Title: Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients

AMG 334

Amgen Protocol Number (AMG 334) 20140207

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Investigator's Agreement

I have read the attached protocol entitled Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients, dated 01 September 2016, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients

Study Phase: 1

Indication: Migraine Prophylaxis

Primary Objective: To evaluate the inhibition of PACAP-38 induced migraine-like attacks by AMG 334

Secondary Objectives:

- To evaluate the inhibition of PACAP-38 induced headaches by AMG 334
- To evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of a single intravenous (IV) dose of AMG 334 in migraine patients

Exploratory Objectives:

- To evaluate the reduction in severity of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the duration of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the safety and tolerability of a single intravenous (IV) dose of exogenous PACAP-38
- To evaluate CGRP and PACAP-38 levels in migraine patients

Hypotheses: A single dose of 140 mg IV of AMG 334 will inhibit migraine-like attacks in subjects challenged with PACAP-38

Primary Endpoint: Occurrence of a migraine-like attack within 24 hours of challenge-agent infusion

Secondary Endpoints:

- Occurrence of a headache within 24 hours of challenge-agent infusion
- Treatment-emergent adverse events
- Clinical significant changes in vital signs, ECGs, physical examinations, laboratory safety tests and neurological assessments
- AMG 334 PK parameters, including C1 hour and AUC84d
- Anti-AMG 334 antibodies

Exploratory Endpoints:

- Severity of PACAP-38 induced migraine-like attacks and headaches
- Duration of PACAP-38 induced migraine-like attacks and headaches
- Migraine characteristics: localization, accompanying symptoms and pre-monitory symptoms.
- PACAP-38 related treatment-emergent adverse events
- Evaluate the concentration of PACAP-38 and CGRP following administration of AMG 334

Study Design: This is a randomized, double-blind, placebo-controlled, parallel-group study in subjects with episodic migraines. This study will evaluate the efficacy of AMG 334 as measured by inhibition of PACAP-38 induced migraine-like attacks after a single dose of AMG 334. Migraine-like attacks (MLA) will be defined as attacks fulfilling one of the two criteria:

(1) Headache fulfilling criteria C and D for migraine without aura (IHS 2004)

C. Headache has at least two of the following characteristics:
- unilateral location
- pulsating quality
- moderate or severe pain intensity (≥ 4 on headache questionnaire)
- aggravation by or causing avoidance of routine physical activity

D. During headache at least one of the following:
- nausea and/or vomiting
- photophobia and phonophobia

(2) Headache described as mimicking usual migraine attack treated with triptan.

Part A: PACAP-38 Dose Selection Phase

There are a number of published clinical studies in which pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) was used to trigger MLA in migraneurs (Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014). In those studies, 10 pmol/kg/min over 20 minutes (total dose 200 pmol/kg) was administered. Approximately 90% of migraineurs experienced a headache and approximately 66% of the same migraineurs experienced MLA with a median time of headache onset of 4 hours, though the half-life of PACAP-38 is only 3.5 minutes. As PACAP-38 is involved in various biological processes, including sensory processing, vasodilation, inflammation, and nociceptive transmission (Dickinson et al., 1999; Vaudry et al., 2000), nearly all healthy subjects and migraineurs also experienced the expected adverse events of flushing and heat sensation, along with a transient elevation in heart rate and blood pressure (Birk et al, Regulatory Peptides 2007; Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014) (see Investigator Brochure for details).

Based on the low assay values observed during Amgen's testing of the PACAP-38 formulation used in the aforementioned published clinical studies, it was concluded that adhesion of the polypeptide to the product container surfaces probably occurred. Although the data were variable, it is estimated that on average, approximately 50% of the peptide may have been lost to surface binding. Amgen formulation modifications using albumin and acetic acid have eliminated this problem.

Therefore, in order to ensure subject safety and select the lowest PACAP-38 dose that will ideally trigger headache in all subjects within a given cohort and moderate to severe MLAs in the majority of the subjects within the same cohort, a dose selection strategy, along with Safety Review Meetings and Dose-Level Review Meetings (DLRM) have been implemented. Dosing of PACAP-38 shall not exceed a total dose of 115 pmol/kg, providing an approximate 10X exposure margin over the non-clinical NOAEL dose. However, the trigger of headaches in the majority of the subjects within a given cohort and mild, moderate or severe MLAs in the majority of the subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B).

Up to five cohorts consisting of approximately 2 to 5 subjects are planned. Based on emerging safety and tolerability data, as well as the number of subjects experiencing a headache and/or MLA, the voting members of the Safety Review Meetings or DLRM (the PI, Medical Monitor and Global Safety Officer), may decide cohorts should be removed or additional cohorts should be added, with a maximum of 5 total cohorts. Subject numbers within each cohort may also be increased or decreased based on the decision from the Safety Review Meeting or DLRM. Doses to be administered within each cohort may be repeated, higher or lower than the last dosed cohort. Dosing of any subject shall not exceed 115 pmol/kg. Possible future PACAP-38 doses and associated cohorts beyond 100 pmol/kg (Cohort 4) are as follows: 115 pmol/kg (Cohort 5).

On Day 1, approximately 2 subjects in Cohort 1 will receive an infusion of 10 pmol/kg/min over 2.5 minutes (total dose 25 pmol/kg). The PI will be responsible to review heart rate (HR) and blood pressure (BP). The BP assessment is based on a single measurement of systolic blood pressure (SBP) of >150 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg. If the mean

heart rate increase of the subjects in Cohort 1 is greater than 50% over baseline during a 2 hour period after dosing and SBP does not increase to >150 mm Hg or DBP to >100 mm Hg, then approximately 3 subjects in Cohort 2 will receive an infusion of 10 pmol/kg/min over 5 minutes (total dose 50 pmol/kg). Written documentation from Amgen of the decision to proceed with enrollment in Cohort 2 is required. After dosing Cohort 2 and any subsequent cohort, the PI will again be responsible to review HR and BP using previously outlined criteria. These same criteria shall also be assessed for Cohort 3.

After dosing Cohort 3, up to 5 subjects in Cohort 4 will receive 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg). Following Cohort 4, a Dose-Level-Review Meeting (DLRM) will occur to decide the dose of PACAP-38 to be used in the randomized portion of the study (Part B). This decision will be primarily based on safety and tolerability data, and number of subjects experiencing a headache and/or MLA in Cohort 4, although all of the available data for Cohorts 1 to 4 will be reviewed. The dose- selection for Part B will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B). If this goal is not achieved, following the DLRM review of the Cohort 4 data, then Cohort 5 dosing of 10pmol/kg/ min over 11.5 minutes (total dose 115 pmol/kg) can commence.

Cohorts 2, 3 and 4 enrollment will occur after a Safety Review Meeting between the principal investigator (PI), medical monitor (MM), and global safety officer (GSO) or designee. At that time, available vital signs and adverse events occurring at least 24 hours following PACAP-38 dosing will be reviewed.

If the PI, MM, and GSO or designee decide not to proceed with enrollment into a subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort. Refer to Section 10.4.2 for additional information on the Safety Review Meetings and DLRMs. The Safety Review Meeting or DLRM voting members will decide whether or not to proceed with enrollment in Part B Randomization (AMG 334 or Placebo) Phase and if the decision is made to proceed, the Safety Review or DLRM voting members will select the appropriate PACAP-38 dose. The decision to proceed with Part B of the study will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study.

Part B: Randomization (AMG 334 or Placebo) Phase

A minimum of 16 and a maximum of 36 subjects will be randomized between two treatment groups (AMG 334 or placebo). On Day 1, treatment groups will receive 140 mg IV AMG 334 over 30 minutes or matching placebo, in a one to one allocation ratio. On Day 8, the subjects will be administered the dose of PACAP-38 determined from the PACAP-38 Dose Selection Phase. All subjects will remain in-house for 24 hours of observation following PACAP-38 infusion.

Subjects will be monitored and asked questions from the headache questionnaire (Appendix D), as per the Schedule of Assessment in Table 2 to determine if they have experienced a MLA. After 24 hours of data from the first 16 Randomized (AMG 334 or Placebo) Subjects challenged with PACAP-38 is available, an interim analysis will be conducted to determine if challenge rates are comparable to historical rates (~66%) and if AMG 334 has greater efficacy than placebo. If AMG 334 is found to completely block PACAP-38 induced migraines, or have the same efficacy as placebo, the study will be terminated. Otherwise, approximately 20 Randomized (AMG 334 or Placebo) Subjects will be added.

Sample Size: A total of up to 61 migraine subjects are planned to be enrolled into the study. Up to 25 subjects may participate in Part A and up to 36 in Part B of the study. If ambiguous results in Part A occur regarding the ability of PACAP-38 ideally safely trigger a headache in all subjects within a given cohort (although, safely triggering headaches in the majority of subjects within a

given cohort may be considered acceptable to advance to Part B of the study) and moderate to severe MLAs in the majority of subjects within the same cohort, then a previously dosed cohort sample size may be expanded to up to 5 subjects per cohort. Once the PACAP-38 dose has been selected, 8 subjects will be randomized to placebo and 8 subjects will be randomized to AMG 334. The data collected for the 16 Randomized (AMG 334 or Placebo) Subjects will be included in the interim analysis (See Section 10.4.1). Following the interim analysis, if the decision is to continue enrollment for the study, an additional 10 subjects will be randomized to placebo, and another 10 subjects will be randomized to AMG 334.

The sample size is based on practical considerations and is consistent with this type of study. If, PACAP-38 produces MLA in 70% of placebo treated subjects, and AMG 334 is effective in blocking MLA such that only 20% of AMG 334 treated subjects have a headache, then there is approximately a 91% chance of overall trial success (Section 10.4.1).

Summary of Subject Eligibility Criteria: Subjects in this study will be males and females ≥ 18 to ≤ 45 years of age, with history of migraine without aura for ≥ 6 months and who experience 5 or fewer migraine days per month. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Randomized (AMG 334 or Placebo) Subjects will receive a single dose of AMG 334 or placebo by intravenous (IV) administration after completion of pre-dose procedures on study Day 1. See Section 6.2.

Non-Investigational Product

Non-Amgen Non-Investigational Product Dosage and Administration: Randomized (AMG 334 or Placebo) Subjects will receive a challenge-agent (PACAP-38 up to a total dose of 115 pmol/kg; 521 ng/kg) by IV administration on Day 8. For Non Randomized (PACAP-38 Only) Dose Selection Subjects, Cohort 1 will receive PACAP-38 infusion of 10 pmol/kg/min over 2.5 minutes, Cohort 2 will receive PACAP-38 infusion of 10 pmol/kg/min over 5 minutes, Cohort 3 will receive PACAP-38 infusion of 10 pmol/kg/min over 7.5 minutes, and Cohort 4 will receive PACAP-38 infusion of 10 pmol/kg/min over 10 minutes. Optional Cohort 5 may receive PACAP-38 infusion of 10 pmol/kg/min over 11.5 minutes. See Section 6.3.

Procedures: After informed consent has been obtained, all screening procedures and tests establishing eligibility will be performed within a period of 21 days before study product administration.

For Part A Non Randomized (PACAP-38 Only) Dose Selection, eligible subjects will return to the research facility on Day -1, one day prior to PACAP-38 administration, at which time baseline procedures will be completed. After completion of all pre-dose procedures on the day of dosing (Day 1), subjects will receive PACAP-38. Subjects will reside at the research facility on Day 1 after dosing for at least 24 hours post PACAP-38 infusion and then be discharged and provided with instructions to return to the research facility according to the procedures provided in the Schedule of Assessment (Table 3).

For Part B Randomized (AMG 334 or Placebo) Subjects, eligible subjects will be randomized to receive either AMG 334 or matching placebo. Subjects will return to the research facility on Day -1, one day prior to investigational product administration, at which time baseline procedures will be completed. After completion of all pre-dose procedures on the day of dosing (Day 1), subjects will receive AMG 334 or matching placebo. Subjects will reside at the research facility on Day 1 after dosing for at least 1 hour and then be discharged. Subjects will then return to the research facility on Day 8 for the infusion of PACAP-38 and stay for at least 24 hours post PACAP-38 infusion and then discharged and provided with instructions to return to the research facility according to the procedures provided in the Schedule of Assessment (Table 2). Subjects will be followed 85 days with two in-clinic (Day 29 and Day 57) study visits during that time.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2 and Table 3).

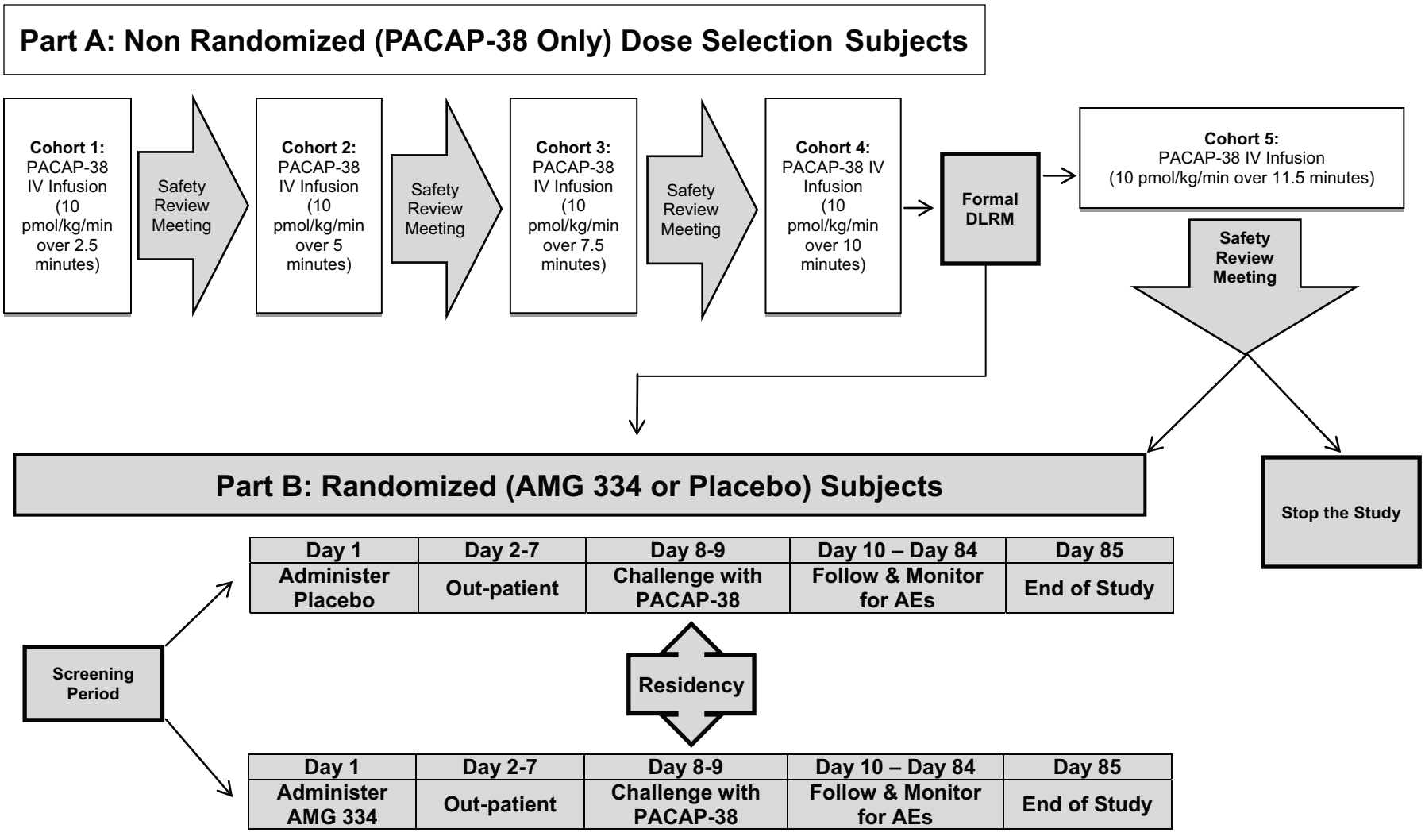
Statistical Considerations: Descriptive statistics will be provided for selected endpoints. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

Comparison of PACAP-38 ability to produce MLA between AMG 334 and placebo will be done with Fisher's Exact test.

