distal human coronary

arteries (noted to be devoid of atherosclerotic lesions upon macroscopic examination) with and without human α-CGRP. Sumatriptan was included as a positive control. AMG 334 (1 μM) antagonized CGRP-induced vasodilation of distal (not proximal) segments but had no vasoconstrictive effects on proximal or distal segments (1 nM-1 μM). In contrast, sumatriptan induced vasoconstriction in both segments. AMG 344 (1 μM) had no effect on sumatriptan-induced vasoconstriction.

A summary of selected published literature was provided in the sponsor's Pharmacology Written Summary. The sponsor reviewed information on the distribution of CGRP and its receptors in tissues, physiological mechanism(s) of action, and on the effects of CGRP on systemic blood pressure, the potential to cause vasoconstriction, and the potential to "promote cardiac ischemic vulnerability." The published studies cited by the sponsor characterized the physiological mechanisms by which CGRP induces vasodilation and the potential consequences of antagonism of CGRP, primarily in experiments involving exogenous application of CGRP and by administration of various CGRP antagonists in animals and humans.

The first CGRP antagonist used experimentally was $CGRP_{(8-37)}$, which was noted by Russell et al. (2014; citing Chiba et al., 1989) to have been used since 1989 "as a valuable experimental tool to interrogate CGRP-derived responses" and by Walker et al. (2010) as having "been used extensively to probe and elucidate the actions of CGRP." The studies cited by the sponsor, in which $CGRP_{(8-37)}$ was used to assess the effects of CGRP antagonist effects on cardiovascular function, demonstrated that pharmacological blockade of CGRP receptors does not cause direct vasoconstriction in vitro, does not have hemodynamic effects in vivo in normal animals or adversely affect coronary vessel size, blood flow, or coronary infarct size under ischemic conditions. The results of studies of AMG 334 in animals (and humans) conducted by the sponsor are consistent with the published findings in normal animals after acute or chronic administration of $CGRP_{(8-37)}$ and other CGRP antagonists. The sponsor did not assess in animals (or humans) the effects of AMG 334 under ischemic conditions.

The sponsor (citing Burley et al., 2007) attributed the seeming lack of effects to the observation that "…CGRP is one of a number of neuropeptides including ADM [adrenomedullin], kinins, natriuretic peptides, and urocortins that function as cardio protective mediators…The relative importance of CGRP in vasodilation, as compared to other neuropeptides and paracrine factors, has not been established." $CGRP_{(8-37)}$ did antagonize beneficial effects of exogenously administered CGRP in animal models; however, the sponsor notes that plasma levels of CGRP, following exogenous administration, are substantially higher (8-fold) than endogenous increases (2-fold) under ischemic conditions. This suggests that inhibition of the effects on exogenous CGRP may not be relevant to inhibition of changes in endogenous levels.

The sponsor also addressed the potential for antagonism of CGRP to adversely impact the beneficial effects of ischemic preconditioning (IPC). IPC has been defined as "…the protective adaptive mechanism produced by brief periods of myocardial ischemic trigger, which provides…protection against myocardial necrosis from a subsequent prolonged

period of ischemia and reperfusion" (Lu et al., 1999). Published studies cited by the sponsor demonstrated that exogenous administration of CGRP induces preconditioning in vitro and in vivo animal models, which was inhibited in in vitro studies by $CGRP_{(8-37)}$. However, the sponsor concludes that "…clinical existence of preconditioning has not been demonstrated and the clinical relevance of findings from preclinical ischemic preconditioning protocols is unknown," citing Napoli et al. (2000). Actually, Napoli et al. (2000) do not state that the phenomenon of preconditioning has not been demonstrated in humans. These authors appear to acknowledge the existence of preconditioning in humans, and focus on potential mechanisms underlying preconditioning and possible pharmacological modulation of the process in animals and humans. They conclude that "Large prospective multicenter trial studies are needed to better understand the possible pathophysiological role of the endogenous protection induced by PC…" According to a more recent publication (Rana et al., 2015), "IPC-induced cardioprotection is well demonstrated in various species, including human beings…"

There are numerous publications on preconditioning and its potential beneficial effects, not only on the cardiovascular system but also on other (e.g., neurological, and renal) systems (e.g., Stetler et al., 2014). Recent publications discuss the evidence for cardiac ischemic preconditioning in animal models and in humans (Iliodromitis et al., 2007; Williams et al., 2015). Iliodromitis et al. (2007) divide preconditioning studies in humans into three types, "observational, provocative, and pharmacological." Most relevant to the current concern is observational preconditioning, such as when "patients report an episode of angina early in the morning…and they remain free of symptoms later and for the rest of the day…" The authors note that "There are a large number of clinical studies which have shown that pre-infarction angina acts as preconditioning stimulus and the patients develop smaller CI-determined myocardial infarction in comparison to the patients without pre-infarction angina." They further note that the "clinical results suggest that the cardioprotective effects of preconditioning, well described in animal studies, do appear to translate to clinical settings" but also that "the translation of the laboratory findings in the clinical practice should be performed very cautiously and with prudence." Most important for this discussion, several publications (Napoli et al., 2000; Rana et al., 2015; Stetler et al., 2014) point out that multiple endogenous factors may be involved in the complex process(es) underlying the phenomenon and the current limited understanding of the role of any one of these factors, including CGRP.

The DCaRP consult memo (DCRP Consult BLA 761077, Preston M Dunnmon, MD, John E. Koerner, Ph.D., April 11, 2018) addressed two primary theoretical risks of chronic CGRP antagonism:

- antagonism of CGRP-mediated compensatory vasodilation secondary to ischemic vascular events
- antagonism of preconditioning, a "phenomenon whereby pre-exposure of heart to a preconditioning agent can attenuate subsequent damage incurred by an ischemic episode"

Drs. Koerner and Dunnmon discuss the results of published studies which demonstrated (1) a lack of an effect of a CGRP antagonist on baseline hemodynamic parameters or regional blood flow in a study in healthy Sprague-Dawley rat and mongrel dog, (2) the potential vasodilatory effects of CGRP, in coronary arterial (and collateral) vessels, and CGRP antagonist-induced inhibition of these effects in coronary arteries, (3) a lack of direct vasoconstrictive effects of a CGRP antagonist in an in vitro human coronary artery study, consistent with the results of the sponsor's Study 121150, (4) a lack of effect of a CGRP antagonist on microvascular diameter during an myocardial ischemic event in mongrel dog or on infarct size following coronary artery occlusion in farm pigs, (5) no effect of a CGRP antagonist on reactive hyperemic response to a brief (15 s) occlusion of a coronary artery in beagle and mongrel dogs, (6) a lack of effect of a CGRP receptor antagonist on severity of myocardial ischemia in anesthetized mongrel dogs with coronary artery stenosis, and (7) a lack of an effect of a CGRP antagonist on hemodynamic parameters in a mongrel dog model of chronic heart failure.