If at the interim analysis 3 or fewer of the 8 placebo subjects have a MLA, the study will be stopped and it will be concluded that PACAP-38 does not induce a sufficient proportion of MLA for the study to test the hypothesis. If 4 or more placebo subjects have a MLA, yet more subjects receiving AMG 334 have them than placebo subjects, then the study will be stopped and it will be concluded that AMG 334 is ineffective in blocking PACAP-38 induced MLA. On the other hand, if the difference at the interim in the proportion of subjects with MLA (placebo-AMG 334) is greater than or equal to 75%, then the study will stop early and it will be concluded that AMG 334 is effective in blocking PACAP-38 induced MLA. If none of these conditions hold, then an additional 20 subjects will be enrolled in the trial. If the p-value from the one-sided Fisher's Exact test is less than 0.1, it will be concluded that AMG 334 is effective in blocking MLA. For a full description of statistical analysis methods, please refer to Section 10.

Sponsor: See Protocol Title Page

Study Design and Treatment Schema



Abbreviations:
DLRM = Dose Level Review Meeting
IV = Intravenous

Study Glossary

Abbreviation	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{84d}	area under the concentration-time curve from study Day 1 to 85
BP	blood pressure
BMI	body mass index
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
C_{max}	maximum observed concentration
C_o	serum concentration at time 0
$C_{1\ hour}$	serum concentration at time 1 hour
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DILI	drug-induced liver injury
DLRM	Dose Level Review Meeting
ECG	Electrocardiogram
CRF	case report form
eCRF	electronic case report form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	end of study
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GPCR	G-protein couple receptor
GSO	Amgen Global Safety Officer
HBcAB	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	Heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual

Abbreviation	Definition/Explanation
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IV	Intravenous
kg	kilogram
MDRD	Modification of Diet in Renal Disease
MLA	Migraine-like attacks
MM	Amgen Medical Monitor
ng	nanogram
NOAEL	no observed adverse effect level
PACAP-38	Pituitary adenylate cyclase-activating polypeptide-38
PI	Principal Investigator
PK	Pharmacokinetic
pmol	picomole
PR	the interval measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by electrocardiogram
QRS	the interval between the Q wave and the S wave in the heart's electrical cycle as measured by electrocardiogram; represents the time it takes for depolarization of the ventricles
QT	the interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by electrocardiogram
QTc	QT interval corrected for heart rate using accepted methodology
QTcB	QT interval corrected for heart rate using Bazzetts formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	respiration rate
SBP	Systolic blood pressure
SD	Standard deviation
SC	Subcutaneous
TBL	total bilirubin
TEAE	Treatment emergent adverse events
t_{max}	time to maximum concentration
µg	microgram
ULN	upper limit of normal

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1. OBJECTIVES

1.1 Primary

To evaluate the inhibition of PACAP-38 induced migraine-like attacks by AMG 334

1.2 Secondary

- To evaluate the inhibition of PACAP-38 induced headaches by AMG 334
- To evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of a single intravenous (IV) dose of AMG 334 in migraine patients

1.3 Exploratory

- To evaluate the reduction in severity of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the duration of PACAP-38 induced migraine-like attacks and headaches by AMG 334
- To evaluate the safety and tolerability of a single intravenous (IV) dose of exogenous PACAP-38
- To evaluate CGRP and PACAP-38 levels in migraine patients

2. BACKGROUND AND RATIONALE

2.1 Disease

2.1.1 Migraines

Migraines are episodic headaches that can involve significant pain and are sometimes preceded by sensory warning symptoms or signs (auras) and are often accompanied by nausea, vomiting, and extreme sensitivity to light (photophobia) and sound (phonophobia). Migraine is a highly prevalent disease world-wide with approximately 15% of the European population and 12% of the United States population suffering from migraine attacks. A study to assess the prevalence of migraine in the United States reported that nearly half the migraine patient population had experienced three or more migraines per month. Based on existing treatment guidelines, roughly 40% of the migraine patient population would benefit from preventive therapy (Lipton *et al.,* 2001). Globally, migraines affect more than 10% of the world's population (Robbins & Lipton 2010) and have been found to be associated with a number of psychiatric and medical comorbidities such as depression and vascular disorders (Buse *et al.,* 2010, Bigal *et al.,*2009).

Migraine was historically considered to be due to vasodilatation of cranial blood vessels and is currently treated primarily with a class of drugs called triptans (Houston & Van Houtte 1986, Humphrey *et al.,* 1990). More recent understanding of the pathophysiology of migraine indicates that the vasodilatation of the cranial blood vessels

is secondary to activation of the trigeminal nociceptive pathway (Goadsby *et al.,* 2002). Over the last 20 years two peptides, Calcitonin gene-related peptide (CGRP) and Pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) have been implicated in the pathophysiology of migraines and are the focus of novel therapies.

2.1.2 Calcitonin Gene-Related Peptide (CGRP)

Calcitonin gene-related peptide (CGRP) has been implicated as a key mediator in the initiation and progression of migraine pain. CGRP is a potent vasodilator and nociceptive modulator that has been associated with migraine pathophysiology due to several lines of evidence: 1) it is expressed in the trigeminal system, which is implicated in the pathophysiology of migraines; 2) CGRP levels are elevated in migraineurs during an attack (Goadsby *et al.*, 1988, 1990; Gallai *et al.*, 1995; Ashina *et al.*, 2000; Bellamy *et al.*, 2006); 3) CGRP infusion triggers the onset of migraine headaches in migraine sufferers (Lassen *et al*., 2002; Hansen et al., 2010). Additionally, CGRP has been implicated as a key mediator in the initiation and progression of migraine pain (Durham 2004; Poyner 1992). Taken together, these data suggest a role for this neuropeptide and its receptor in the pathogenesis of migraine.

Recently, 2 small molecule inhibitors of the CGRP receptor have demonstrated reversal of acute migraine in large clinical trials (Ho *et al.,* 2008; Connor *et al.,* 2009, Hewitt 2009). The positive efficacy data generated by these CGRP receptor antagonist programs has clinically validated the CGRP receptor as a target for migraine.

2.2 Amgen Investigational Product Background

Refer to the specific section of the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

AMG 334 is a human monoclonal immunoglobulin (IgG2) against the CGRP receptor. AMG 334 binds to the CGRP receptor complex with high affinity (Kd of 20 pM) which competitively and reversibly blocks the binding of the native ligand, CGRP. AMG 334 functions as a CGRP receptor antagonist.

The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Durham, 2004; Poyner, 1992; Wang et al, 1995; Zimmermann et al, 1996). Many of these components associated with migraine pathophysiology are outside the blood-brain barrier, and thus a

peripherally restricted CGRP receptor antagonist could be efficacious. More recently, a positron emission tomography (PET) study with telcagepant, a small molecule CGRP receptor antagonist, showed little central nervous system receptor occupancy at a clinically efficacious dose (Vermeersch et al, 2013). Therefore, it is hypothesized that AMG 334, a CGRP receptor antibody, will selectively antagonize the CGRP receptors for prolonged periods, preventing and/or reversing the activation of the trigeminal-vascular system, resulting in the prevention of migraine headaches.

The preclinical toxicology data were generated in cynomolgus monkey as it was the only laboratory species in which AMG 334 had suitable binding and functional activity. There were no significant findings in the toxicology studies that would predict a risk to human subjects. The no-observed adverse effect level (NOAEL) was the maximum dose evaluated in the 6-month Good Laboratory Practice (GLP) toxicology study, 150 mg/kg subcutaneous (SC). There were no significant effects on electrocardiogram (ECG) parameters, blood pressure (BP) or respiration rate (RR) in the single dose cardiovascular study in cynomolgus monkeys

2.2.1 Pharmacology

AMG 334 is a competitive inhibitor of the endogenous ligand, CGRP, which binds the CGRP receptor complex with high affinity (K_d 20 pM) in a competitive and reversible manner and has a slow off-rate. AMG 334 is a potent full antagonist of the human and cynomolgus monkey CGRP receptors. AMG 334 has relatively poor affinity (~230-260 nM Ki) at the dog and rabbit CGRP receptors and negligible binding or activity at the rat CGRP receptor. AMG 334 is highly selective for the human CGRP receptor and is devoid of activity across the family of structurally related G-protein couple receptors (GPCRs): adrenomedullin-1, adrenomedulin-2, calcitonin and amylin receptors.

In cynomolgus monkeys, AMG 334 inhibited capsaicin-induced increases in DBF. Capsaicin induces an increase in DBF by stimulating the release of a variety of factors, including CGRP, which alter vascular tone. The inhibition by AMG 334 is dose-dependent with a dose of 0.3 mg/kg showing a minimally detectable inhibition and doses of 3 mg/kg and above producing maximal inhibition. Trend analysis of the data shows that the inhibition is statistically significant at doses of 0.3 mg/kg and above. These studies provide PD evidence of CGRP receptor antagonism by AMG 334 in a non-human primate model.

2.2.2 AMG 334 Clinical Experience

2.2.2.1 Study 20101267 - First in Human Study in Healthy Adult Volunteers and Subjects With Migraine

2.2.2.1.1 Subject Disposition and Demographic Characteristics

A total of 61 subjects enrolled in this study and 60 subjects (48 healthy subjects and 12 subjects with migraine) received investigational product and completed the study. Of the 60 subjects, 42 (36 healthy subjects and 6 subjects with migraine) received AMG 334 at single doses of 1 to 210 mg SC or 140 mg IV, and the remainder of the subjects received placebo. The mean (standard deviation [SD]) age of the healthy subjects was 27.4 (6.8) years and all were men. The majority of healthy subjects (97.9%) were white. The mean age (SD) of the subjects with migraine was 26.2 (9.6) years; 9 were women, and 3 were men, all 12 (100%) were white.

2.2.2.1.2 Pharmacokinetics

AMG 334 exhibited nonlinear pharmacokinetics after single-dose SC administrations over the dose range of 1 to 210 mg. AMG 334 exposure increased more than dose proportionally from 1 to 70 mg and appeared to increase approximately dose proportionally from 70 to 210 mg after a single SC administration of AMG 334. The mean area under the serum concentration-time curve from time 0 to the last quantifiable time point (AUC_{last}) increased from 171 to 650 µg•day/mL (3.8-fold) and mean C_{max} increased from 6.25 to 15.2 µg/mL (2.5-fold) following the 3-fold increase in dose from 70 to 210 mg. The cohort median time of maximum concentration (t_{max}) ranged from 4 to 11 days within the dose range of 1 to 210 mg. The relative exposure (area under the concentration-time curve [AUC]) for SC administration compared with IV administration was approximately 54% for the 140-mg AMG 334 dose. There was no apparent difference in pharmacokinetic parameters between the healthy and migraine subjects.

2.2.2.1.3 Safety

Treatment-emergent adverse events were reported for 30 of the 36 healthy subjects (83.3%) who received AMG 334 at any dose and for 10 of the 12 healthy subjects (83.3%) who received placebo. Treatment-emergent adverse events were reported for 11 of 12 migraine subjects (91.7%; 5 subjects [83.3%] placebo, 6 subjects [100%] 140 mg SC AMG 334). No adverse events with a Common Terminology Criteria for Adverse Events (CTCAE) of grade ≥ 3 were reported in the study; all events were mild (grade 1) or moderate (grade 2) in severity. The types and frequency of adverse events were similar for healthy and migraine subjects. No relationship was apparent between

the subject incidence of adverse events and the dose of AMG 334, or between the subject incidence of adverse events and the route of administration of AMG 334 (SC versus IV). No adverse events were reported as serious, and no subjects discontinued study due to an adverse event. There were no deaths on study. Likewise, there were no trends indicative of clinically important effects of AMG 334 on laboratory variables, ECGs, or vital signs. One healthy subject who received 70 mg SC AMG 334 developed binding, non-neutralizing antibodies to AMG 334 at the end-of-study visit (day 98).

2.2.2.2 Study 20101268- Phase 1 Multiple Ascending-dose Study in Healthy Adults and Subjects With Migraine

2.2.2.2.1 Subject Disposition and Demographic Characteristics

A total of 48 subjects enrolled in this study and 47 subjects (31 healthy subjects and 16 subjects with migraine) received investigational product and completed the study. Of the 47 subjects, 35 (23 healthy subjects and 12 subjects with migraine) received AMG 334 (21 to 280 mg) or placebo administered SC on days 1, 29, and 57, and the remainder of the subjects received placebo. One subject described below received 2 SC injections of AMG 334 and discontinued the study due to a serious adverse event. The mean (standard deviation [SD]) age of the healthy subjects was 32 (11.6) years and 3 subjects (12.5%) were women, and 21 subjects (87.5%) were men, and all 32 subjects were white. The mean age (SD) of the subjects with migraine was 33 (11.0) years; 9 subjects (75%) were women, and 3 subjects (25%) were men, and all 16 subjects (100%) were white.

2.2.2.2.2 Pharmacokinetics

After the first SC administration of AMG 334 on Day 1, the exposure, measured by the mean maximum measured concentration (C_{max}) and area under the concentration-time curve (AUC), increased in an approximately dose proportional manner over the dose range of 21 to 280 mg for healthy subjects and 21 to 140 mg for migraine patients. The mean C_{max} and AUC from time zero to 28 days (AUC_{tau}) after the first SC dose increased from 2.15 to 24.9 µg/mL (11.6-fold) and from 34.7 to 486 day•µg/mL (14-fold) for healthy subjects following a 13.3-fold increase in dose from 21 mg to 280 mg, respectively. The mean C_{max} and AUC from time zero to 28 days (AUC_{tau}) after the first SC dose increased from 1.76 to 11.0 µg/mL (6.3-fold) and from 28.7 to 244 day•µg/mL (8.5-fold) for migraine subjects following a 6.7-fold increase in dose from 21 mg to 140 mg, respectively. After three single dose SC administrations, the mean AMG 334 C_{max}, AUC from time zero to 28 days (AUC_{tau}), and AUC_{last} increased from 2.60 to 23.7 µg/mL

(9.1-fold), from 49.5 to 476 day•µg/mL (9.6-fold), and from 59.3 to 848 day•µg/mL (14-fold) for healthy subjects following a 6.7-fold increase in dose from 21 mg to 140 mg, respectively. The mean C_{max}, AUC from time zero to 28 days (AUC_{tau}), and AUC_{last} after the last SC dose increased from 2.00 to 18.4 µg/mL (9.2-fold), from 37.9 to 417 day•µg/mL (11-fold), and from 45.0 to 773 day•µg/mL (17-fold), for migraine subjects following a 6.7-fold increase in dose from 21 mg to 140 mg, respectively. The nonlinearity of PK was mainly from 21 mg to 70 mg, AMG 334 $AUC_{0\text{-}tau}$ and AUC_{last} increased approximately 4.3-fold and 5.7-fold, respectively, which were greater than a 3.3-fold dose increase. AMG 334 $AUC_{0\text{-}tau}$ and AUC_{last} increased approximately dose proportionally from 70 mg to 140 mg. After the third SC administration of AMG 334 on Day 57, the accumulation ratios (AR) were 1.42 and 1.69 for the 21 mg and 140 mg cohorts, respectively, for healthy subjects and were 1.50 and 1.78 for the 21 mg and 140 mg cohorts, respectively, for migraine patients. The median time to maximum concentration (t_{max}) ranged from approximately 3-13 days following the first single SC dose for all dose ranges, and ranged from approximately 6-14 days following the third SC dose for all dose ranges.

2.2.2.2.3 Safety

Treatment-emergent adverse events were reported for 22 (91.7%) of the 24 healthy subjects who received AMG 334 at any dose and for 5 (62.5%) of the 8 healthy subjects who received placebo. Treatment-emergent adverse events were reported for 12 (100%) of 12 migraine subjects who received AMG 334 at any dose and for 4 (100%) of the 4 migraine subjects who received placebo. No adverse events with a Common Terminology Criteria for Adverse Events (CTCAE) of grade ≥ 3 were reported in the study other than for the 2 subjects reported below. The types and frequencies of adverse events were similar for healthy and migraine subjects. No relationship was apparent between the subject incidence of adverse events and the dose of AMG 334. There were 2 subjects with reported adverse events classified as serious. One was a healthy subject in the 70-mg cohort who developed polyarthritis possibly related to study and drug and the second was a migraine subject in the 21-mg cohort who developed suicidal ideation classified as not related to drug. There were no deaths on study. Likewise, there were no trends indicative of clinically important effects of AMG 334 on laboratory variables, ECGs, or vital signs.

Five (10.4%) of the 48 total subjects tested developed persistent binding antibodies to AMG 334. Of these 5 subjects with positive binding antibodies, 1 (2.1%) subject also showed neutralizing capability to AMG 334.

2.2.2.3 Study 20120130 - Phase 1 Multiple Ascending-dose Study in Healthy Japanese Adults

2.2.2.3.1 Subject Disposition and Demographic Characteristics

A total of 32 subjects (24 AMG 334; 8 placebo) were screened and enrolled in this study, and all subjects received and completed treatment with the investigational product. Twenty-six subjects (81.3%) completed the study; 6 subjects (18.8%; 5 AMG 334, 1 placebo) discontinued the study and were lost to follow-up. The mean (SD) age was 33.1 (8.4) years (range: 18 to 45 years) and all were men; 24 subjects (75%) were Asian of Japanese ancestry and 8 (25%) were white.

2.2.2.3.2 Pharmacokinetics

AMG 334 exposure (C_{max}, AUC_{last}, and AUC_{inf}) increased greater than dose proportionally from 21 mg to 70 mg and increased proportionally with dose from 70 mg to 140 mg in the healthy Japanese subjects. The t_{max} ranged from 4.0 to 7.0 days following a single SC dose in the 21 mg to 140 mg dose range. The pharmacokinetics of AMG 334 at 70 mg SC was similar for healthy Japanese and white subjects (ratio of geometric means or C_{max}, AUC_{last}, and AUC_{inf} = 1.02, 1.12, and 1.12 respectively).

2.2.2.3.3 Safety

All 32 enrolled subjects received a single dose of investigational product (24 AMG 334; 8 placebo) and were included in the safety analysis set. Nine subjects (37.5%) who received AMG 334 and 3 subjects (37.5%) who received placebo had treatment-emergent adverse events. All adverse events were mild or moderate (CTCAE grade 1 or 2) in severity. There were no deaths, serious adverse events, adverse events leading to discontinuation of investigational product or study, or adverse events considered by the investigator to be related to treatment. There was no apparent effect of AMG 334 on clinical laboratory values, vital signs, or ECGs recorded during the study. One Japanese subject who received 140 mg AMG 334 tested positive for anti-AMG 334 neutralizing antibodies. The AUC_{inf} value for this subject (196 day•µg/mL) was lower than the mean AUC_{inf} value in the other 5 subjects in the 140-mg dose group (478 day•µg/mL; range: 301 to 585 day•µg/mL).

2.2.2.4 Other Indications – Hot Flash Prophylaxis

2.2.2.4.1 Study 20120180 – Phase 1b Placebo-controlled Study in Subjects With Hot Flashes Associated With Menopause

Study 20120180 was a phase 1b, randomized, stratified, parallel-group, double-blind, placebo-controlled, study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of AMG 334 in women with hot flashes associated with menopause. The primary objective was to evaluate the frequency of moderate to severe daily hot flashes at week 4 after a single dose of AMG 334 in women with hot flashes associated with menopause.

2.2.2.4.2 Pharmacokinetics

After a single SC administration of 70 mg AMG 334, the mean (SD) C_{max} was 6.13(2.86) µg/mL. The mean (SD) AUC_{last} and the mean (SD) AUC_{inf} were 173 (84.6) day•µg/mL and 190 (96.3) day•µg/mL, respectively. The median time to maximum concentration (t_{max}) was 7.0 days and the mean terminal half-life ($t_{1/2,z}$) was 12.1 days.

2.2.2.4.3 Safety

All 103 enrolled subjects received a single dose of investigational product (51 subjects received AMG 334 and 52 received placebo) and were included in the safety analysis set. All adverse events with the exception of one woman with a grade 3 event, were mild or moderate (CTCAE grade 1 or 2) in severity. There were no deaths, serious adverse events, adverse events leading to discontinuation of investigational product or study considered by the investigator to be related to study drug. There was no apparent effect of AMG 334 on clinical laboratory values, vital signs, or ECGs recorded during the study. One 51-year-old woman, with a medical history of hypertension, had elevated systolic and diastolic blood pressure 9 days after receiving investigational drug. This adverse event was rated as grade 3 (severe) per CTCAE and was deemed not related to study drug by the investigator. The lack of relationship to study drug was based on this subject's having a history of poorly controlled hypertension prior to entering the study, with reported past blood pressure readings of 219/125 mm Hg and 237/149 mm Hg and noncompliance with her blood pressure medications.

Five (4.9%) of the 103 total subjects tested developed persistent binding antibodies to AMG 334. Of these 5 subjects with positive binding antibodies, 4 (3.8%) also showed neutralizing capability to AMG 334.

2.2.3 AMG 334 Toxicology

The toxicology program was conducted in the cynomolgus monkey, as it was the only laboratory species in which AMG 334 had suitable binding and functional activity. The studies conducted included an exploratory 1-month repeat dose toxicology study (SC, twice weekly), a GLP 1-month repeat dose toxicology study (SC, twice weekly) with a single dose IV arm and a single dose SC cardiovascular, respiratory and neurobehavioral safety pharmacology study in the telemetered monkey. An in vitro human tissue cross-reactivity study with fluorochrome-labeled AMG 334 was also conducted.

There were no toxicology findings in these studies that predict a risk to human subjects.

One animal at 25 mg/kg SC in the 1-month repeat-dose study was euthanized 1 day early due to complications from anti-AMG 334 antibodies and subsequent immune complex associated pathology. No animals in the 1-month exploratory study or other animals in the 1-month GLP study had similar pathology changes. Administration of human proteins to cynomolgus monkeys is often associated with development of antibodies to the human protein, but antigenicity in animal models has low predictive value and often overestimates immunogenicity rates and the incidence of adverse immune-mediated events in humans (Bugelski and Treacy, 2004; Ponce *et al.*, 2009).

There were no findings in the safety pharmacology or tissue cross-reactivity studies which suggest an increased risk to human subjects. The no-observed adverse effect level (NOAEL) was the highest dose tested in the 1-month GLP toxicology study, 225 mg/kg SC. The NOAEL provides significant exposure margins over the anticipated human exposures and the preclinical toxicology data support the proposed clinical study plan. For more information on the toxicology studies, please refer to the Investigator's Brochure.

2.3 AMG 334 Risk Assessment

AMG 334 is currently in phase 3 development for episodic and chronic migraine. Exposures of greater than or equal to the 140 mg IV dose administered in this study have been given to three cohorts in the phase 1 programs and the top dose of both the chronic migraine and episodic migraine program is 140 mg SC. The identified risks for AMG 334 are documented in Appendix A of the currently approved IB (Edition 6: 31 March 2016). To date, there are no important identified risks for AMG 334, while important potential risks identified include, cardiovascular effects, immunogenicity and

developmental effects. Available safety data for the clinical trials with AMG 334 are summarized in section 6.2 of the AMG 334 Investigator's Brochure, Annex 2.

Risk mitigation strategies include the monitoring of vital signs, serial ECGs, and adverse events for all subjects at protocol-defined timepoints.

2.4 Non-Amgen Non-Investigational Medicinal Product Background for PACAP-38 Challenge Agent

Pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) is a neuropeptide belonging to the VIP/secretin/glucagon superfamily (Miyata et al., 1989). Recent research suggests it is involved in various biological processes, including sensory processing, vasodilation, inflammation, and nociceptive transmission (Dickinson et al., 1999; Vaudry et al., 2000). It is a pleiotropic peptide acting on many systems; within the nervous system it acts as a neurotransmitter, neuromodulator, and exerts neuroprotective anti-apoptotic effects. These effects are mediated through three G-protein-linked receptors: $VPAC_1$, $VPAC_2$, and PAC_1. Further studies have shown PACAP-38 to have a much higher affinity for PAC_1 than the other two receptors (Arimura and Shioda, 1995). Recently, PAC_1 receptor activation has been linked to migraine attacks (Amin et al., 2014; Schytz et al., 2009). This pathway involves the increase of cellular cyclic adenosine monophosphate (cAMP), a secondary messenger molecule that has been shown to be involved in sensitization of trigeminal neurons in rat and guinea pig models (Ingram and Williams, 1996).

PACAP-38 has also been shown to reliably induce MLA in migraine patients and headaches in healthy subjects (Amin et al., 2014; Vecsei et al., 2014; Schytz et al., 2009). For migraineurs the median onset of a MLA is within 4 hours with some patients experiencing a MLA as late as 12 hours following PACAP-38 infusion. Possible mechanisms of PACAP-38-induced migraines may include prolonged dilatation of cranial arteries, increases in the diameter of the superficial temporal arteries, and decreases in mean blood flow velocity of the middle cerebral arteries (Amin et al., 2014; Schytz et al., 2009). Other mechanisms proposed for the role PACAP-38 plays in MLA are mast cell degranulation, leading to stimulation of sensory trigeminal fibers, and activation of pain receptors by central second order trigeminal neurons (Schytz et al., 2009).

As PACAP-38 is involved in various biological processes, including sensory processing, vasodilation, inflammation, and nociceptive transmission (Dickinson et al., 1999; Vaudry et al., 2000), nearly all of the healthy subjects and migraineurs also experienced

the expected adverse events of flushing and heat sensation, along with a transient elevation in heart rate and blood pressure (Birk et al, Regulatory Peptides 2007; Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014) (see Investigator Brochure for details).

IV PACAP-38 Toxicology

Since PACAP-38 is to be used in the clinic only as a pharmacodynamic (PD) biomarker and has been tested in several clinical studies, the nonclinical safety program was evaluated in a single rodent species. An exploratory cardiovascular safety pharmacology telemetry study and a Good Laboratory Practice (GLP) extended, single-dose toxicity study were conducted with an intravenous (IV) administration of 0, 5, 50, or 500 μg/kg PACAP-38. In the rat telemetry study, increased heart rate and decreased blood pressure and body temperature were considered to be mediated by PACAP-38 because of the dose- and time-dependency and were an expected pharmacologic response. In the single-dose GLP toxicology study, acute myocardial necrosis was observed at the mid and high dose, which is an anticipated pharmacologic effect of potent vasodilators in nonclinical species (Greaves, 2012) and believed not relevant to humans at the proposed clinical doses. The no-observed adverse effect level (NOAEL) was determined to be the low dose of 5 μg/kg, which is approximately 10 times higher than the proposed clinical dose of PACAP-38. Refer to Table 6. In conclusion, there were no significant toxicology findings in the rat that would indicate a risk to human subjects administered PACAP-38 IV at doses up to a total dose of 115 pmol/kg.

Table 1. Safety Margins for PACAP-38 Based on the GLP Rat Toxicology Study (121072)

Clinical Dose (pmol/kg)ǂ	Safety margin* (based on NOAEL of 5 μg/kg)	Safety margin^ (based on high dose of 500 μg/kg)
25	45.5x	4550x
50	22.7x	2270x
100	11.4x	1140x
115	10.0x	1000x

* based on NOAEL in GLP rat toxicology study (#121072) of 5 μg/kg
^ based on highest dose tested in GLP rat toxicology study of 500 μg/kg (NOAEL driven by a rat-specific finding)
ǂ PACAP-38 MW=4354 g/mol

IV PACAP-38 Safety and Tolerability

To date, 7 subjects in Cohorts 1 to 3 have received PACAP-38 in doses up to 75 pmol/kg: 2 subjects received an infusion of 10 pmol/kg/min of PACAP-38 over 2.5 minutes (total dose 25 pmol/kg), 3 subjects received an infusion of 10 pmol/kg/min of PACAP-38 over 5 minutes (total dose 50 pmol/kg) and 2 subjects received an infusion of 10 pmol/kg/min of PACAP-38 over 7.5 minutes (total dose 75 pmol/kg). Treatment emergent adverse events (TEAE) were reported for 7 of the 7 healthy subjects (100%) who received PACAP-38 at all doses. The most frequently reported adverse events were flushing (100%), headache (71.4%), palpitations (57.1%), head discomfort (42.9%), migraine (42.9%) and feeling hot (42.9%). All other events were reported in $\leq$ 2 subjects. All but one adverse events were mild or moderate (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2) in severity. One CTCAE grade 3 adverse event of migraine (verbatim: migraine like attack) was reported in one subject. Transient effects on blood pressure and heart rate were noted in subjects. Overall, the safety profile has been consistent with the anticipated pharmacological effects of PACAP-38.

The goal of Part A is to safely trigger general headaches in all subjects in any given cohort, as well as to safely trigger moderate to severe MLAs in the majority of subjects in any given cohort. In Cohort 1 (25 pmol/kg), both subjects experienced a mild headache. In Cohort 2 (50 pmol/kg), 1 subject experienced a mild headache, and 2 subjects experienced a moderate MLA. In Cohort 3 (75 pmol/kg), one subject experienced a moderate MLA, and the other subject did not experience either a headache or MLA, though they did report “a heavy feeling on the forehead”.

Therefore, the safety and tolerability to date support the decision to proceed with dosing the next cohort 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg) and the optional cohort of 10 pmol/kg/min over 11.5 minutes (total dose 115 pmol/kg).

IV- PACAP-38 Risk Assessment

The risk mitigation strategies include an infusion of PACAP-38 during which the subjects will be closely monitored and remain in-house for 24 hours after the infusion. All subjects participating in the clinical study will be monitored for any clinically significant events with ECGs, labs, vital signs and physical examinations conducted at screening, baseline, and at clinically appropriate timepoints throughout the study. In addition, Safety Review Meetings or DLRMs are scheduled to occur prior to any increase in

PACAP-38 dosing. Lastly, the highest dosing cohort is 115 pmol/kg, which provides an approximate 10X safety margins based on the NOAEL in the rodent study. Refer to Table 6.

2.5 Rationale

The primary purpose of this study is to further our understanding of migraine trigger pathology using an established experimental medicine model of migraine. The two major challenge agents which have been used in experimental medicine migraine models are CGRP and PACAP-38 both of which reliably elicit migraines. The main objective of this study is to test the hypothesis of whether these pathways are independent of one another or if CGRP is downstream of PACAP-38. If PACAP-38 causes MLA due to release of CGRP one might expect that AMG 334 would inhibit these attacks. This is relevant for the treatment of migraine as there are currently several anti CGRP medications under development and if these are efficacious in inhibiting an additional pathway it may expand their therapeutic effect.

2.6 Clinical Hypotheses

A single dose of 140 mg IV of AMG 334 will inhibit migraine-like attacks in subjects challenged with PACAP-38.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study in subjects with episodic migraines. This study will evaluate the efficacy of AMG 334 as measured by inhibition of PACAP-38 induced migraine-like attacks after a single dose of AMG 334. Migraine-like attacks (MLA) will be defined as attacks fulfilling one of the two criteria:

(1) Headache fulfilling criteria C and D for migraine without aura (IHS 2004)

C. Headache has at least two of the following characteristics:
- unilateral location
- pulsating quality
- moderate or severe pain intensity (≥ 4 on headache questionnaire)
- aggravation by or causing avoidance of routine physical activity

D. During headache at least one of the following:
- nausea and/or vomiting
- photophobia and phonophobia

(2) Headache described as mimicking usual migraine attack treated with triptan.

Part A: PACAP-38 Dose Selection Phase: There are a number of published clinical studies in which pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) was used to trigger MLA in migraneurs (Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014). In those studies, 10 pmol/kg/min over 20 minutes (total dose 200 pmol/kg) was administered. Approximately 90% of migraineurs experienced a headache and approximately 66% of the same migraineurs experienced MLA with a median time of headache onset of 4 hours, though the half-life of PACAP-38 is only 3.5 minutes. As PACAP-38 is involved in various biological processes, including sensory processing, vasodilation, inflammation, and nociceptive transmission (Dickinson et al., 1999; Vaudry et al., 2000), nearly all healthy subjects and migraineurs also experienced the expected adverse events of flushing and heat sensation, along with a transient elevation in heart rate and blood pressure (Birk et al, Regulatory Peptides 2007; Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014) (see Investigator Brochure for details).

Based on the low assay values observed during Amgen's testing of the PACAP-38 formulation used in the aforementioned published clinical studies, it was concluded that adhesion of the polypeptide to the product container surfaces probably occurred. Although the data were variable, it is estimated that on average, approximately 50% of the peptide may have been lost to surface binding. Amgen formulation modifications using albumin and acetic acid have eliminated this problem.