Drs. Koerner and Dunnmon note the limitations in the published data, e.g., in vitro studies conducted in isolated tissues, "almost all the coronary flow data…derives from in vivo canine studies using human CGRP and the peptide antagonist $CGRP_{(8\text{-}37),}$" most of the in vivo studies are "quite old" and come from a single lab. (In addition, the in vivo studies cited were conducted in non-traditional, poorly characterized animals, i.e., mongrel dog or farm pig, which could have resulted in increased variability in response, among other effects.) However, Drs. Koerner and Dunnmon note that the in vivo studies "appeared well done" and some of the studies included positive controls, to "ensure assay sensitivity." It is concluded that, overall, the published literature indicates that chronic antagonism of the CGRP system, resulting in blocking of CGRP-induced vasodilation, "does not result in tissue threatening vasoconstriction" because of the "multiple redundant mechanisms controlling regional and tissue specific blood flow."

Regarding the phenomenon of preconditioning, the DCaRP memo discusses several in vitro studies in isolated guinea pig or rat (normal or diabetic) heart preparations. The data from these studies were considered sufficient to support the role of CGRP in preconditioning, as evidenced by protection from myocardial injury by preconditioning or exogenous CGRP, which were abolished by a CGRP antagonist or capsaicin (depletes CGRP). It was noted that one publication (Chai W et al., 2006) demonstrated no change in area of risk with preconditioning, exogenous CGRP, or CGRP antagonist, alone or combined. The risk area was expressed as a percent of the left ventricle and was 49.8-53.5% in all groups, including control. However, the risk area represents the vulnerable area (i.e., the area perfused by the occluded vessel). The infarct size (expressed as % of the risk area) was significantly reduced by both preconditioning and exogenous CGRP, effects which were antagonized by the CGRP antagonist (see Figure 3 of the publication).

Drs. Koerner and Dunnmon do not reach a conclusion regarding the potential for AMG 334 to antagonize the potential beneficial effects of preconditioning.

Conclusions and Recommendations

The sponsor conducted a battery of nonclinical studies of AMG 334 to support clinical development and a BLA. These studies were adequate by design and conduct. The sponsor was also asked to assess the potential adverse effects of AMG 334 on cardiovascular function. The nonclinical studies conducted by the sponsor demonstrate that AMG 334 does not have direct vasoconstrictive effects or cause vasospasm in an in vitro human coronary artery study and has minimal, if any, systemic cardiovascular effects in intact animals, consistent with the results of published studies of $CGRP_{(8-37)}$ and other small molecule CGRP antagonists. However, these studies did not address the potential for adverse effects in patients with cardiovascular risk. The sponsor did not investigate the effects of AMG 334 in animal models of acute ischemic injury. Instead, the sponsor provided a summary of selected published studies to address concerns regarding the potential for chronic CGRP antagonism by AMG 334 to inhibit beneficial effects of compensatory vasodilation induced by CGRP released as a result of an acute ischemic event and of ischemic preconditioning (IPC). This information was considered important for determining whether there is a need for post-marketing studies to further investigate these concerns.

Published studies suggest a lack of an effect of $CGRP_{(8-37)}$ on compensatory vasodilation induced in animals by an acute ischemic event, although the studies have limitations, as noted in the DCaRP consult memo. The studies cited by the sponsor and reviewed by DCaRP suggest that CGRP antagonism has the potential to adversely inhibit IPC. However, it is the sponsor's position that the available data do not establish that IPC exists in humans. This contrasts with recent publications that claim that IPC is well-established in animals and humans.

Overall, while concerns regarding the potential for AMG 334 to have adverse effects in patients with cardiovascular risks may be mitigated, they cannot be dismissed based on the available information. However, there appears to be recognition that the issues are complex. There are likely multiple endogenous factors involved in acute ischemic events and IPC, as well as in normal hemodynamic processes, and that the role(s) of CGRP in these is unclear. There do not appear to be sufficient data, from a nonclinical standpoint, to understand the contribution of CGRP to potentially protective endogenous cardiovascular processes. The available data (as discussed in the DCaRP memo), although limited, suggest that the contribution of CGRP to compensatory vasodilation may be relatively small. It is unlikely that nonclinical studies of AMG 334, even if well-designed and conducted, would provide useful information, considering the current state of knowledge. Importantly, as noted by Drs. Koerner and Dunnmon, published studies in humans suggest that AMG 334 would not interfere with the therapeutic effects of nitrates.

Therefore, the nonclinical studies of AMG 334 conducted by the sponsor are considered adequate to support approval of the BLA, with no nonclinical post-marketing requirement to assess potential cardiovascular risk. A PMR for a juvenile animal toxicology study to support expanded clinical trials in pediatric patients is recommended.

REFERENCES

Burley DS et al. Cardioprotective actions of peptide hormones inmyocardial ischemia. Heart Fail Rev 12:279-291, 2007.

Chai W et al. The role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning in isolated rat hearts. Eur J Pharm 531:246-253, 2006.

Chiba T et al. Calcitonin gene-related peptide receptor antagonist human CGRP-(8-37). Am J Physiol Endocrinol Metab 256:E331-E315, 1989.

Iliodromitis EK et al. Ischemic preconditioning: protection against myocardial necrosis and apoptosis. Vasc Health Risk Manag 3(5):629-637, 2007.

Lu R et al. Evidence for calcitonin gene-related peptide-mediated ischemic preconditioning in the rat heart. Regul Pept 82:53-57, 1999.

MaassenVanDenBrink A et al. Wiping Out CGRP: Potential Cardiovascular Risks. Trend Pharm Sci 37(9):779-788, 2016.

Napoli C et al. Pharmacological modulation, preclinical studies, and new clinical features of myocardial ischemic preconditioning. Pharm Therap 88:311-331, 2000.