Therefore, in order to ensure subject safety and select the lowest PACAP-38 dose that will ideally trigger headache in all subjects within a given cohort and moderate to severe MLAs in the majority of the subjects within the same cohort, a dose selection strategy, along with Safety Review Meetings and Dose-Level Review Meetings (DLRM) have been implemented. Dosing of PACAP-38 shall not exceed a total dose of 115 pmol/kg, providing an approximate 10X exposure margin over the non-clinical NOAEL dose. However, the trigger of headaches in the majority of the subjects within a given cohort and mild, moderate or severe MLAs in the majority of the subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B).

Up to five cohorts consisting of approximately 2 to 5 subjects are planned. Based on emerging safety and tolerability data, as well as the number of subjects experiencing a headache and/or MLA, the voting members of the Safety Review Meetings or DLRM (the PI, Medical Monitor and Global Safety Officer), may decide cohorts should be removed

or additional cohorts should be added, with a maximum of 5 total cohorts. Subject numbers within each cohort may also be increased or decreased based on the decision from the Safety Review Meeting or DLRM. Doses to be administered within each cohort may be repeated, higher or lower than the last dosed cohort. Dosing of any subject shall not exceed 115 pmol/kg. Possible future PACAP-38 doses and associated cohorts beyond 100 pmol/kg (Cohort 4) are as follows: 115 pmol/kg (Cohort 5).

On Day 1, approximately 2 subjects in Cohort 1 will receive an infusion of 10 pmol/kg/min over 2.5 minutes (total dose 25 pmol/kg). The PI will be responsible to review heart rate (HR) and blood pressure (BP). The BP assessment is based on a single measurement of systolic blood pressure (SBP) of >150 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg. If the mean heart rate increase of the subjects in Cohort 1 is greater than 50% over baseline during a 2 hour period after dosing and SBP does not increase to >150 mm Hg or DBP to >100 mm Hg, then approximately 3 subjects in Cohort 2 will receive an infusion of 10 pmol/kg/min over 5 minutes (total dose 50 pmol/kg). Written documentation from Amgen of the decision to proceed with enrollment in Cohort 2 is required. After dosing Cohort 2 and any subsequent cohort, the PI will again be responsible to review HR and BP using previously outlined criteria. These same criteria shall also be assessed for Cohort 3.

After dosing Cohort 3, up to 5 subjects in Cohort 4 will receive 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg). Following Cohort 4, a Dose-Level-Review Meeting (DLRM) will occur to decide the dose of PACAP-38 to be used in the randomized portion of the study (Part B). This decision will be primarily based on safety and tolerability data, and number of subjects experiencing a headache and/or MLA in Cohort 4, although all of the available data for Cohorts 1 to 4 will be reviewed. The dose- selection for Part B will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B). If this goal is not achieved, following the DLRM review of the Cohort 4 data, then Cohort 5 dosing of 10pmol/kg/ min over 11.5 minutes (total dose 115 pmol/kg) can commence.

Cohorts 2, 3 and 4 enrollment will occur after a Safety Review Meeting between the principal investigator (PI), medical monitor (MM), and global safety officer (GSO) or

designee. At that time, available vital signs and adverse events occurring at least 24 hours following PACAP-38 dosing will be reviewed.

If the PI, MM, and GSO or designee decide not to proceed with enrollment into a subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort. Refer to Section 10.4.2 for additional information on the Safety Review Meetings and DLRMs. The Safety Review Meeting or DLRM voting members will decide whether or not to proceed with enrollment in Part B Randomization (AMG 334 or Placebo) Phase and if the decision is made to proceed, the Safety Review or DLRM voting members will select the appropriate PACAP-38 dose. The decision to proceed with Part B of the study will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study.

Part B: Randomization (AMG 334 or Placebo) Phase: A minimum of 16 and a maximum of 36 subjects will be randomized between two treatment groups (AMG 334 or placebo). On Day 1, treatment groups will receive 140 mg IV AMG 334 over 30 minutes or matching placebo, in a one to one allocation ratio. On Day 8, the subjects will be administered the dose of PACAP-38 determined during PACAP-38 Dose Selection. All subjects will remain in-house for 24 hours of observation following PACAP-38 infusion.

Subjects will be monitored and asked questions from the headache questionnaire (Appendix D), as per the Schedule of Assessment in Table 2, to determine if they have experienced a MLA. Previous challenge studies have shown that for migraineurs the median onset of a MLA is within 4 hours with some patients experiencing a MLA as late as 12 hours following PACAP-38 infusion. Therefore a headache questionnaire covering the 24 hours after infusion will ensure capture of all the PACAP-38 induced MLAs. After 24 hours of data from the first 16 Randomized (AMG 334 or Placebo) Subjects challenged with PACAP-38 is available, an interim analysis will be conducted to determine if challenge rates are comparable to historical rates (~66%) and if AMG 334 has greater efficacy than placebo. If AMG 334 is found to completely block PACAP-38 induced migraines, or have the same efficacy as placebo, the study will be terminated. Otherwise, approximately 20 Randomized (AMG 334 or Placebo) Subjects will be added.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately three sites globally will be utilized in this study. Additional sites may be added as necessary to complete enrollment.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

A total of up to 61 migraine subjects are planned to be enrolled into the study. Up to 25 subjects may participate in Part A and up to 36 in Part B of the study. If ambiguous results in Part A occur regarding the ability of PACAP-38 ideally safely trigger a headache in all subjects within a given cohort (although, safely triggering headaches in the majority of subjects within a given cohort may be considered acceptable to advance to Part B of the study) and moderate to severe MLAs in the majority of subjects within the same cohort, then a previously dosed cohort sample size may be expanded to up to 5 subjects per cohort. Once the PACAP-38 dose has been selected, 8 subjects will be randomized to placebo and 8 subjects will be randomized to AMG 334. The data collected for the 16 Randomized (AMG 334 or Placebo) Subjects will be included in the interim analysis (See Section 10.4.1). Following the interim analysis, if the decision is to continue enrollment for the study, an additional 10 subjects will be randomized to placebo, and another 10 subjects will be randomized to AMG 334.

The sample size justification is described in Section 10.2.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study prior to receiving PACAP-38 will be replaced, at the discretion of the Amgen Medical Monitor and Principal Investigator by notifying the unblinded study pharmacist or designee. The new subject will receive the identical treatment as the replaced subject but will be assigned a replacement number associated with this new record. The unblinded study pharmacist or designee will retain the randomization list.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

For Part A: Non Randomized (PACAP-38 Only) Dose Selection Subjects, the planned length of participation in the study for an individual subject is approximately 29 days,

which includes the initial screening phase up to 3 weeks, 1 day of challenge agent administration, and 7 day safety follow-up.

For Part B: Randomized (AMG 334 or Placebo) Subjects, the planned length of participation in the study for an individual subject is approximately 106 days, which includes the initial screening phase up to 3 weeks, 1 day of treatment, 6 days to allow drug distribution, 1 day of challenge agent administration, and 11-week safety follow-up.

3.5.2 End of Study

See Section 3.5.1 for study duration for individual subjects.

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, when the last subject completes the migraine questionnaire 24 hours after challenge agent administration or is discontinued from the study).

End of Trial: The time when the last subject is assessed or receives an intervention for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit 11 weeks after the challenge agent administration, or is discontinued from the study).

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

To be eligible for the study, subjects must provide written informed consent to participate and must fulfill the following criteria:

4.1.1 Subject has provided informed consent prior to initiation of any study-specific activities/procedures

4.1.2 Adults ≥ 18 to ≤ 45 years of age upon entry into screening

4.1.3 History of migraine headaches without aura for ≥ 6 months prior to screening according to the IHS Classification ICHD-II (Headache Classification Committee of the International Headache Society, 2004) based on medical records and/or patient self-report

4.1.4 Migraine frequency: ≥ 1 and ≤ 5 migraine days per month in each of the 3 months prior to screening

4.1.5 Body mass index between 18 and 35 kg/m^2, inclusive at screening

4.1.6 No history or evidence of clinically relevant medical disorders as determined by the investigator in consultation with the Amgen physician

4.1.7 Physical, neurological, clinical laboratory values and ECGs are clinically acceptable to the investigator and Amgen

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria are not eligible for the study:

4.2.1 History of migraine with aura, cluster headache or hemiplegic migraine headache according to the IHS Classification ICHD-II (Headache Classification Committee of the International Headache Society, 2004) based on medical records and/or patient self-report

4.2.2 Greater than or equal to 6 migraine days per month in the last 3 months prior to study enrollment and during screening period

4.2.3 Other headache disorders (except for episodic tension-type headache <5 days/month)

4.2.4 Recent nicotine or tobacco users (should have stopped approximately 6 months prior to screening)

4.2.5 History or evidence of clinically significant disorder (including psychiatric), condition or disease that, in the opinion of the Investigator or Amgen physician would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

4.2.6 Pregnant or breastfeeding, or is a female expecting to conceive during the study, including through 12 weeks after the last dose of investigational product

4.2.7 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with investigational product through 12 weeks after the last dose of investigational product. Acceptable methods of effective birth control include not having intercourse (true abstinence, when this is in line with the preferred and usual lifestyle of the subject), hormonal birth control methods (pills, shots/injections, implants, or patches), intrauterine devices, surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two barrier methods (each partner must use one barrier method) with spermicide - males must use a condom with spermicide; females must choose either a diaphragm with spermicide, OR cervical cap with spermicide, OR contraceptive sponge with spermicide. Female subjects not of childbearing potential are defined as any female who:

- Is post-menopausal by history, defined as:
  - Age ≥ 55 years with cessation of menses for 12 or more months, OR
  - Age < 55 years but no spontaneous menses for at least 2 years, OR

- Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

OR

- Underwent bilateral oophorectomy OR
- Underwent hysterectomy OR
- Underwent bilateral salpingectomy

4.2.8 A history of hypertension, hypotension, myocardial ischemia, angina, palpitations, flushing, tachydysrythmias (eg, atrial fibrillation), coronary artery bypass surgery, stroke, or transient ischemic attack, coronary artery disease with or without angina pectoris, percutaneous angioplasty procedure, any cerebrovascular events included but not limited to Cerebral Vascular Accident and Transient Ischemic Attack, Peripheral Vascular Disease

4.2.9 A baseline systolic BP ≥ 135 mmHg / diastolic BP ≥ 85 mmHg

4.2.10 A baseline ECG QTc ≥ 450 ms

4.2.11 A baseline heart rate >85 beats/min

4.2.12 Estimated glomerular filtration rate (eGFR) within the screening period of less than 60 mL/min/1.73m^2 as calculated using the estimated Modification of Diet in Renal Disease (MDRD) formula

4.2.13 Subjects with Hemoglobin A1C > 6% at screening

4.2.14 Positive for HIV antibodies, hepatitis B surface antigen, positive hepatitis core antibody, or hepatitis C antibodies at screening

4.2.15 A history of malignancy of any type, other than surgically excised non-melanomatous skin cancers or in situ cervical cancer within 5 years before the day of dosing

4.2.16 Has donated or lost 500 mL or more of blood or plasma within 8 weeks of Day 1 or has a history of chronic anemia

4.2.17 Subject previously has entered this study or has been previously exposed to AMG 334 or PACAP-38

4.2.18 History of hypersensitivity or allergic reaction to PACAP-38, CGRP receptor antagonist and any components to be administered during the study

4.2.19 Receiving or has received any investigational drug (or is currently using an investigational drug or device) within 30 days or 5 half-lives (whichever is longer), prior to receiving the first dose of AMG 334

4.2.20 Treatment with any biologic agent (such as monoclonal antibodies) within 3 months or 5 half-lives (whichever is greater) prior to dosing or have received a vaccination within 1 month prior to dosing

4.2.21 Use of any over-the-counter or prescription medications (specifically including, but not limited to triptans, ergotamine & topiramate) within the 14 days or 5 half-lives (whichever is longer), prior to receiving the first dose of AMG 334. Paracetamol (up to 2 g per day) for analgesia and hormone replacement therapy (eg, estrogen, thyroid) will be allowed. Simple analgesics including NSAIDs will be allowed, but not within 48 hours prior infusion of PACAP38. Any preventive medication is contra-indicated

4.2.22 Any herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within 21 days prior to receiving the first dose of AMG 334, and continuing use if applicable, will be reviewed by the PI and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement are required for subject participation

4.2.23 Prior or current history of psychiatric illness, such as anxiety, depression, or schizophrenia

4.2.24 History of suicidal behavior and/or ongoing suicidal ideation as assessed using the Columbia Suicide Severity Rating Scale (C-SSRS)

4.2.25 Known substance abuse (eg, alcohol, illicit or illegal drugs) within 1 year of dosing

4.2.26 Positive test for drug, cotinine or alcohol use at screening

4.2.27 Inability or unwillingness to refrain from alcohol consumption 24 hours prior to study visits

4.2.28 Subject unwilling to refrain from strenuous exercise during screening, in-clinic visits, and the outpatient visits

4.2.29 Subject will not be available for protocol-required study visits or procedures, to the best of the subject and investigator's knowledge

4.2.30 Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures

4.2.31 Troponin I or Troponin T at screening > upper limit of normal (ULN)

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the IRB/IEC approved informed consent form before commencement of study-specific procedures. Adverse Events are to be collected for a subject once they are enrolled in the study.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment eCRF page.

Provided all eligibility criteria have been met, all eligible subjects will be enrolled on Day 1. Following Part A: PACAP-38 Dose Selection Phase, a minimum of 16 and a maximum of 36 Randomized (AMG 334 or Placebo) Subjects in Part B will be randomized on Day 1 (day of investigational product administration) to receive either AMG 334 or matching placebo in a one to one allocation ratio.

Each subject who enters into the screening period for the study (Day -21 to Day -1) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Screen failed subjects may be rescreened at the discretion of the PI with agreement from the MM.

PPD

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Randomization/Treatment Assignment

Section 5.1 does not apply to Part A: Non Randomized (PACAP-38 Only) Dose Selection Subjects.

For Randomized (AMG 334 or Placebo) Subjects in Part B, randomization to AMG 334 or matching placebo will be based on a randomization schedule prepared by Amgen before the start of the study. Eligible subjects must be randomized on Day 1 during which time they will be receiving a unique randomization number and assigned to receive either AMG 334 or matching placebo. Once eligibility for study participation has been confirmed (based on data collected during screening visit and on Day -1), a randomization number will be assigned in sequential order in which eligibility was met. At no time will the same randomization number be assigned to more than one subject.

In the event a subject is randomized, but withdraws before receiving study medication, or during the study for reasons other than adverse events (Section 9.1), a replacement subject may be enrolled at the discretion of the Amgen Medical Monitor and Principal Investigator by notifying the unblinded study pharmacist or designee. The new subject will receive the identical treatment as the replaced subject but will be assigned a replacement number associated with this new record. The unblinded study pharmacist or designee will retain the randomization list.

The randomization date is to be documented in the subject's medical record and on the enrollment eCRF.

5.2 Site Personnel Access to Individual Treatment Assignments

Treatment assignments will be unblinded after database lock. After initial database lock and receipt of written authorization from Amgen to unblind, the unblinded pharmacist or designee will release the specified unblinded pharmacy records to site staff designated to enter the subject treatment into each subject's Unblinded Investigational Product Administration Electronic Case Report Form (eCRF).

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of subjects currently enrolled. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product and/or placebo (except if required by local regulation) used in this study include AMG 334 and matching placebo.

The Non-Amgen Non-investigational product used in this study include: PACAP-38.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of AMG 334, placebo, and PACAP-38.

6.2 Investigational Product

All investigational products will be administered at the research facility by a qualified staff member. A physician must be present at the time of Investigational Product administration.

6.2.1 Amgen Investigational Product AMG 334

AMG 334 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Active AMG 334 will be packaged in open label 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted] % (w/v) polysorbate [redacted] at pH [redacted]. Placebo will be presented in identical containers and stored/packaged the same as AMG 334, but will not contain AMG 334 protein.

All AMG 334 and matching placebo supplies will be shipped to the study site frozen and should be stored at [redacted] °C to [redacted] C in a non frost-free freezer until ready to use.

For more information regarding investigational product handling and preparation please see the study specific IPIM which is provided as a separate document.