Rana A et al. Mechanisms involved in attenuated cardio-protective role of ischemic preconditioning in metabolic disorders. Perfusion 30(2):94-105, 2015.

Russell FA et al. Calcitonin gene-related peptide physiology and pathophysiology. Physiol Rev 94:1099-1142, 2014.

Stetler RA et al. Preconditioning provides neuroprotection in models of CNS disease: paradigms and clinical significance. Prog Neurobiol 0:58-83, 2014 (doi:10.1016/j.pneurobio.2013.11.005).

Walker CS et al. Regulation of signal transduction by calcitonin gene-related peptide receptors. Trends Pharmacol Sci 31:476-483, 2010.

Williams TM et al. Ischemic preconditioning – an unfulfilled promise. Cardiovasc Revascul Med 16:101-108, 2015.

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/s/

LOIS M FREED
05/17/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	761077
Supporting document/s:	1
Applicant's letter date:	May 17, 2017
CDER stamp date:	May 17, 2017
Product:	Aimovig/Erenumab/AMG 334
Indication:	Migraine Prophylaxis
Applicant:	Amgen
Review Division:	DNP
Reviewer:	Edmund Nesti, PhD
Supervisor:	Lois M. Freed, PhD
Division Director:	Billy Dunn, MD
Project Manager:	Lana Y. Chen, RPh

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1 Executive Summary

1.1 Introduction

Erenumab is a human IgG2 monoclonal antibody that antagonizes calcitonin gene-related peptide receptor (CGRP-R) activity by inhibiting binding of endogenous CGRP to the receptor. During a migraine attack, CGRP levels increase, causing vasodilation and nociceptive signaling. It is hypothesized that inhibiting CGRP-R activity will prevent migraine pain. The sponsor is, therefore, proposing erenumab as a prophylactic treatment for migraine.

1.2 Brief Discussion of Nonclinical Findings

Erenumab has high affinity for the monkey and human CGRP-R, but not for rodent CGRP-R or closely related CGRP-R family members. In monkey and human tissue cross-reactivity studies, erenumab colocalized with the CGRP-R in brain and spinal cord tissue. Erenumab antagonized monkey and human CGRP receptor activity *in vitro* and inhibited capsaicin-induced dermal blood flow increases in monkey. Safety pharmacology and toxicology studies in monkey showed no adverse cardiovascular, pulmonary, neurobehavioral, or general toxicity concerns, at exposure (AUC) values that exceed 10x the plasma exposure in humans at the clinical dose. The most common non-adverse finding was injection site inflammation. A human isolated coronary artery study also showed no potential for erenumab to cause vasoconstriction. A carcinogenicity study waiver was granted because erenumab is not active in rodents and the literature and submitted toxicity studies indicate that erenumab has a low potential for carcinogenicity. An enhanced PPND study conducted in monkey did not reveal any adverse findings.

1.3 Recommendations

1.3.1 Approvability

The nonclinical BLA package supports approval of erenumab.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Statements were removed in sections 8.2, (b) (4) (b) (4) Safety margins were to reflect the AUC multiple based on values from the pivotal toxicology study in monkeys and the actual human exposure values at 140 mg, (b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 1582205-90-0

Generic Name: Erenumab

Proposed Proprietary Name: Aimovig

Code Name: AMG 334

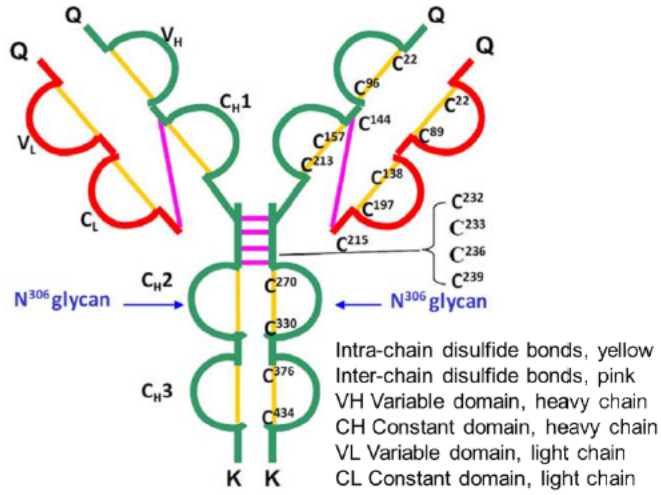
Chemical Name: n/a

Molecular Weight: 145.876 kDa

Amino acids: 1344

Structure:

Figure 1. Schematic Structure of AMG 334



Sponsor's figure

Pharmacologic Class: Human immunoglobulin G2 (IgG2) monoclonal antibody against the CGRP receptor.

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND: 116098

2.3 Drug Formulation

70 mg/mL of AMG 334 is formulated in (b) (4) acetate, 7.3% (w/v) sucrose, 0.010% (w/v) polysorbate 80, pH 5.2 in a prefilled 1 mL syringe or SureClick autoinjector.

2.4 Comments on Novel Excipients

No novel excipients are included in the drug product.

2.5 Comments on Impurities/Degradants of Concern

No concerns.

2.6 Proposed Clinical Population and Dosing Regimen

Erenumab is indicated for prevention of migraine in adults. 140 mg of erenumab is to be administered once monthly, as 2 consecutive subcutaneous injections (70 mg each), using a prefilled syringe or autoinjector.

2.7 Regulatory Background

The IND was submitted September 18, 2012, and allowed to proceed on October 16, 2012. The End of Phase 2 meeting was held on March 4, 2015. At the Pre-BLA meeting on January 31, 2017, the sponsor was told that the results of an *ex vivo* human coronary artery study would need to be submitted with the BLA. The BLA was submitted on May 17, 2017.