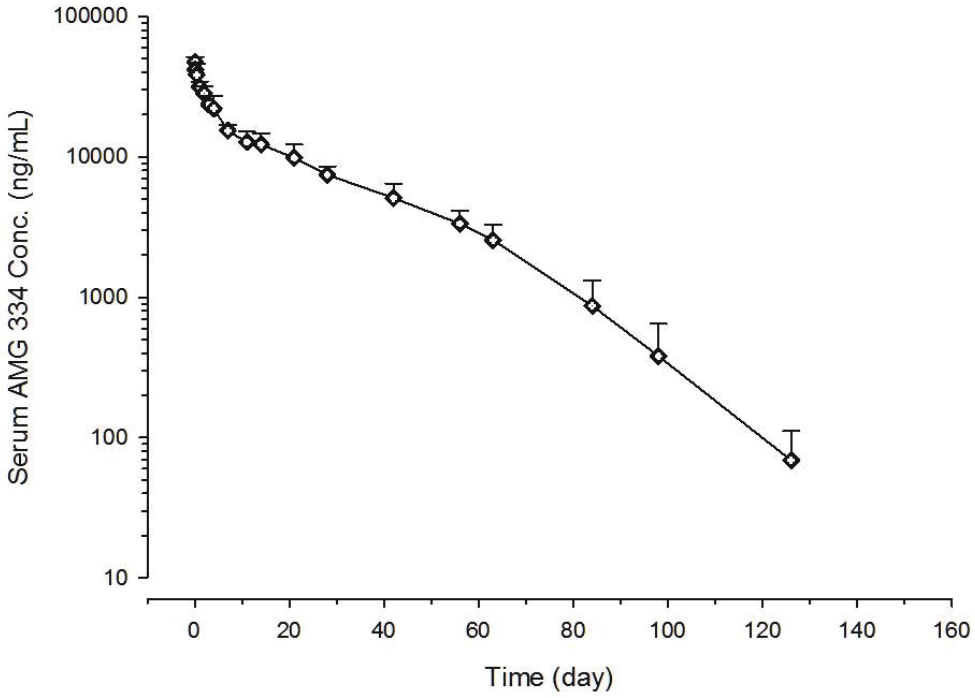
6.2.1.1 Dosage, Administration, and Schedule for AMG 334

Single doses of AMG 334 up to 210 mg SC or 140 mg IV were found to be generally well tolerated in both healthy subjects and migraine subjects (FIH Study 20101267). While the AMG 334 exposure and its migraine prevention efficacy relationship is to be established, a high dose of AMG 334 (140 mg intravenous, IV) is selected for this study in order to provide maximum CGRP receptor blockade against the PACAP-38 challenge.

After a single IV administration of AMG 334 at 140 mg, the distribution phase of serum AMG 334 was approximately completed by Day 8 (20101267, Figure 1). The mean serum AMG 334 concentration on Day 8 was 15.4 µg/mL, which is similar to the C_{avg} (15.9 ug/mL) of AMG 334 after the third 140 mg SC monthly dose administration. Monthly SC 140 mg administration is one of the higher dose regimens currently being evaluated in Phase 2 migraine clinical trials. Based on this information, Day 8 is considered as an appropriate time point to provide similar target coverage as in AMG 334 Phase 2 migraine clinical trials coverage and thus is selected for PACAP-38 challenge.

IV route is being chosen over subcutaneous (SC) as it is the faster route to achieve the target concentration after AMG 334 administration.

Figure 1. Mean (+SD) Serum AMG 334 Concentration-time Profiles After Intravenous Administration of AMG 334 at 140 mg



A single dose of 140 mg of AMG 334 or matching placebo will be administered intravenously on Day 1. The quantity, volume, start date/time, stop date/time, and blinded investigational product concentration will be recorded on the individual subject's Blinded Investigator Product Administration eCRF prior to initial database lock. Following initial database lock, upon written authorization from Amgen, the package lot number and unblinded dose of the investigational product will be recorded on each subject's Investigational Product Administration eCRF.

The effects of overdose of AMG 334 are not known. Overdose with this product has not been reported. All overdose occurrences must be documented and corresponding adverse events must be recorded on the appropriate eCRF and in the source documents.

The dosing schedule is described by a schema in the protocol synopsis.

6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation for AMG 334

Further dosing of AMG 334 will be stopped or modified to a lower dose if suspected adverse drug reactions and/or changes in safety data (including but not limited to vital signs, ECG, or clinical laboratory results) are observed and these changes pose a health risk.

Clinically or medically significant suspected adverse drug reactions, and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable. The study may be terminated at any point in time at the discretion of the sponsor.

The dosing schedule is described by a schema in the protocol synopsis.

6.3 Non-Amgen Non-Investigational Product

6.3.1 Non-Amgen Non-Investigational Product PACAP-38

Non Amgen non-investigational product PACAP-38 will also be used in this study.

All non-Amgen non-investigational products will be administered at the research facility by a qualified staff member. A study physician must be present at the time of product administration.

Additional details regarding the products are provided in the IPIM.

6.3.1.1 Dosage, Administration, and Schedule for PACAP-38

GMP PACAP-38 will be used in this study. For additional information, please refer to the IPIM.

0.1% HSA in 0.9% saline will be used for the dosing vehicle. The quantity, volume, concentration, start date/time and stop date/time, will be recorded on the individual subject Investigational Product Administration eCRF.

Randomized (AMG 334 or Placebo) Subjects will receive a single dose of a challenge-agent (PACAP-38 up to 115 pmol/kg; 521 ng/kg) by IV administration on Day 8. For Non Randomized (PACAP-38 Only) Dose Selection Subjects, Cohort 1 will receive PACAP-38 infusion of 10 pmol/kg/min over 2.5 minutes, Cohort 2 will receive PACAP-38 infusion of 10 pmol/kg/min over 5 minutes. Cohort 3 will receive PACAP-38 infusion of 10 pmol/kg/min over 7.5 minutes, and Cohort 4 will receive PACAP-38 infusion of 10 pmol/kg/min over 10 minutes. Optional Cohort 5 may receive PACAP-38 infusion of up to 10 pmol/kg/min over 11.5 minutes. Refer to Section 3.1 for the Study Design. Subjects should remain supine for approximately one hour after administration of PACAP-38.

Additional details regarding the products are provided in the IPIM.

6.3.1.2 Dose-cohort Study Escalation and Stopping Rules for PACAP-38

In order to ensure subject safety and select the lowest PACAP-38 dose that will ideally trigger headache in all subjects within a given cohort and moderate to severe MLAs in

the majority of the subjects within the same cohort, a dose selection strategy, along with Safety Review Meetings and Dose-Level Review Meetings (DLRM) have been implemented. Dosing of PACAP-38 shall not exceed a total dose of 115 pmol/kg, providing an approximate 10X exposure margin over the non-clinical NOAEL dose. However, the trigger of headaches in the majority of the subjects within a given cohort and mild, moderate or severe MLAs in the majority of the subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B).

Up to five cohorts consisting of approximately 2 to 5 subjects are planned. Based on emerging safety and tolerability data, as well as the number of subjects experiencing a headache and/or MLA, the voting members of the Safety Review Meetings or DLRM (the PI, Medical Monitor and Global Safety Officer), may decide cohorts should be removed or additional cohorts should be added, with a maximum of 5 total cohorts. Subject numbers within each cohort may also be increased or decreased based on the decision from the Safety Review Meeting or DLRM. Doses to be administered within each cohort may be repeated, higher or lower than the last dosed cohort. Dosing of any subject shall not exceed 115 pmol/kg. Possible future PACAP-38 doses and associated cohorts beyond 100 pmol/kg (Cohort 4) are as follows: 115 pmol/kg (Cohort 5).

On Day 1, approximately 2 subjects in Cohort 1 will receive an infusion of 10 pmol/kg/min over 2.5 minutes (total dose 25 pmol/kg). The PI will be responsible to review heart rate (HR) and blood pressure (BP). The BP assessment is based on a single measurement of systolic blood pressure (SBP) of >150 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg. If the mean heart rate increase of the subjects in Cohort 1 is greater than 50% over baseline during a 2 hour period after dosing and SBP does not increase to >150 mm Hg or DBP to >100 mm Hg, then approximately 3 subjects in Cohort 2 will receive an infusion of 10 pmol/kg/min over 5 minutes (total dose 50 pmol/kg). Written documentation from Amgen of the decision to proceed with enrollment in Cohort 2 is required. After dosing Cohort 2 and any subsequent cohort, the PI will again be responsible to review HR and BP using previously outlined criteria. These same criteria shall also be assessed for Cohort 3.

After dosing Cohort 3, up to 5 subjects in Cohort 4 will receive 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg). Following Cohort 4, a Dose-Level-Review Meeting (DLRM) will occur to decide the dose of PACAP-38 to be used in the randomized portion of the study (Part B). This decision will be primarily based on safety and tolerability data,

and number of subjects experiencing a headache and/or MLA in Cohort 4, although all of the available data for Cohorts 1 to 4 will be reviewed. The dose- selection for Part B will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to the randomized portion of the study (Part B). If this goal is not achieved, following the DLRM review of the Cohort 4 data, then Cohort 5 dosing of 10pmol/kg/ min over 11.5 minutes (total dose 115 pmol/kg) can commence.

Cohorts 2, 3 and 4 enrollment will occur after a Safety Review Meeting between the principal investigator (PI), medical monitor (MM), and global safety officer (GSO) or designee. At that time, available vital signs and adverse events occurring at least 24 hours following PACAP-38 dosing will be reviewed.

If the PI, MM, and GSO or designee decide not to proceed with enrollment into a subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort. Refer to Section 10.4.2 for additional information on the Safety Review Meetings and DLRMs. The Safety Review Meeting or DLRM voting members will decide whether or not to proceed with enrollment in Part B Randomization (AMG 334 or Placebo) Phase and if the decision is made to proceed, the Safety Review or DLRM voting members will select the appropriate PACAP-38 dose. The decision to proceed with Part B of the study will be based on the goal of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and mild, moderate or severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study.

All available study data, including the headache questionnaires, demographics, investigational product administration, medical history, concomitant medications, adverse events (including MLA), ECGs, vital signs, and laboratory results will be reviewed. Data to be reviewed at the DLRMs during the PACAP-38 Dose Selection Phase will not be blinded. Data to be reviewed for any unscheduled DLRM post the PACAP-38 Dose Selection Phase will be reviewed blinded (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make

dosing decisions. If deemed necessary, unblinding will be performed to assist dose decisions in accordance with Amgen standard procedures.

6.3.1.3 PACAP-38 - Dosage Adjustments, Delays, Rules for Withholding, or Restarting Stopping or Permanent Discontinuation

Dosing of PACAP-38 will be stopped or modified by the DLRM voting members if suspected unexpected treatment related adverse events of Grade 2 or greater in the same system organ class occur in 2 or more subjects or Grade 3 occur in 1 or more subject. Dosing of PACAP-38 will also be stopped or modified by the DLRM voting members under the following circumstances:

a) Blood pressure:

   a. Systolic BP > 150 mm Hg OR
   b. Diastolic BP > 100 mm Hg OR
   c. Decrease in SBP from baseline > 30 mm Hg OR
   d. Decrease in DBP from baseline > 15 mm Hg and considered clinically relevant after consultation between the investigator and the medical monitor.

   Any changes in blood pressure as defined above must be confirmed with 3 consecutive measurements taken approximately 5 minutes apart and with the subject remaining in a semi-recumbent position. The mean of the 3 measurements will be the final recorded value.

b) Mean heart rate increase of subjects in a given cohort is greater than 50% or greater than 20% decrease over baseline during a 2 hour period after dosing
c) Changes in other vital signs or clinical laboratory results considered to pose a significant health risk to subjects

In addition, any clinically or medically significant suspected adverse drug reactions and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

The study may be terminated at any point in time at the discretion of the sponsor.

6.4 Criteria for Additional Safety Assessment Due to Potential Hepatotoxicity

Following the single-dose administration of study drug, the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment

Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2x upper limit of normal (ULN) or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT Value	AST or ALT Elevation
< ULN	≥ 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBL values include, but are not limited to:
    - Hepatobiliary tract disease
    - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
    - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
    - Exposure to hepatotoxic agents/drugs or hepatotoxins including herbal and dietary supplements, plants, and mushrooms
    - Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
    - Alpha-one antitrypsin deficiency
    - Alcoholic hepatitis
    - Autoimmune hepatitis
    - Wilson's disease and hemochromatosis
    - Nonalcoholic fatty liver disease including steatohepatitis
    - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9. Concomitant therapies are to be collected from informed consent through the EOS. Details (name, indication and dates) of all concomitant medications will be recorded in the subject's source documents and on the eCRF.

6.6 Alcohol and Tobacco Restrictions

A urine screen for drugs of abuse (cannabis, cocaine, amphetamines, benzodiazepines, opiates, barbiturates) and urine (or breath) ethanol screens will be performed at the time points referenced in the schedule of assessments.

Subjects are not permitted to consume any alcohol within 24 hours of study enrollment. During the study, the use of alcohol by adults will be limited to no more than 1 drink per day (one drink being equivalent to 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80 proof distilled spirits). Subjects must refrain from alcohol consumption for the 24-hour period prior to study visits.

The use of nicotine or tobacco containing products (including but not limited to: snuff, chewing tobacco, cigars, cigarettes, pipes, or nicotine patches) will not be permitted throughout the study. A recent nicotine or tobacco user (should have stopped approximately 6 months prior to screening) must be excluded.

6.7 Other Treatment Procedures

6.7.1 Caffeine Restrictions

Throughout the study (beginning at screening), subjects will continue their usual caffeine intake, but not to exceed 2 cups per day (or the equivalent total daily intake of less than 200 mg caffeine per day).

6.7.2 Exercise Restrictions

Subjects are required to refrain from strenuous exercise beginning at screening until the end of study.

6.7.3 Oral Hydration

Subjects are required to receive oral hydration (~500 mL of water) within 1 hour prior to the start of PACAP-38 infusion.

6.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug provisioned and/or repackaged /modified by Amgen. Drug includes investigational product.

Any product complaint associated with an investigational product (AMG 334) or non-investigational product (PACAP-38) supplied by Amgen or designee are to be reported according to the instructions provided in the IPIM.

6.9 Excluded Treatments and/or Procedures During Study Period

Use of any over-the-counter or prescription medications within the 14 days or 5 half-lives (whichever is longer), prior to receiving the first dose of AMG 334 or PACAP-38. Simple

analgesics including NSAIDs will be allowed, but not within 48 hours prior to infusion of PACAP38. Subjects are not allowed to be on preventive therapies for migraine.

Paracetamol (up to 2 g per day) for analgesia and hormone replacement therapy (eg, estrogen, thyroid) will be allowed. Simple analgesics including NSAIDs will be allowed, but not within 48 hours prior infusion of PACAP-38. Subjects are allowed to take rescue medication for a migraine attack (their usual migraine treatment or a triptan) and for adverse events, such as emesis and allergic reactions (clemastin 2 mg, prednisolone 100 mg). Any herbal medicines (eg, St. John's wort), vitamins, and supplements consumed by the subject within 21 days prior to receiving the first dose of AMG 334, and continuing use if applicable, will be reviewed by the investigator and the Amgen Medical Monitor. Written documentation of this review and Amgen acknowledgement are required for subject participation. Refer to Section 6.5 for guidance on concomitant therapy.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 2. Schedule of Assessments For Part B: Randomized (AMG 334 or Placebo) Subjects

Activity	**Screening**		**Treatment Period**													**Follow-Up Period**				**EOS Visit**
Study Day	-21 to -2	-1	Day 1 [a]				Day 8 [b f g]									Day 9	Day 10	Day 29	Day 57	85
Time (in hours)			Pre-Dose	0	0.5	1	Pre-Dose	0	0.25	0.5	1	2	3	4	8	24	48			
General & Safety Assessments																				
Informed Consent	X																			
Residency							X [b]	X	X	X	X	X	X	X	X	X				
Medical History	X																			
Body Weight	X	X																		X
Height	X																			
Vital Signs (BP, HR, RR, TEMP) [g]	X	X	X		X	X	X [g]		X	X [g]	X	X [g]	X	X	X	X [g]	X	X	X	X
Physical Examination	X	X																X		X
Neurological Examination	X		X				X									X		X		X
12-lead Electrocardiogram [c]	X		X		X		X			X	X	X		X	X	X	X			X
Adverse Event Recording				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																				
Creatinine Clearance [i]	X	X					X									X				
Clinical Chemistry [l]	X	X					X									X				X
Clinical Hematology [l]	X	X					X									X				X
Urinalysis [l]	X	X					X									X				X
Drug, Alcohol & Cotinine Screen	X	X [j]					X [h j]													
HIV, HepCAb, HBsAg, HBcAb	X																			
Postmenopausal status test, (females only) [k]	X																			
Cardiac Enzymes [l]	X	X					X					X		X	X	X				
Pregnancy Test (females only) [d]	X	X					X													X
Questionnaires																				
Headache Questionnaire		X						X	X	X	X	X	X	X	X	X				
Columbia-Suicide Severity Rating Scale	X	X	X				X									X		X	X	X

Footnotes are defined on the next page of table

Table 2. Schedule of Assessments For Part B: Randomized (AMG 334 or Placebo) Subjects

Activity	**Screening**		**Treatment Period**													**Follow-Up Period**				**EOS Visit**
Study Day	-21 to -2	-1	Day 1 [a]				Day 8 [b f g]									Day 9	Day 10	Day 29	Day 57	85
Time (in hours)			Pre-Dose	0	0.5	1	Pre-Dose	0	0.25	0.5	1	2	3	4	8	24	48			
Dosing																				
Study Drug Administration				X																
Challenge-agent (PACAP-38) [f]								X [f]												
Pharmacokinetic and Other Blood Samples																				
Antibody Sample Collection			X															X	X	X
AMG 334 Serum PK Collection [e]			X			X	X			X [e]								X	X	X
CGRP Plasma Collection			X				X		X	X										X
PACAP-38 Plasma Collection							X		X	X										
Cell Pellet for Pharmacogenetics			X																	

Abbreviations: ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; HBcAB = hepatitis B core antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic

[a.] Subjects will return to the research facility one day prior to investigational product administration (Day -1), at which time baseline procedures will be completed. After completion of all pre-dose and baseline laboratory and vital sign procedures on the day of dosing (Day 1), subjects will receive AMG 334 or matching placebo.
-Subjects will reside at the research facility for at least 1 hour and then be discharged home.

[b.] Subjects will return to the research facility on Day 8, at which time pre-dose procedures will be completed. After completion of pre-dose procedures on Day 8, subjects will receive PACAP-38. Subjects will reside at the research facility for at least 24 hours post PACAP-38 infusion and then be discharged home.

[c.] At Screening ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Single ECGs will be performed from Day 1 to EOS.

[d.] A serum pregnancy test will be performed at screening. Serum or highly sensitive urine (cutoff of 20 mIU/L) pregnancy tests will be performed at Day -1, Day 8 Pre-Dose and EOS.

[e.] Flexible PK sampling point, that could be collected at any time on Day 8 between pre-PACAP-38 to 2 hours post-PACAP-38 administration.

[f.] PACAP-38 should not be administered if subject reports having a headache within 72 hours prior to Day 8. Subject should return to the research facility from Day 8 – Day 12 for PACAP-38 administration.

[g.] Rectal temperature will be collected after obtaining blood pressure, prior to PACAP-38 infusion and post PACAP-38 infusion at Hours 0.5, 2 and 24.

[h.] Negative drug, alcohol and cotinine test is required prior to PACAP-38 dose. Positive results will be reviewed between the PI and MM on a case by case basis.

[i.] Laboratory results required prior to AMG 334 and PACAP-38 dose. Abnormal lab results will be reviewed between the PI and MM on a case by case basis prior to PACAP-38 dose.

[j.] A reliable urine drug test performed at the site is allowed.

[k.] Additional serum will be collected for an FSH, LH, or estradiol test for postmenopausal women at screening as defined in Section 7.2.22.

[l.] Cardiac enzymes include CPK-MB and Troponin I or Troponin T.

Table 3. Schedule of Assessments Part A: For Non Randomized (PACAP-38 Only) Dose Selection Subjects

Activity	Screening		Treatment Period									Follow-Up Period		EOS Visit
Study Day	-21 to -2	-1	Day 1 [c d]									Day 2	Day 3	Day 8
Time (in hours)			Pre-Dose	0	0.25	0.5	1	2	3	4	8	24	48	
General & Safety Assessments														
Informed Consent	X													
Residency			X	X	X	X	X	X	X	X	X	X		
Medical History	X													
Body Weight	X	X												X
Height	X													
Vital Signs (BP, HR, RR, TEMP) [d]	X	X	X [d]		X	X [d]	X	X [d]	X	X	X	X [d]	X	X
Physical Examination	X	X												X
Neurological Examination	X		X									X		X
12-lead Electrocardiogram [a]	X		X			X	X	X		X	X	X	X	X
Adverse Event Recording				X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
Creatinine Clearance	X	X										X		
Clinical Chemistry	X	X										X		X
Clinical Hematology	X	X										X		X
Urinalysis	X	X										X		X
Drug, Alcohol & Cotinine Screen	X	X [e]												
HIV, HepCAb, HBsAg, HbcAb	X													
Postmenopausal status test (females only) [f]	X													
Pregnancy Test (females only) [b]	X	X												X
Cardiac Enzymes [g]	X	X	X					X		X	X	X		
Questionnaires														
Headache Questionnaire		X		X	X	X	X	X	X	X	X	X		
Columbia-Suicide Severity Rating Scale	X	X	X									X		X
Dosing														
Challenge-agent (PACAP-38) [c]				X [c]										
Pharmacokinetic and Other Blood Samples														
CGRP Plasma Collection			X		X	X								X
PACAP-38 Plasma Collection			X		X	X								
Cell Pellet for Pharmacogenetics			X											

Footnotes are defined on the next page of table

Abbreviations: ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; HBcAB = hepatitis B core antibody; HIV = human immunodeficiency virus; PK = pharmacokinetic;

[a.] At Screening ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures.-Single ECGs will be performed from Day 1 to EOS.

[b.] A serum pregnancy test will be performed at screening. Serum or highly sensitive urine (cutoff of 20 mIU/L) pregnancy tests will be performed at Day -1 and EOS.

[c.] PACAP-38 should not be administered if subject reports having a headache within 72 hours prior Day 1. Subject should return to the research facility from Day 1 – Day 5 for PACAP-38 administration.

[d.] Rectal temperature will be collected after obtaining blood pressure, prior to PACAP-38 infusion and post PACAP-38 infusion at Hours 0.5, 2 and 24.

[e.] A reliable urine drug test performed at the site is allowed.

[f.] Additional serum will be collected for an FSH, LH or estradiol test for screening for postmenopausal women as defined in Section 7.2.22.

[g.] Cardiac enzymes include CPK-MB and Troponin I or Troponin T.

7.2 General Study Procedures

Any blood sample collected according to the Schedule of Assessments (Table 2 and Table 3) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

Throughout the study, the permitted time windows for scheduled assessments will be as follows:

- +4 day for Day 1 For Non Randomized (PACAP-38 Only) Dose Selection Subjects Only
- + 4 day for Day 8 for Randomized (AMG 334 or Placebo) Subjects
- ± 30 minutes for Headache Questionnaire
- ± 3 days for Days 29, Day 57 and EOS (Day 8 for Non Randomized (PACAP-38 Only) Dose Selection Subjects and Day 85 for Randomized (AMG 334 or Placebo) Subjects)

If informed consent is provided by the subject, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand neurological disorders, the dose response and/or prediction of response to AMG 334, characterize antibody response, and characterize aspects of the molecule. Results from this analysis will be documented and maintained, but may not be reported as part of this study.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.1 Informed Consent

Before any study-related screening or baseline procedure can be completed, a subject must sign and date the IRB/IEC-approved ICF. After informed consent has been obtained, all screening procedures and tests establishing eligibility will be performed. Screening procedures are summarized in the Schedule of Assessments (Table 2 and Table 3).

7.2.2 Screening and Day -1

After informed consent is obtained, all screening procedures will be performed between Day -21 and Day -1 at the time points designated in the Schedule of Assessments

(Table 2 and Table 3). Study eligibility must be met per inclusion/exclusion criteria prior to enrollment.

7.2.3 Subject Residency

7.2.3.1 Non Randomized (PACAP-38 Only) Dose Selection Subjects

After eligibility for enrollment is determined, subjects will be admitted to the research facility on study Day 1 and will receive PACAP-38 dose. Subject will remain in residency for 24 hours post PACAP-38 infusion. After discharge from residency, subjects will return to the research facility on Day 8 for an EOS visit (see Schedule of Assessments Table 3).

7.2.3.2 Randomized (AMG 334 or Placebo) Subjects

Subjects will be admitted to the research facility on study Day 8 and will receive PACAP-38 dose. Subject will remain in residency for 24 hours post PACAP-38 infusion. After discharge from residency, subjects will return to the research facility on an outpatient basis for scheduled study procedures, including blood draws for PK assessments, safety laboratory tests, and other assessments according to the Schedule of Assessments (Table 2).

7.2.4 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject. The treatment procedures are to be completed during the Treatment Visits at time points designated in the Schedule of Assessments (Section 7.1).

If any subject stops treatment (eg, due to an adverse event), the subject will be asked to continue to complete protocol-required visits for safety monitoring as determined by the Principal Investigator in consultation with the Amgen Medical Monitor and Amgen Global Safety Officer.

When multiple post dose procedures are required to be conducted at the same nominal time point, the following order of precedence will be used: (1) vital signs, (2) ECGs, (3) PK sample collection.

7.2.5 Safety Follow-up Visits/End of Study Visit/Early Termination

Subjects will return to the clinic for follow-up visits in accordance with the Schedule of Assessments (Section 7.1) and be followed through the completion of the EOS procedures. If an EOS test result demonstrates a clinically significant clinical or laboratory abnormality, the subject will be followed until resolution of the abnormality or

until it is considered clinically stable by the investigator. Subjects who terminate early will be asked to return to the research facility for the EOS assessments.

7.2.6 Medical History

The Investigator or designee will collect a complete medical history. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF.

7.2.7 Adverse Event

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF for the duration of the study. Determination of the severity of all adverse events will be consistent with CTCAE Version 4.0 unless specified otherwise.

7.2.8 Concomitant Medications

Concomitant medication(s) will be recorded throughout the study in the source documents and eCRF. Sites will collect therapy name, indication, dose, unit, frequency, route, and start and stop dates for all concomitant medications.

7.2.9 Physical Examination

A physical examination will be performed by the investigator or designated physician at time points specified in the Schedule of Assessments (Table 2 and Table 3).
Pre-Dose abnormal findings will be reported on the medical history eCRF. Abnormal findings found after the subject has received study medication will be reported on the Adverse Event eCRF.

7.2.10 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign eCRF. Record all measurements on the vital signs eCRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. Rectal temperature will be collected at the time points designated in Table 2 and Table 3. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be recorded by the principal investigator or designee at time points specified in the Schedule of Assessments (Table 2 and Table 3).

Blood pressure will be measured in the following manner:

- Subjects should be lying in a semi-recumbent position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- Three consecutive measurements separated by approximately 5 minutes must be taken to establish baseline (ie, pre-dose) systolic/diastolic blood pressure. The mean of the three measurements should be recorded.
- Any clinically significant decrease in blood pressure readings must be confirmed with three consecutive measurements taken approximately 5 minutes apart. The mean of the three measurements should be recorded.
- Caffeine and exercise should be avoided for at least 30 minutes prior to measurement.
- An appropriately sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least 2 measurements should be made and the average recorded.
- Neither the subject nor the observer (measurer) should talk during measurement.

Subjects should be lying in a semi-recumbent position quietly and comfortably for at least 5 minutes for respiration and heart rate assessments. Respiration will be assessed by a full minute count. Abnormal measurements may be repeated upon investigator discretion. Record all measurements on the vital signs eCRF.

7.2.11 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinical rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items. The Baseline/Screening version of the C-SSRS will be administered at screening (Day -21 to -2), while the Since Last Visit version of the C-SSRS will be administered at the other time points on the Schedule of Assessments (Table 2 and Table 3). Reports of suicidal ideation with intent to act (endorse item 4 or 5) and reports of actual, aborted, or interrupted suicide attempts or a behavior preparatory for making an attempt indicate subjects at high risk for suicide. If such reports are identified, the investigator is to appropriately manage the subject in accordance with standard of care.

An example of the C-SSRS is presented in Appendix E and Appendix F.

7.2.12 Headache Questionnaire

Subjects will be asked questions from the headache questionnaire as indicated in the Schedule of Assessments (Table 2 and Table 3) and site to record information, such as the date of headache, severity of pain, headache symptoms, and medications taken on the headache questionnaire and in the applicable Adverse Event or Concomitant Medication eCRF page. An example of the headache questionnaire can be found in

Appendix D. The headache questionnaire can be updated during the study at the discretion of the MM.

7.2.13 Height, Weight, and Body Mass Index

Height in centimeters will be measured without shoes at screening.

Weight in kilograms will be measured without shoes at time points specified in the Schedule of Assessments (Table 2 and Table 3).

Subject BMI will be calculated using height and weight measurements taken at screening according to the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)}/(\text{height [cm]}/100)^2$$

7.2.14 Neurological Examination

A neurological examination including assessment of cranial nerves, motor system, sensory system (including testing for pain sensation [pin prick], light touch sensation [brush], von Frey, and vibratory sense), reflexes, and cerebellar function will be performed by the principal investigator or qualified physician as indicated in the Schedule of Assessments (Table 2 and Table 3).

The individual performing the neurological examination will characterize their findings as either normal or abnormal. Any subjects with abnormal findings found during baseline will not be allowed to enroll in the study. Abnormal findings found after subject has received study medication will be reported on the adverse event eCRF.

7.2.15 Electrocardiograms

During the study, 12-lead electrocardiograms (henceforth referred to as electrocardiogram or ECG) will be performed at the time points indicated in the Schedules of Assessments (Table 2 and Table 3).

The subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

At Screening, ECGs will be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. From Day 1 to EOS visit, ECGs will be performed as a single electrocardiogram. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

The Principal Investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

7.2.16 Creatinine Clearance

For determining eligibility, estimated glomerular filtration rate (eGFR) will be calculated by the estimated **Modification of Diet in Renal Disease (MDRD) formula** based on serum creatinine, age, sex and race values at time points indicated in the Schedule of Assessments (Table 2 and Table 3).

7.2.17 Clinical Chemistry

Blood samples for clinical chemistry will be collected at time points specified in the Schedule of Assessments (Table 2 and Table 3). All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety.

The tests listed below will be conducted and analyzed by standard laboratory procedures:

Table 4. Clinical Chemistry

Albumin	Blood urea nitrogen (BUN) or Urea
Calcium	Chloride
Glucose	Phosphorus or Phosphate
Potassium	Creatinine
Magnesium	Sodium
Carbon Dioxide or Bicarbonate	Uric acid
Aspartate aminotransferase (AST / SGOT)	Alanine aminotransferase (ALT / SGPT)
Cholesterol	Total bilirubin (TBIL)
Alkaline phosphatase (ALP)	Direct bilirubin
Total protein	Triglycerides
High-density lipoprotein (HDL)	Creatinine Phosphokinase (CPK)
Cardiac enzymes (CPK-MB and Troponin I or Troponin T)	Hemoglobin A1C

7.2.18 Hematology

Blood samples for hematology tests will be collected at time points specified in the Schedule of Assessments (Table 2 and Table 3). All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety.

The tests listed below will be conducted and analyzed by standard laboratory procedures:

Table 5. Hematology

Red blood cells	White Blood Cell (WBC)
Hemoglobin	White blood cells differential count: • Total neutrophils (OR segmented neutrophils and band cells) • Eosinophils • Lymphocytes • Basophils • Monocytes
Hematocrit	
Mean corpuscular volume	
Mean corpuscular hemoglobin	
Platelet count	
Mean corpuscular hemoglobin concentration	

7.2.19 Urinalysis

Urine samples will be collected at time points specified in the Schedule of Assessments (Table 2 and Table 3).

All laboratory tests must be reviewed and signed by the principal investigator or qualified designee. Additional safety laboratory assessments may be performed for subject safety.

The tests listed below will be conducted and analyzed by standard laboratory procedures:

Table 6. Urinalysis

Specific gravity	pH
Blood	Protein
Glucose	Ketones
Bilirubin	Urobilinogen
Microscopic exam (performed at the discretion of the principal investigator or qualified designee):	
White blood cells	Red blood cells
Epithelial Cells	Bacteria
Casts	Crystals

7.2.20 Drug, Alcohol, and Cotinine Screen

Drug, alcohol, and cotinine assessments are to be completed at time points indicated in the Schedule of Assessments (Table 2 and Table 3). The drug and alcohol tests will include testing for drugs with a high potential for abuse, including amphetamines, barbiturates benzodiazepines, cocaine, ethanol, opiates, and tetrahydrocannabinol.