3 Studies Submitted

3.1 Studies Reviewed

- In vitro binding studies: R20100182 and R20100183.
- Cell based activity studies: R20100181, R20100184, and R20100185.
- In vivo pharmacodynamics study: R20100184.
- Pharmacokinetic studies: 115653 and 113591; Analytical methods and validation reports: 114076, 115031, 115901, 121057, ICD447-1, ICD612-1, MET-002549, MET-002751, MET-002752, MET-002803, MET-002805, MVR-000376, MVR-000401, MVR-000415.
- Cardiovascular, respiratory, and neurological safety pharmacology studies: 113726 and 121150.
- One-, 3-, and 6-month toxicity studies: 113724, 114005, and 113732.
- Enhanced pre- and postnatal development study: 223734.
- Tissue cross-reactivity studies: 113722 and 117454.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- IND 116098, D. Charles Thompson, Ph.D., October 16, 2012
- IND 116098, D. Charles Thompson, Ph.D., February 1, 2016

4 Pharmacology

4.1 Primary Pharmacology

In vitro, erenumab had pM binding affinity (K_d =56 pM) for the human calcitonin gene-related peptide (CGRP) receptor, which was >1000-fold higher than endogenous CGRP (with a binding affinity > 500 nM). Erenumab binding affinity to the rabbit and dog CGRP receptors was modest with Ki values of 230 and 260 nM, respectively.

In cell based cAMP assays, erenumab antagonized human and cynomolgus monkey CGRP receptor activity at low nM concentrations (IC_{50} of 2.3 nM and 5.7 nM, respectively). In contrast, no antagonist activity was observed at the rat CGRP receptor or closely related human adrenomedullin 1 (ADM1), adrenomedullin 2 (ADM2), calcitonin, or amylin (AMY) CGRP receptors at concentrations up to 10 μM.

A pharmacodynamics study in male cynomologus monkeys assessed the prophylactic effect of IV erenumab (0.1 to 30 mg/kg, 6/group) on capsaicin-induced increase in dermal blood flow (DBF) measured on Days 0, 2, and 4. The study results showed a dose dependent response, with a statistically significant minimal DBF inhibition at 0.3 mg/kg and maximal inhibition at ≥3 mg/kg.

4.2 Secondary Pharmacology

None

4.3 Safety Pharmacology

Study title: Single-Dose Cardiovascular Study with Respiration Rate and Neurobehavioral Evaluation of AMG 334 Administered by Subcutaneous Injection To Telemetry-Instrumented Conscious Male Cynomolgus Monkeys.

Study no.:	113726
Study report location:	EDR
Conducting laboratory and location:	Amgen Inc. Thousand Oaks, CA, USA
Date of study initiation:	May 17, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AMG 334, lot: 0010081147, purity 98.9% HPLC

Methods

Doses:	0, 25, and 225 mg/kg
Frequency of dosing:	Once (all animals received vehicle control article on Study Day 1 and AMG 334 on Study Day 8)
Route of administration:	Subcutaneous injection
Dose volume:	3.21 mL/kg
Formulation/Vehicle:	10 mM sodium acetate, 9.0% sucrose, and 0.004% polysorbate 20, pH 5.2
Species/Strain:	Monkey/cynomolgus (Macaca fascicularis)
Number/Sex/Group:	6/males/group
Age:	3.6-5.3 years at dosing initiation
Weight:	3.3-6.9 kg
Satellite groups:	None
Unique study design:	Vehicle control was given a week prior to dosing.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Summary

In a single-dose study, telemetry-instrumented conscious male monkeys were assessed for cardiovascular and pulmonary function, which included monitoring heart rate, arterial pressures, respiratory rate (no other measures of respiratory function were assessed), intra-abdominal body temperature, and ECG parameters (PR, QT, QTc, and QRS). Additionally, neurobehavioral effects were assessed during the predose phase and on Days 4 and 11. Observations included behavior, posture, gait, and head and limb movements (while restrained).

All animals survived to study termination on Day 15 and there were no drug-related findings, compared to control animals. The respiratory assessment was inadequate because the assessment of respiratory rate was not supported by other measures of respiratory function, such as tidal volume or hemoglobin oxygen saturation.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 16, 2012)

Study title: AMG 334 – Human Isolated Coronary Artery Study

Study no.:	121150
Study report location:	EDR
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	None given
GLP compliance:	No
QA statement:	No
Drug, lot #, and concentration:	AMG 334, lot: 0010081147, concentration: 70 mg/mL

Summary
The purposed of the isolated human coronary artery study was to determine the contractile potential of AMG 334, due to a concern that inhibiting vasodilation with AMG334 may cause vasoconstriction in coronary arteries. The study showed 1 µM AMG 334 did not induce contractions or interact with sumatriptan (1 nM – 100 µM) induced contractions of proximal or distal coronary artery preparations. However, AMG 334 inhibited relaxation normally induced by CGRP binding in the proximal and distal coronary artery preparations.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

AMG 334 serum concentrations were measured using enzyme-linked immunosorbent assays (ELISA). The lower limit of quantification for AMG 334 in serum was 10 ng/mL and the upper limit was 5,000 ng/mL. The accuracy the assay was within ± 15% of nominal.

The PK of AMG 334 was assessed in cynomolgus monkeys following single IV doses ranging from 0.1 to 300 mg/kg, 2x weekly SC doses ranging from 25 to 225 mg/kg, and 3x weekly dosing at 75 mg/kg. In the single dose study, $t_{1/2}$ was approximately 23 h. Exposure (C_{max} and AUC) increased greater than dose proportionally between 0.1 and 3 mg/kg IV and between 3 and 300 mg/kg IV. In repeat dose studies, 2x weekly dosing for 4 weeks did not result in drug accumulation; while in 3 and 6 month studies 2x weekly dosing resulted in a 1.5 to 3-fold increase in AUC values.

No distribution, metabolism, or excretion studies were conducted.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 1-Month Subcutaneous Injection Exploratory Toxicity Study of AMG 334 in Male Cynomolgus Monkeys

Study no.:	114005
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 9, 2010
GLP compliance:	No
QA statement:	No
Drug, lot #, and concentration:	AMG 334, lot: not specified; concentration 74.2 mg/mL

Methods

Doses:	0, 75, 75, and 225 mg/kg (groups 1, 2, 3, and 4, respectively)
Frequency of dosing:	Dose administration was 2x weekly for groups 1, 2, and 4, and 3x weekly for group 3.
Route of administration:	SC
Dose volume:	3 mL/kg
Formulation/Vehicle:	10 mM sodium acetate pH 5.2, 9.0% w/v sucrose, 0.004% w/v polysorbate 20 (A%2SuT)
Species/Strain:	Monkey/cynomolgus (Macaca fascicularis)
Number/Sex/Group:	3/males/group

Summary
The toxicity of repeated SC injections (2-3x per week for 4 weeks) of AMG 334 was assessed in monkeys. All animals survived to scheduled necropsy. There were no drug-related effects observed on clinical observations, food consumption, body weight, or clinical chemistry parameters. Gross necropsy observations and organ weights were reported by the sponsor to have no drug-related changes; however, no data were presented. An adequate histopathology battery was assessed. Findings consisted of drug-related hemorrhage and infiltration around the injection sites.

TK parameters, CSF: serum drug concentration ratios, anti-drug antibodies (ADA), and circulating immune complexes (CIC) data were collected. One group 3 animal was positive for CIC; ADAs were not detected in any animals. Drug exposure increased dose-proportionally between the twice weekly 75 and 225 mg/kg dose groups. CSF drug levels were <0.1% of serum concentrations 24 h following the last dose.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 16, 2012)

Study title: 1-Month Subcutaneous and Single Dose Intravenous Toxicity Study of AMG 334 in Cynomolgus Monkeys with a 4-Month Recovery Period

Study no.:	113724
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 9, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	AMG 334, lot: 0010081147; concentration 69.9 mg/mL

Methods

Doses:	SC: 0, 25, 75, 100, and 225 mg/kg IV: 0 and 100 mg/kg
Frequency of dosing:	SC: Twice a week (Days 1, 4, 8, 11, 15, 18, 22, 25, and 29); IV: (slow bolus) once on Day 15
Route of administration:	SC or IV
Dose volume:	3 mL/kg
Formulation/Vehicle:	10 mM sodium acetate pH 5.2, 9.0% w/v sucrose, 0.004% w/v polysorbate 20 (A%2SuT)
Species/Strain:	Monkey/cynomolgus (Macaca fascicularis)
Number/Sex/Group:	3/sex/group in the Main study; 2/sex/group (control and HD, SC) Recovery.
Age:	2.5 - 3.5 years (M); 3.0 - 4.3 years (F) at dosing initiation
Weight:	2.2-3.0 kg
Satellite groups:	Recovery group
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Summary

The toxicity of SC or IV injections of AMG 334 was assessed in monkeys. There was one unscheduled euthanasia, the animal (LDF) “exhibited pathology consistent with inflammation secondary to the development of anti-AMG 334 antibodies.” There were no drug-related effects on clinical signs, body weights, food consumption, ophthalmoscopy, ECG (raw data were not included), hematology, clinical chemistry, urinalysis, gross pathology, or organ weights. An adequate histopathology battery was assessed on main study animals only. There were no drug-related findings.

All animals were analyzed for ADA and group 2 animals were also analyzed for CIC. There was no ADA detected in the Main Study animals. However, ADA was detected in all the Recovery animals, including one control male on Day 148; three of the 4 animals had neutralizing antibodies. CIC was detected in a single group 2 animal on Day 22; this

animal was euthanized prematurely on Day 29. According to the sponsor, high circulating drug concentrations interfered with ADA detection in the Main Study animals.

Drug exposures were similar between sexes and increased dose proportionally. Drug accumulated between Day 1 and Day 22. "TK parameters were not estimated during the recovery period; however, measurable serum concentrations were detected up to at least Day 113 and as long as Day 148." The NOAEL was 225 mg/kg, corresponding to a Day 22 AUC of 16,800 µg·day/mL (male and female).

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 16, 2012)

Study title: AMG 334: 3-Month and 6-Month Subcutaneous Toxicology Study in the Cynomolgus Monkey with a 15-Week Recovery Period

Study no.:	113732
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 11, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and concentration:	AMG 334, lot: 0010081147; concentration 69.9 mg/mL

Methods

Doses:	0, 25, and 150 mg/kg
Frequency of dosing:	Twice per week for 13 or 26 weeks
Route of administration:	SC
Dose volume:	2.14 mL/kg
Formulation/Vehicle:	10 mM sodium acetate pH 5.2, 9.0% w/v sucrose, 0.004% w/v polysorbate 20 (A%2SuT)
Species/Strain:	Monkey/cynomolgus (Mauritius)
Number/Sex/Group:	3/sex/group in the Interim Study; 4/sex/group in the Main Study; 2/sex/group (control and HD) in the Recovery.
Age:	5.1-6.5 years (M) and 4.3-7.4 years (F) at dosing initiation
Weight:	3.0-6.7 kg
Satellite groups:	Recovery group
Deviation from study protocol:	Minor deviations were reported, with no impact on study validity.

Summary

The toxicity of twice weekly SC injections of AMG 334 was assessed in cynomolgus monkeys over 3- and 6-months followed by a 15-month recovery period. "All animals survived to scheduled necropsy." There were no drug-related effects on clinical signs,

body weights, food consumption (qualitative assessment only), ophthalmoscopy, ECG, hematology, urinalysis, gross pathology, or organ weights. There were clinical chemistry findings in one HD male, consisting of an "acute phase of protein response on Day 181, with mildly increased globulin and decreased albumin causing a reduction in the A:G ratio." These changes were correlated with histological evidence of inflammation in the coronary artery, gallbladder, and femorotibial joint. The kidney had a multifocal increase in glomerular cellularity and scattered tubular red cell casts. These changes were attributed to ADA drug complexes. The histopathological assessment, which included an adequate battery of tissues, showed no other drug-related findings.

Systemic drug exposures (C_{max} and AUC_{7day}) were comparable between sexes and increased less then dose proportionally. "Exposures at both Days 78 and 169 were greater than Day 1"; however, exposures declined from Day 78 to Day 169, at both doses. Reduced exposure due to neutralizing ADA was observed in three low dose animals. At the end of the recovery period (Day 289), all animals had drug exposures <0.5% of those at the end of the dosing period (Day 181).

Overall, drug effects were unremarkable. The NOAEL was at the HD, corresponding to C_{max} and AUC values of 2620 µg/mL and 15300 µg·day/mL, respectively.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 16, 2012)

9 Reproductive and Developmental Toxicology

9.2 Prenatal and Postnatal Development

Study title: AMG 334: Enhanced Pre-Postnatal Development Study in the Cynomolgus Monkey with a 6-Month Postnatal Evaluation

Study no.:	113734
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 20, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	AMG 334, lot: 0010081147, purity: 98.9% (HPLC)

Methods

Doses:	0 and 50 mg/kg
Frequency of dosing:	Once every two weeks
Dose volume:	0.71 mL/kg
Route of administration:	SC
Formulation/Vehicle:	A52SuT buffer (10 mM sodium acetate, 9.0% (w/v) sucrose, 0.0004% (w/v) polysorbate 20, pH 5.2)
Species/Strain:	Female cynomolgus monkey
Number/Sex/Group:	Planned: 30/AMG 334 group and 20/control group Actual: 23/AMG 334 group and 20/control group
Satellite groups:	None
Study design:	A total of 50 pregnant females between 6.0 and 9.2 years of age and weighing between 3.0 and 7.1 kg were initially assigned to the AMG 334 group (30) or the control group (20). Dosing was initiated between GD20 and GD22, and on GD35; and then continued every two weeks until parturition. The infants were sacrificed between PND 179 and 181.
Deviation from study protocol:	Minor deviations were reported, with no impact on study validity.