Subjects who test positive for drug, alcohol, and cotinine will not qualify for study product administration. Subjects with a positive drug test may be retested once at the discretion of the investigator.

7.2.21 Hepatitis B Surface Antigen, Hepatitis C Antibody and HIV Status

Hepatitis B surface antigen and core antibody, HepCAb, and HIV status will be assessed at time points indicated in the Schedule of Assessments (Table 2 and Table 3) and must be confirmed negative to be eligible for this study.

7.2.22 Menopausal Status Test

Additional tests to confirm postmenopausal status will be performed for any women age < 55 years and with spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy). Postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL), or according to the definition of "postmenopausal range" for the laboratory involved, must be consistent with postmenopausal status per local laboratory ranges to be eligible for this study. Postmenopausal status will be recorded on the medical history eCRF.

7.2.23 Pregnancy Test

A serum or highly sensitive urine pregnancy test will be collected at Day -1 and EOS as specified in the Schedule of Assessments (Table 2 and Table 3). The screening (serum) and Day -1 (serum or urine) pregnancy test must be confirmed negative to be eligible for this study.

7.2.24 Blood Sample Collection for AMG 334 Serum Concentrations

Blood samples will be collected for determination of AMG 334 serum concentrations at time points indicated in the Schedule of Assessments (Table 2). Sample collection, handling, and shipping procedures are specified in a separate manual.

7.2.25 Blood Sample Collection for CGRP Concentrations

Blood (plasma) samples will be collected for determination of CGRP concentrations at the time points indicated in the Schedule of Assessments (Table 2 and Table 3). Detailed instructions outlining the collection, processing and shipping of the CGRP samples are located in a separate manual.

7.2.26 Blood Sample Collection for PACAP-38 Concentrations

Blood samples for PACAP-38 plasma concentrations will be collected for all subjects at time points specified in the Schedule of Assessments (Table 2 and Table 3). Detailed

instructions on sample collection, processing, and shipping will be provided in a separate manual.

7.3 Antibody Testing Procedures

Blood samples for antibody testing will be collected at time points specified in the Schedule of Assessments (Table 2) for the measurement of anti-AMG 334 binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 334 antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to AMG 334. If results are not provided, no neutralizing antibodies to AMG 334 have been detected.

Subjects who test positive for neutralizing antibodies to AMG 334 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 334. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive AMG 334.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 334 antibody response may also be asked to return for additional follow-up testing. Refer to the Schedule of Assessments (Table 2), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.4 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 334.

Blood Samples

Blood samples are to be collected for biomarker development at the time points in the Schedule of Assessments (Table 2 and Table 3).

7.5 Pharmacogenetic Studies (Optional)

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of study indications (eg, migraines), neurological diseases, and/or AMG 334 immunogenicity, and/or in the identification of subjects who may have positive or negative response to AMG 334. For subjects who consent to this/these analysis/analyses, DNA may be extracted. Refer to the central laboratory manual for details regarding the collection, processing and shipping of the pharmacogenetic samples.

7.6 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2 and Table 3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand migraine pain, the dose response and/or prediction of response to AMG 334, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, protocol-specified criteria, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-Related Events

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected by the investigator for the subject's condition.

Disease-Related Events and/or Disease-Related Outcomes that do not qualify as Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease-Related Event.
- Death due to the disease under study is to be recorded on the Event CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than expected by the investigator's assessment. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

Migraines and non-migraine headaches are study endpoints.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease-Related Event as defined in Section 9.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A Disease-Related event is to be reported as a serious adverse event if,

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI) (see Appendix A for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Disease-Related Events

Migraine is considered a disease related event; however, worsening of migraine (ie, increased in severity, frequency, and/or duration more than expected by the investigator's assessment) should be reported as an AE.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the EOS are reported using the Adverse Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- Dates of onset and resolution (if resolved)
- Severity
- Assessment of relatedness to investigational product
- Action taken

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product, and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product, and/or other protocol-required therapies?

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device(s)), and/or procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable,

clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

MLA and non-migraine headaches should be recorded on the headache questionnaires and on the adverse event eCRF page.

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through EOS are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Adverse Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.2.2.4 Serious Adverse Events That are not to be Reported In an Expedited Manner

Migraine requiring hospitalization does not need to be reported in an expedited manner. AEs, SAEs, safety labs will be reviewed by the GSO, MM, and PI throughout the study and at the DRLM.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 12 weeks after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 12 weeks.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Occurrence of a migraine-like attack within 24 hours of challenge-agent infusion

10.1.1.2 Secondary Endpoints

- Occurrence of a headache within 24 hours of challenge-agent infusion
- Treatment-emergent adverse events
- Clinical significant changes in vital signs, ECGs, physical examinations, laboratory safety tests and neurological assessments
- AMG 334 PK parameters, including $C_{1\ hour}$ and AUC_{84d}
- Anti-AMG 334 antibodies

10.1.1.3 Exploratory Endpoints

- Severity of PACAP-38 induced migraine-like attacks and headaches
- Duration of PACAP-38 induced migraine-like attacks and headaches

- Migraine characteristics: localization, accompanying symptoms and pre-monitory symptoms.
- PACAP-38 related treatment-emergent adverse events
- Evaluate the concentration of PACAP-38 and CGRP following administration of AMG 334

10.1.2 Analysis Sets

10.1.2.1 Safety Analysis Set

The safety analysis set will consist of all subjects who receive investigational product and PACAP-38. Subjects will be analyzed according to the treatment received (AMG334 or Placebo).

10.1.2.2 Pharmacokinetic Concentration Analysis Set

The pharmacokinetic (PK) concentration analysis set will contain all subjects who received investigational product and have at least one PK sample collected.

10.1.3 Covariates and Subgroups

No subgroup analyses are planned.

10.2 Sample Size Considerations

A total of up to 61 migraine subjects are planned to be enrolled into the study. Up to 25 subjects may participate in Part A and up to 36 in Part B of the study. If ambiguous results in Part A occur regarding the ability of PACAP-38 ideally safely triggering a headache in all subjects within a given cohort (although, safely triggering headaches in the majority of subjects within a given cohort may be considered acceptable to advance to Part B of the study) and moderate to severe MLAs in the majority of subjects within the same cohort, then a previously dosed cohort sample size may be expanded to up to 5 subjects per cohort. Once the PACAP-38 dose has been selected, 8 subjects will be randomized to placebo and 8 subjects will be randomized to AMG 334. The data collected for the 16 Randomized (AMG 334 or Placebo) Subjects will be included in the interim analysis (See Section 10.4.1). Following the interim analysis, if the decision is to continue enrollment for the study, an additional 10 subjects will be randomized to placebo, and another 10 subjects will be randomized to AMG 334.

The sample size is based on practical considerations and is consistent with this type of study. If, PACAP-38 produces MLA in 70% of placebo treated subjects, and AMG 334 is effective in blocking MLA such that only 20% of AMG 334 treated subjects have a headache, then there is approximately a 91% chance of overall trial success (Section 10.4.1).

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2.2).

Unless otherwise specified in this section, subjects, site personnel, or Amgen staff and their designees will not have access to unblinding information until the study is formally unblinded. Unblinded individuals, as designated in this section, are to ensure unblinding information and potentially unblinding data are not distributed to blinded individuals until the study is formally unblinded.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of subjects currently enrolled. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen clinical study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's eCRF.

Individual subject treatment assignments will be unblinded to personnel from Pharmacokinetics and Drug Metabolism, Clinical Immunology, Biological Sample Management, and Molecular Sciences & Computational Biology departments associated with tracking, assaying, and analyzing the PK samples, biomarker development samples. Furthermore, individual subject treatment assignments will be unblinded to designated personnel from Biostatistics at 2 timepoints during the study: 1) the interim analysis (personnel from Biostatistics performing the interim analysis only), and 2) after formal unblinding (see below). Access to individual subject data will be limited to unblinded staff until the official unblinding occurs. Prior to unblinding, when knowledge of the treatment assignment is essential for the further management of the subject or potentially affects the safety of subjects, the randomization code may be broken.

10.4 Planned Analyses

10.4.1 Interim Analyses

Once 24 hours of data is collected from 16 Randomized (AMG 334 or Placebo) Subjects (8 per group) after PACAP-38 infusion on Day 8, an interim analysis will be performed to

determine if the challenge-agent, PACAP-38, invokes historical rates (~66%) of MLA and if AMG334 has greater efficacy than placebo. If AMG334 is found to block PACAP-38 induced migraines completely, or have the same efficacy as placebo, the study will be terminated. Otherwise, another 20 Randomized (AMG 334 or Placebo) Subjects will be added. Appropriate decision rules, outlined below were developed to determine whether to increase the sample size (up to 10 per treatment) or to stop, either due to demonstration of treatment effect or treatment utility.

Decision rules to be applied during the trial are:

1. At the interim analysis, if 3 or less of the 8 placebo subjects have a MLA, the study will be stopped and concluded that PACAP-38 does not induce a sufficient proportion of MLA for the study to test the hypothesis. (TRIAL FAIL (ASSAY)-EARLY)
2. At the interim analysis, if 4 or more placebo subjects have a MLA, yet more subjects receiving AMG 334 have them than placebo subjects, then the study will be stopped and concluded that AMG 334 is ineffective in blocking PACAP-38 induced MLA. (TRIAL FAIL--EARLY)
3. If the difference at the interim analysis in the proportion of subjects with MLA (placebo-AMG 334) is greater than or equal to 75% then the study will stop early and concluded that AMG 334 is effective in blocking PACAP-38 induced MLA. (TRIAL SUCCESS-EARLY)
4. If none of the first 3 decision rules apply at the interim analysis, an additional 20 subjects will be enrolled in the trial. At the end of trial, if the p-value from the one-sided Fishers Exact test is less than 0.1, it will be concluded that AMG 334 is effective in blocking MLA (TRIAL SUCCESS –LATE),, or if the p-value from the one-sided Fishers Exact test is greater than or equal to 0.1, it will be concluded that AMG 334 is ineffective at blocking MLA (TRIAL FAIL –LATE)

The results from 10,000 simulated trials demonstrating the probability of failing at the interim analysis, as well as the probability of overall trial result, for different potential scenarios of the proportion of subjects with MLA in each treatment group are shown below.

Probability of Fail at the Interim Analysis:

Placebo subjects with MLA

20%	35%	50%	70%		
95%	**72%**	36%	6%	20%	AMG 334 subjects with MLA
	73%	40%	8%	35%	
		50%	15%	50%	
			40%	70%	

Probability of Overall Trial Success:

Placebo subjects with MLA

20%	35%	50%	70%		
1%	14%	48%	91%	20%	AMG 334 subjects with MLA
	4%	23%	72%	35%	
		6%	38%	50%	
			5%	70%	

From the above, it can be seen that, if PACAP-38 does not induce a sufficient proportion of MLA for the study to test the hypothesis, or AMG 334 appears to be ineffective in blocking PACAP-38 induced MLA, the trial is more likely to fail at the interim analysis stage (highlighted in bold and underlined in the results with respect to the probability of fail at the interim analysis). However, should the study continue from the interim analysis stage, even by chance, the overall type I error is controlled such that the study is highly unlikely to conclude AMG 334 is effective in blocking PACAP-38 induced MLA (overall trial success) when it is not (highlighted in bold and underlined in the results with respect to the probability of overall trial success).

Designated personnel from Biostatistics will be unblinded for the interim analysis (see Section 10.3). After interim analysis, the designated unblinded Biostatistics personnel will recommend to the study team whether the sample size remains at 8 per group or needs to be increased to 18 per group.

10.4.2 Data Monitoring Committee (DMC), Data Review Team (DRT) or Dose Level Review Team (DLRT)

A Safety Review Meeting or DLRM will be held after PACAP-38 dosing has been completed in each cohort in Part A. Available vital signs and adverse events occurring at least 24 hours following PACAP-38 dosing for each cohort will be reviewed by the PI,

MM, and GSO or designee to decide enrollment in subsequent cohort. If the PI, MM, and GSO or designee decide not to proceed with enrollment in the subsequent cohort, then a Safety Review Meeting or DLRM will be held after the last dosed cohort.

The DLRM members will be composed of the investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer (GSO) or designee, Early Development Leader or designee, Clinical Study Manager or designee, and Biostatistics representative or designee. Additional members may be added as needed (eg, PK Scientist). The Safety Review Meeting Members include the investigator(s), Amgen Medical Monitor, and Amgen GSO or designee. The DLRM and Safety Review Meeting voting members will include the investigator(s), Amgen Medical Monitor, and Amgen GSO or designee.

A DLRM is planned for the Non Randomized (PACAP-38 Only) Dose Selection Subjects only. Unscheduled DLRMs can be called at any time by any of the DLRM voting members.

The Safety Review Meeting and DLRM voting members will decide whether or not to proceed with enrollment in the Randomization (AMG 334 or Placebo) Phase and if the decision is to proceed with enrollment in the Randomization (AMG 334 or Placebo) Phase, the Safety Review Meeting and DLRM voting members will select a PACAP-38 dose. The maximum dose of PACAP-38 will not exceed 115 pmol/kg. At any time the PI, MM, and GSO or designee may decide to add additional Non Randomized (PACAP-38 Only) Dose Selection Subjects pending review of emerging safety, and/or tolerability data. A future modification of the PACAP-38 dose may occur based on emerging safety, and/or tolerability findings.

All available study data, including the headache questionnaires, demographics, investigational product administration, medical history, concomitant medications, adverse events (including MLA), ECGs, vital signs, and laboratory results will be reviewed. Data to be reviewed at the Safety Review Meeting and DLRMs during the PACAP-38 Dose Selection Phase will not be blinded. Data to be reviewed for any unscheduled DLRM post the PACAP-38 Dose Selection Phase will be reviewed blinded (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing decisions. If deemed necessary, unblinding will be performed to assist dose decisions in accordance with Amgen standard procedures.

10.4.3 Primary Analysis

The primary analysis will take place after all subjects have completed the study.

10.4.4 Final Analysis

The final analysis will take place after final database lock.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety and PK data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Comparison of PACAP-38 ability to produce MLA between AMG 344 and placebo will be done with Fisher's Exact Test. Unless otherwise specified, data will be summarized using the safety analysis set, by actual treatment group. If a subject receives IP, but does not receive PACAP-38, their data will be listed only; their data will not be included in any summaries or analyses.

10.5.2 Primary Endpoint

The number and percent of subjects experiencing a MLA within 24 hours after PACAP-38 infusion will be summarized for each treatment group. Comparison of PACAP-38 ability to produce MLA between AMG 334 and placebo will be done using the Fisher's Exact test.

10.5.3 Secondary Endpoints

10.5.3.1 Number of Headaches

The number and percent of subjects experiencing a headache within 24 hours after PACAP-38 infusion will be summarized for each treatment group. Comparison of PACAP-38 ability to produce headaches between AMG 334 and placebo will be done using the Fisher's Exact test.

10.5.3.2 Safety Endpoints

Subject incidence of adverse events will be summarized by system organ class and preferred term for all treatment-emergent, serious treatment emergent, IP related, those leading to withdrawal of investigational product, fatal, and of special interest (if applicable). The identification of adverse events of special interest is a continuous process. Events may be identified and documented as the safety profile of the drug is characterized.

Vital signs will be listed and reviewed for each subject. Depending on the size and scope of change in vital signs, summaries may be provided.

For ECGs measurements following PACAP-38, summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Baseline will be defined measurements taken on Day 8 Pre-Dose. A subject's maximum change from baseline in QTcF and QTcB will be categorized and the number and percentage of subjects in each treatment group will be summarized. A subject's maximum post baseline values will also be categorized and the number and percentage of subjects in each treatment group will be summarized.

Hematology, biochemistry, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided.

Subject incidence of treatment-emergent suicidal ideation and behaviour as assessed by C-SSRS will be listed.

Binding antibody and neutralizing antibody formation will be assessed at predose and at various time points throughout the study including EOS. Antibody data will be listed for each subject. The incidence and percentage of subjects who develop anti-AMG 334 antibodies (binding and if positive, neutralizing) at any time may be tabulated.