Observations and Results

F_0 Dams

Survival:	All animals survived
Clinical signs:	Animals were observed once daily for clinical signs beginning on the first day of dosing through PPD180 ± 2 days. There were no drug-related findings.
Body weight:	Animals were weighed weekly from study enrollment through PPD180 (± 2 days). There were no drug-related findings.
Food consumption:	Food consumption was assessed once daily starting on the first day of dosing through PPD180 ± 2 days. There were no drug-related findings.
Uterine content:	Ultrasounds were conducted to determine pregnancy (GD8 - GD20), confirm pregnancy (GD20 - GD22), and determine embryofetal viability (every two weeks beginning on GD32 ±1). There were no drug-related effects on gestation length or male:female ratio.
Necropsy observation:	Necropsy observations were not performed.
ADA, mCG, Hematology, Clinical chemistry, and Toxicokinetics:	Whole blood was collected by venipuncture from the femora vein when possible, or from the cephalic/saphenous vein. Samples were collected from fasted animals. mCG: Samples for mCG testing were collected predose between GD20 and GD22. One animal tested negative and was removed from the study. ADA: Samples for ADA testing were collected between GD20 and PPD180 ±2 days, but were not analyzed. Hematology: Samples were collected on GD140 (168 h postdose) and a standard battery of hematology parameters was assessed. There were no drug-related findings. Clinical chemistry: Samples were collected on GD140 and a standard battery of clinical chemistry parameters was assessed. There were no drug-related findings. Toxicokinetics: Samples were collected between GD20 and PPD180 ±2 days. TK data were assessed to confirm AMG 334 exposure during gestation. Six animals in the AMG 334 group were

removed due to low AMG 334 exposure during gestation. On GD133 (the only day were serum concentrations were measured at multiple time points), C_{max} was 422 µg/mL and AUC_{last} was 4280 µg*day/mL, approximately 20-fold higher then human AUC_{last} values after 3, once monthly SC monthly doses. During postpartum evaluation, serum AMG 334 concentrations decrease steadily in both adult females and infants. Serum concentrations were higher in infants than in adult females. Serum concentrations were below the LLOQ in adult females and infants by PPD91 and PND180, respectively (see table below).

Mean Infant and Maternal Serum AMG 334 Concentration after Biweekly Subcutaneous Administration of 50 mg/kg/dose to Females after Parturition

Mean **Maternal** Serum Concentration (µg/mL)	PPD14	PPD28	PPD91	PPD180
	66	23	.009	<LLOQ
Mean **Infant** Serum Concentration (µg/mL)	PND14	PND28	PND91	BD180
	117	46	0.188	<LLOQ

AMG 334 was detected in two maternal and two infant control animals (see table 16 below), with no cause identified.

Control Animals with Detectable Serum Levels of AMG 334

Animal No.	Study Interval	Serum level of AMG 334 (µg/mL)	Corresponding Group 2 AMG 334 mean value (µg/mL)
1502	GD48	330	129
	GD62	55	138
	GD67	4	136
1511	PPD14	29	66
	PPD28	5	23
1111*	PND14	56	117
	PND28	21	46
	PND98	0.013	0.188
1519	GD104	122	139
	GD127	9	NA
1141	PND14	0.0175	117

* Offspring of 1511

Dosing Solution Analysis	Samples were analyzed prior to the first dose, at the first dose, and then every two months during the dosing period. All dosing formulations were found to have mean concentrations that were within ±10% of intended solution concentration, and individual sample concentrations were within ±15% of intended solution concentration.
Other:	None

F_1 Generation

Survival: In the AMG 334 group, there was a 30% (7/23) mortality rate, 4 fetuses and 3 infants. In the control group, there was a 25% (5/20) mortality rate, 3 fetuses and 2 infants. The sponsor reported a 29.1% historical control mortality rate at the testing facility between 2008 and 2015.

Clinical signs: Infants were observed once daily for clinical signs beginning at birth through necropsy detailed observations were made weekly. There were no drug-related findings.

Body weight: Infants were weighed weekly. There were no drug-related findings.

Food consumption: Nursing was documented throughout the day of delivery and during the PND2 evaluations. There were no drug-related findings.

Physical development: Physical development was assessed on the following days:

- The day of delivery (PND1), the placenta was examined and nursing behavior was observed.
- On PND2, infants were either evaluated for nursing behavior, body weight, hard palate, spinal cord closure, digits, limbs, joint angles for normal morphology, lymph node palpation, heart rate, and respiration.
- On PND28, PND91, and at necropsy, external assessments and the following morphometric measurements were made: crown-rump length, bilateral femur length, bilateral foot length, horizontal head circumference, biparietal diameter, occipitofrontal diameter, chest circumference, and anogenital distance.

There were no drug-related findings.

Neurological assessment: The following battery of neurobehavioral tests was conducted on PND7 and PND14: righting, palmar grasp, clasp-grasp, visual following, prone progression, lipsmack orient, oral reflexes (rooting, sucking, and snout reflex), eye reflexes (pupil constriction, nystagmus, and glabellar tap), Moro reflex, negative geotaxis, and buildup (increasing arousal levels in response to manipulation). No complex learning and memory tasks were performed.

There were no drug-related findings.
Reproduction: None

10 Special Toxicology Studies

Study title: Tissue Cross-Reactivity of AMG 334 with Human Tissues *Ex Vivo*.

Study no.:	113722
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 22, 2011
GLP compliance:	Yes, except for characterization of the test and control articles.
QA statement:	Yes
Drug, lot #, and concentration:	Alexa Fluor 488-labeled AMG 334, lot: 103858; concentration 3.54 mg/mL

Summary
Alexa 488 labeled-AMG 334 was used to assess human tissue cross-reactivity on cryosections from a panel of the following tissues (from 3 individuals): adrenal, bladder, blood, bone marrow, breast, cerebellum, cerebral cortex, colon, endothelium blood vessels, eye, fallopian tubes, stomach, small intestine, heart, kidney (glomerulus and tubule), liver, lung, lymph node, peripheral nerve, ovary, pancreas, parathyroid, parotid (salivary gland), pituitary, placenta, prostate, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid, tonsil, ureter, and uterus (cervix and endometrium). Staining was observed in the cerebellum, pituitary, and spinal cord. In the cerebellum, mild staining localized in the neuropil of the gray matter. In the pituitary, there was mild granular cytoplasmic staining of many cells in the pars distalis. In the spinal cord, there was mild staining in the neuropil. These findings are consistent with published CGRP-R expression in nervous system tissues (Eftekhari and Edvinsson 2011).

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 116098, D. Charles Thompson, Ph.D., October 16, 2012)

Study title: AMG 334 – Tissue Cross-Reactivity Study in Limited Cynomolgus Monkey tissues

Study no.:	117454
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 16, 2013
GLP compliance:	Yes,
QA statement:	Yes
Drug, lot #, and concentrations:	Alexa Fluor 488-labeled AMG 334, lot: 103858-34, concentration: 3.54 mg/mL Biotin-AMG 334, lot: 103858-33, concentration: 3.46 mg/mL

Summary

Alexa 488 labeled-AMG 334 (5 µg/mL and 25 µg/mL) was used to assess cynomologus monkey tissue cross-reactivity on cryosections of brain and spinal cord tissues from 3 monkeys. Staining was positive in the cerebellum and spinal cord in all 3 animals at both concentrations. In the cerebellum, mild to moderate staining localized in the neuropil of the gray matter, including the Purkinje cell cytoplasm and processes. In the spinal cord, there was mild to moderate diffuse staining of the neuropil of the gray matter and in the peripheral white matter of the neuroglial processes. No specific staining was observed in any of the cerebral sections.

11 Integrated Summary and Safety Evaluation

Erenumab is a human monoclonal antibody that binds the CGRP receptor, inhibiting endogenous CGRP binding. The CGRP receptor is expressed in peripheral and central nervous system tissues, including those implicated in migraine pain. During a migraine episode CGRP levels increase, which induce vasodilation and nociceptive signaling though the CGRP receptor. It is hypothesized that inhibiting CGRP receptor activity will also inhibit migraine pain. The sponsor is proposing once-a-month administration of erenumab as a prophylaxis for migraine.

In *in vitro* assays, erenumab specifically bound to human and monkey CGRP receptors with pM affinity, which is more than 1000-fold greater than endogenous CGRP. In cell based cAMP assays, erenumab antagonized human and monkey CGRP receptor activity at low nM concentrations. In contrast, erenumab showed no antagonist activity (up to µM concentrations) at the rat CGRP-R or closely related (human) adrenomedullin 1 (ADM1), adrenomedullin 2 (ADM2), calcitonin, and amylin (AMY) CGRP-R family members.

In a pharmacodynamic study conducted in monkeys, the prophylactic effect of erenumab (IV) on capsaicin-induced dermal blood flow (DBF) increase was assessed. Maximal inhibition of DBF was at ≥3 mg/kg.

In a safety pharmacology study, telemetry-instrumented conscious monkeys treated with 0, 25, or 225 mg/kg (SC) erenumab (6 males/group) showed no adverse cardiovascular, pulmonary, or neurobehavioral effects. Additionally, cardiovascular safety was supported by an *ex vivo* study assessing 1 nM to 1 µM erenumab on isolated human coronary arteries. Erenumab did not induce contractions or interact with sumatriptan-induced contractions.

The safety pharmacology and isolated coronary artery studies do not address the theoretical concern that blockade of CGRP-R signaling may remove a key mechanism for cardiovascular (CV) protection. Rodent models of hypertension (Smillie et al., 2014), myocardial ischemia (Homma et al., 2014), and heart failure (Li et al., 2013) support the idea that CGRP may be CV protective, while canine models of myocardial ischemia (Lynch et al., 2009; Regan et al., 2009) and heart failure (Shen et al., 2003) do not. In patients, elevated CGRP levels may prevent focal cerebral ischemia following subarachnoid hemorrhage (Schebesch et al., 2013) and pre-eclampsia during pregnancy (Fei et al., 2012; Yadav et al., 2014). While the focus of these studies is on the CGRP peptide, it is reasonable these findings could also apply to blockade of the CGRP-R. Overall, the body of literature validate the theoretical concern that blockade of CGRP-R signaling could increase the number and severity of cardiovascular events in patients with preexisting CV risk factors. A nonclinical post-marketing study could provide some clarity on this issue, if a suitable model could be identified.

General toxicology studies were conducted exclusively in monkeys, due to a lack of pharmacological activity in other species. The general toxicology package consisted of a 1-month exploratory toxicity study, 1-month toxicity study with 4-month recovery period, and a 3- and 6-month toxicity study with 15-week recovery period.

In the non-GLP 1-month exploratory toxicity study, SC doses of 0, 75, 75, and 225 mg/kg (3 males/group) were administered 2 or 3x per week. A standard battery of toxicity parameters, including a complete histology battery, was assessed. The only drug-related finding was minimal to mild injection site hemorrhage and infiltrate. No animals tested positive for ADA; however, 1 of 3 animals in the 75 mg/kg group tested positive for CIC.

In the 1-month toxicity study with 4-month recovery period, SC doses of 0, 25, 75, 100, and 225 mg/kg were administered 2x per week or a single IV dose of 0 or 100 mg/kg was administered (3/sex/group, SC and IV). One LDF (SC) had to be euthanized due to inflammation attributed to ADA. There were no other drug-related findings. No ADA was reported in the remaining Main Study animals; however, ADA was detected in all HD recovery animals and one control animal. According to the sponsor, ADAs in the Main Study animals may have been masked by erenumab in the circulation.

In the pivotal 3- and 6-month toxicity study with 15-week recovery period, SC doses of 0, 25, and 150 mg/kg were administered 2x per week (4/sex/group). A complete toxicological assessment included an ECG, which showed no drug-related findings. One HD male had an “acute phase of protein response on Day 181,” with histological correlates consisting of inflammation in the coronary artery, gallbladder, and femorotibial joint. In the same animal, there were also multifocal glomerular cellularity and scattered tubular red cell casts in the kidney. These observations were attributed to ADA. ADA was also observed in 3 LD animals, which resulted in reduced drug exposures (C_{max} and $AUC_{0\text{-}7d}$). At the end of the recovery period, all animals had drug exposures <0.5% of drug levels at the end of the dosing period. Although there was no dose-limiting toxicity, the HD was adequate based on an $AUC_{0\text{-}7d}$ value that exceeded a 10-fold exposure multiple over therapeutic drug levels in humans.

Carcinogenicity studies were waived, based on the lack of erenumab activity in rodents, histopathological data from the submitted toxicology studies showing no carcinogenic risk factors (i.e. hyperplasia or neoplasia), and CGRP KO studies, from published literature, showing no impairment of the immune response or findings of hyperplasia or neoplasia (Huebner et al. 2008). Additionally, in a published study using CGRP KO mice implanted with tumors, the mice displayed reduced tumor size and vascularization compared to mice with endogenously expressed CGRP (Toda et al. 2008).

The reproductive and developmental toxicology package consisted of a single enhanced PPND study in monkey, with dosing at 0 and 50 mg/kg (20 and 23

animals/group, respectively). A single dose level was adequate because, the AUC exceeded a 10-fold exposure multiple over therapeutic drug levels in humans. The results from the enhanced PPND study were unremarkable; therefore, the NOAEL was 50 mg/kg.

Summary

Overall, erenumab was shown to positively stain brain and spinal cord tissue, which are known to contain CGRP-R; have high affinity and specificity for human and monkey CGRP-R, relative to endogenous CGRP and other CGRP-R family members; and effectively antagonize CGRP-R activity. In a pharmacodynamics study in monkey, erenumab inhibited capsaicin-induced dermal blood flow increases. Both safety pharmacology and toxicology studies showed no adverse cardiovascular, pulmonary, neurobehavioral, general toxicity or reproductive and developmental toxicity concerns. Therefore, the nonclinical BLA package supports approval of erenumab.

REFERENCES

Eftekhari, S., and L. Edvinsson. 2011. 'Calcitonin gene-related peptide (CGRP) and its receptor components in human and rat spinal trigeminal nucleus and spinal cord at C1-level', *BMC Neurosci*, 12: 112.

Fei, X., Z. Hongxiang, C. Qi, and C. Daozhen. 2012. 'Maternal plasma levels of endothelial dysfunction mediators including AM, CGRP, sICAM-1 and tHcy in pre-eclampsia', *Adv Clin Exp Med*, 21: 573-9.

Homma, S., T. Kimura, S. Sakai, K. Yanagi, Y. Miyauchi, K. Aonuma, and T. Miyauchi. 2014. 'Calcitonin gene-related peptide protects the myocardium from ischemia induced by endothelin-1: intravital microscopic observation and (31)P-MR spectroscopic studies', *Life Sci*, 118: 248-54.

Huebner, A. K., J. Keller, P. Catala-Lehnen, S. Perkovic, T. Streichert, R. B. Emeson, M. Amling, and T. Schinke. 2008. 'The role of calcitonin and alpha-calcitonin gene-related peptide in bone formation', *Arch Biochem Biophys*, 473: 210-7.

Li, J., S. P. Levick, D. J. DiPette, J. S. Janicki, and S. C. Supowit. 2013. 'Alpha-calcitonin gene-related peptide is protective against pressure overload-induced heart failure', *Regul Pept*, 185: 20-8.

Lynch, J. J., Y. T. Shen, T. J. Pittman, K. D. Anderson, K. S. Koblan, R. J. Gould, C. P. Regan, and S. A. Kane. 2009. 'Effects of the prototype serotonin 5-HT(1B/1D) receptor agonist sumatriptan and the calcitonin gene-related peptide (CGRP) receptor antagonist CGRP(8-37) on myocardial reactive hyperemic response in conscious dogs', *Eur J Pharmacol*, 623: 96-102.

Regan, C. P., G. L. Stump, S. A. Kane, and J. J. Lynch, Jr. 2009. 'Calcitonin gene-related peptide receptor antagonism does not affect the severity of myocardial ischemia during atrial pacing in dogs with coronary artery stenosis', *J Pharmacol Exp Ther*, 328: 571-8.

Schebesch, K. M., A. Herbst, S. Bele, P. Schodel, A. Brawanski, E. M. Stoerr, A. Lohmeier, S. M. Kagerbauer, J. Martin, and M. Proescholdt. 2013. 'Calcitonin-gene related peptide and cerebral vasospasm', *J Clin Neurosci*, 20: 584-6.

Shen, Y. T., J. J. Mallee, L. K. Handt, D. B. Gilberto, J. J. Lynch, Jr., R. J. Hargreaves, K. S. Koblan, R. J. Gould, and S. A. Kane. 2003. 'Effects of inhibition of alpha-CGRP receptors on cardiac and peripheral vascular dynamics in conscious dogs with chronic heart failure', *J Cardiovasc Pharmacol*, 42: 656-61.

Smillie, S. J., R. King, X. Kodji, E. Outzen, G. Pozsgai, E. Fernandes, N. Marshall, P. de Winter, R. J. Heads, C. Dessapt-Baradez, L. Gnudi, A. Sams, A. M. Shah, R. C. Siow, and S. D. Brain. 2014. 'An ongoing role of alpha-calcitonin gene-related peptide as part of a protective network against hypertension, vascular hypertrophy, and oxidative stress', *Hypertension*, 63: 1056-62.

Toda, M., T. Suzuki, K. Hosono, I. Hayashi, S. Hashiba, Y. Onuma, H. Amano, Y. Kurihara, H. Kurihara, H. Okamoto, S. Hoka, and M. Majima. 2008. 'Neuronal system-dependent facilitation of tumor angiogenesis and tumor growth by calcitonin gene-related peptide', *Proc Natl Acad Sci U S A*, 105: 13550-5.

Yadav, S., Y. S. Yadav, M. M. Goel, U. Singh, S. M. Natu, and M. P. Negi. 2014. 'Calcitonin gene- and parathyroid hormone-related peptides in normotensive and preeclamptic pregnancies: a nested case-control study', *Arch Gynecol Obstet*, 290: 897-903.

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