10.5.3.3 Pharmacokinetic Endpoints

Serum AMG 334 concentrations will be determined using a validated assay. Individual serum concentration-time plots for AMG 334 will be presented for each subject as well as mean concentration-time plots for each treatment group. PK parameters $C_{1\ hour}$, and AUC_{84d} will be estimated using either compartmental (eg, PK modeling) or non-compartmental methods. Actual dosing and sampling times will be used for calculation of PK parameters. Summary statistics will be generated for each PK parameter for each treatment group. The PK concentration analysis set will be used for these analyses.

10.5.4 Exploratory Endpoints

10.5.4.1 Migraine-like Attacks (MLA) and Headaches

The reduction in severity by AMG 334 of MLA and headaches within 24 hours after infusion of PACAP-38 will be assessed and summarised based on a severity score (0-10; 0=pain free; 10=extreme pain). For MLA and headaches separately severity scores will be analysed using a repeated measure analysis of variance model.

Independent variables will be treatment, hour and treatment by hour interaction. Subject will serve as a random effect. For each treatment by hour combination, least square means, ratio to Placebo, 95% confidence intervals and p values for the null hypothesis of no difference from placebo will be presented. Graphical summaries of severity scores will also be provided. In addition, descriptive statistics will be provided for the duration of MLA and headaches.

Descriptive summaries of measured characteristics of MLA and headaches, such as localization and accompanying symptoms and pre-monitory symptoms, within 24 hours after infusion with PACAP-38 will be presented for each treatment group.

10.5.4.2 PACAP-38 Related Treatment Emergent AEs

Subject incidence of PACAP-38 related treatment emergent AEs will be summarized by system organ class and preferred term.

10.5.4.3 Plasma PACAP-38

Summary statistics will be generated for plasma PACAP-38 levels pre/post dosing with AMG 334 and PACAP-38.

10.5.4.4 Plasma CGRP

Summary statistics will be generated for plasma CGRP levels pre/post dosing with AMG 334 and PACAP-38.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager or designee to the investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational product(s) is/ are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. Refer to ICH GCP guideline, Section 4.8.9.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in strict confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRF, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2 and Table 3), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

- Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:
- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org/.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE version 4.0 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronicapplications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4 or who experience AST or ALT elevations > 3 x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis

  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected

- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)

- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. Sample Serious Adverse Event Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture (EDC))

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions
The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Definitions:

- Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.
- Serious Adverse Event – An adverse event that meets serious criteria
- Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.
- Serious Suspected Adverse Reaction – An SAR that meets serious criteria

What types of events to report on this form:

Type of Event	Clinical Trials
Adverse Event that is *not serious*	No
Serious Adverse Event (regardless of relationship)	Yes

Type of Event	Observational Studies
Suspected Adverse Reaction (SAR)	Yes
Serious Suspected Adverse Reaction	Yes
Serious Adverse Events that are not suspected to be related	ONLY if instructed by protocol or by local Amgen office or CRA

1. Site Information

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event form for the previous report as well as the start date for the initial event.

3. Adverse Event

   Provide the date the Investigator became aware of this information

   Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. This is a mandatory field.

   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the Investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. *For observational studies, remember that SARs are, by definition, related to the drug under study.* This is a mandatory field.

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for studies using Electronic Data Capture (EDC))

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

Relationship to Amgen device* – The investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field for serious events.**

- **Resolved** – End date is known
- **Not resolved / Unknown** – End date is unknown
- **Fatal** – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP/drug under study or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**

Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**

Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the Investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study 20140207 AMG 334	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex: ☐F ☐M	Race	If applicable, provide End of Study date

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:
and start date: Day_____ Month_____ Year _____

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day Month Year

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	Reason event Serious Class code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? Reason 1 / Yes? Reason 2 / Yes? Reason 3 / Yes? Reason 4 / Yes?	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure IE Study
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability/incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN
Study 20140207
AMG 334

Electronic Adverse Event Contingency Report Form
For Restricted Use

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device		Date of Initial Dose (Day Month Year)	Prior to or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IPDrug Device	☐Delivered ☐Open Inital							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
IPDrug Device	☐Delivered ☐Open Inital							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete.

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Freq.	Treatment Med No	Treatment Med Yes

7. RELEVANT MEDICAL HISTORY *(Include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(Include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete.

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete.

Date (Day Month Year)	Additional Tests	Results	Units

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AMGEN Study 20140207 AMG 334	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*	Title	Date

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm ▼ / dd ▼ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ▼ /dd ▼ /yyyy ____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ▼ /dd ▼ /yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ▼ / dd ▼ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ▼ / dd ▼ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ▼ / dd ▼ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ▼ / dd ▼ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

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Appendix D. Headache Questionnaire

AMGEN AMG 334 20140207	Site No.	Subject ID No. 207

Date Completed: Day -1

d d - M M M - y y y y

Headache Questionnaire (Day -1)

Baseline Frequency of Migraine:

Month 1 prior to screening:
(Please mark only one answer)

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5

Month 2 prior to screening:
(Please mark only one answer)

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5

Month 3 prior to screening:
(Please mark only one answer)

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5

Rescue Medication:

Does the subject have a usual rescue medication for pain relief from the spontaneous migraine attacks?

☐ No ☐ Yes

Following the use of the subject's usual rescue medication, how long does it take for the subject to achieve complete pain relief from the spontaneous migraine attack?

_____ minutes
_____ hours
_____ days

How effective is the subject's usual rescue medication to abort the spontaneous migraine attack?

- ☐ **0** - Not effective
- ☐ **1** - A little effective
- ☐ **2** - Moderately effective
- ☐ **3** - Extremely effective

AMGEN AMG 334 20140207	Site No.	Subject ID No. 207

Date Completed: d d - M M M - y y y y

Day 8, 0 Hours

Headache Questionnaire

Did the subject report a headache?

☐ No ☐ Yes *(If Yes, please ensure headache is recorded on the Events eCRF)*

If "Did the subject report a headache?" is Yes, please complete the questions below.

Date Headache Onset: d d - M M M - y y y y

Time Headache Onset (24-hour clock): H H : m m

(Please provide Date/Time Headache Stopped, or check Ongoing if unresolved)

Date Headache Stopped: d d - M M M - y y y y

Time Headache Stopped (24-hour clock): H H : m m

Ongoing ☐ No ☐ Yes

Maximum headache severity of pain:
(Please mark only one answer)

- ☐ **1** (Very mild pain; able to carry on with usual activities with no distraction)
- ☐ **2** (Mild pain; can continue with daily activities, but may be more difficult)
- ☐ **3** (Distracting pain; can continue with usual activities, but may be more difficult)
- ☐ **4** (Mild-moderate pain; usual activities become more difficult)
- ☐ **5** (Moderate pain; you feel the need to slow-down; pain is more distracting)
- ☐ **6** (Moderate-severe pain; limits your activities; some activities may be less of a priority)
- ☐ **7** (Severe pain; pain begins to affect ability to concentrate and very difficult to continue with daily activities)
- ☐ **8** (More severe pain; prohibits your activities [e.g., work, child care, self-care, etc...]: likely lying down or sleeping)
- ☐ **9** (Very severe pain; may be unable to speak or think clearly, not able to function; likely lying down or sleeping)
- ☐ **10** (Extreme pain; unable to function; worst pain imaginable; bed rest likely required)

Minimum headache severity of pain:
(Please mark only one answer)

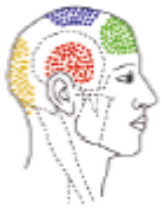
- ☐ **1** (Very mild pain; able to carry on with usual activities with no distraction)
- ☐ **2** (Mild pain; can continue with daily activities, but may be more difficult)
- ☐ **3** (Distracting pain; can continue with usual activities, but may be more difficult)
- ☐ **4** (Mild-moderate pain; usual activities become more difficult)
- ☐ **5** (Moderate pain; you feel the need to slow-down; pain is more distracting)
- ☐ **6** (Moderate-severe pain; limits your activities; some activities may be less of a priority)
- ☐ **7** (Severe pain; pain begins to affect ability to concentrate and very difficult to continue with daily activities)
- ☐ **8** (More severe pain; prohibits your activities (e.g., work, child care, self-care, etc...): likely lying down or sleeping)
- ☐ **9** (Very severe pain; may be unable to speak or think clearly, not able to function; likely lying down or sleeping)
- ☐ **10** (Extreme pain; unable to function; worse pain imaginable; bed rest likely required)

AMGEN AMG 334 20140207	Site No.	Subject ID No. 207

Day 8, 0 Hours

Is the pain limited to one side of the subject's head? ☐ No ☐ Yes

Localization of headache:
(Please mark all that apply)



☐ Lft. forehead
☐ Lft. temple
☐ Lft. neck
☐ Lft. half side
☐ Rt. forehead
☐ Rt. temple
☐ Rt. neck
☐ Rt. half side
☐ Top of head
☐ Diffuse

Is it a usual non-migraine headache? ☐ No ☐ Yes

Is it a usual migraine? ☐ No ☐ Yes

Characteristics of Headache:

Throbbing or pulsating ☐ No ☐ Yes

Aggravated by coughing ☐ No ☐ Yes

Nausea
☐ None
☐ Mild
☐ Moderate
☐ Severe

Vomiting
☐ None
☐ Mild
☐ Moderate
☐ Severe

Sensitivity to light
☐ None
☐ Mild
☐ Moderate
☐ Severe

Sensitivity to sound
☐ None
☐ Mild
☐ Moderate
☐ Severe

Does the headache worsen with any type of movement or physical activity? ☐ No ☐ Yes

Does the subject have visual disturbances (aura)? ☐ No ☐ Yes

AMGEN AMG 334 20140207	Site No.	Subject ID No. 207

Day 8, 0 Hours

Fatigue	☐ No	☐ Yes
Stiff Neck	☐ No	☐ Yes
Yawning	☐ No	☐ Yes
Mood Swings	☐ No	☐ Yes
Poor Concentration	☐ No	☐ Yes
Hunger	☐ No	☐ Yes
Flushing	☐ No	☐ Yes
Warm Sensations	☐ No	☐ Yes
Palpitations	☐ No	☐ Yes
Thirst	☐ No	☐ Yes
Eye Redness	☐ No	☐ Yes
Tearing	☐ No	☐ Yes
Nasal Congestion	☐ No	☐ Yes
Runny Nose	☐ No	☐ Yes
Swollen Eyelid	☐ No	☐ Yes
Droopy Eyelid	☐ No	☐ Yes
Sweating of Entire Face	☐ No	☐ Yes
Sweating of Forehead Only	☐ No	☐ Yes

Describe any other headache symptoms: _____

_____

_____

CONCOMITANT MEDICATIONS

(If Yes, please ensure medications are recorded on the Concomitant Medication eCRF.)

Were there any concomitant medications administered to the subject for the headache?

☐ No ☐ Yes

AMGEN AMG 334 20140207	Site No.	Subject ID No. 207

Day 8, 0 Hours

Rescue Medication:
(To be answered if any Concomitant medications were administered for the Headache as reported above)

Did the subject take his/her usual rescue medication for the headache?	☐ No ☐ Yes
Following the use of the subject's usual rescue medication, how long did it take for the subject to achieve complete pain relief from his/her PACAP-38 induced migraine-like attack?	_____ minutes _____ hours _____ days
How effective was the subject's usual rescue medication in aborting his/her PACAP-38 induced migraine-like attack?	☐ **0** - Not effective ☐ **1** - A little effective ☐ **2** - Moderately effective ☐ **3** - Extremely effective

Appendix E. Columbia Suicide Severity Rating Scale (C-SSRS) – Screening/Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Phase 1 study

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 6 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past 6 Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes No ☐ ☐ Total # of Attempts _____ Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix F. Columbia Suicide Severity Rating Scale (C-SSRS) – Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) *Description of Ideation*

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of* act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes No ☐ ☐ Total # of Attempts _____ Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐
Suicide:	Yes No ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding, sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Amendment 3

Protocol Title: Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients

Amgen Protocol Number AMG 334 20140207

Amendment Date: 01 September 2016

Rationale:

This protocol details an experimental medicine study that uses a formulation of PACAP-38 different than the one utilized in the published studies. The Amgen formulation modifications use human serum albumin and acetic acid to reduce the problem of surface binding that was observed during Amgen's replication testing of the PACAP-38 formulation used in the published clinical studies. Although the data were variable, approximately 50% of the peptide may have been lost to surface binding. The impact of this formulation change may have regarding the ability of IV PACAP-38 to induce migraine-like attacks (MLAs) in migraine patients is unknown. Therefore, the discoveries from this ongoing study, regarding the ability of this challenge agent to induce MLAs in migraine patients must be analyzed and incorporated in an expeditious manner.

The goal of this protocol amendment is to modify the criteria for selection of the appropriate dose of PACAP-38, a challenge agent, in Part A (PACAP-38 dose selection phase) of the aforementioned study, to enable advancement to Part B (randomized phase of the study to evaluate the inhibition of PACAP-38 induced migraine-like attacks by AMG 334).

This modification is based on the observed data to date which demonstrate that out of the 9 subjects dosed, only 1 subject experienced a severe MLA. It appears that the majority of subjects who experience a MLAs report a pain intensity level in the range of mild to moderate. Therefore the word "mild" has been added to the minimally acceptable criteria below:

> *The decision to proceed with Part B will be based on the objective of ensuring subject safety and ideally triggering headache in all subjects within a given cohort*

> *and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and **mild,** moderate **or** severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study.*

Although 2 out of 3 subjects in Cohort 1 (50 pmol/kg), have met the minimal criteria to advance to Part B of the study, the Dose Level Review Team (DLRT) will hold the Dose-Level Review Meeting (DRLM) as planned, following completion of Cohort 4 (100 pmol/kg). The DLRT will review the safety, tolerability, and pharmacodynamic (PD) results of the study in its entirety. Based on preliminary review of the data to date and recent DLRT discussions regarding the dose-level decision for Cohort 5, it is anticipated that at the DLRM, the DLRT will decide not to increase the dose of Cohort 5 up to 115 pmol/kg. Instead, it is more likely the DLRT will decide to expand one of the lower dose cohorts, in order to have a larger sample size and increased confidence in the dose that will be ultimately selected for Part B of the study. If this is decided, a non-substantial amendment will be completed, as the option to expand a previously dosed cohort is described in the protocol Section 6.3.1.2:

> *Up to five cohorts consisting of approximately 2 to 5 subjects are planned. Based on emerging safety and tolerability data, as well as the number of subjects experiencing a headache and/or MLA, the voting members of the Safety Review Meetings or DLRM (the PI, Medical Monitor and Global Safety Officer), may decide cohorts should be removed or additional cohorts should be added, with a maximum of 5 total cohorts. Subject numbers within each cohort may also be increased or decreased based on the decision from the Safety Review Meeting or DLRM.*

To date, IV PACAP-38 has been found to be safe and well tolerated with the majority of subjects experiencing headaches and/or migraine-like attacks. The risk-benefit profile has not changed.

Safety Summary:

To date four cohorts have been dosed with PACAP-38 in an ascending dose manner: 25pmol/kg, 50pmol/kg, 75pmol/kg and 100pmol/kg. Safety review meetings have been held for the first three cohorts and is planned for the 100pmol/kg cohort. To date, there have been no serious adverse events and the majority of adverse events reported are those anticipated with PACAP-38 such as flushing and heat sensation, along with a

transient elevation in heart rate and decrease in diastolic blood pressure. No subject met stopping criteria as outlined in the study protocol (PA2).

PD effect:

To date, 9 subjects have been dosed with IV PACAP, at dose levels of 50 (3 subjects), 75 (2 subjects) and 100 pmol/kg (4 subjects) with the intention of inducing headache or MLA in these subjects. Approximately half of all the subjects experienced a MLA, and about 80% of all subjects experienced either a non-migraine-like headache or MLA. Two of the initial 9 subjects had no headache at all.

Amendment 2

Protocol Title: Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients

Amgen Protocol Number AMG 334 20140207

Amendment Date: 27 May 2016

Rationale:

The primary objective of this protocol amendment is to 1) allow dosing of an additional cohort up to 115 pmol/kg in the non-randomized portion of the study (Part A), 2) clarify the criteria required prior to advancement to the randomized portion of the study (Part B), 3) increase the sample size in Part A to no more than 5 subjects per cohort, and 4) include additional safety monitoring of all subjects throughout the duration of the study.

The aforementioned dosing options support the goal of establishing an appropriate dose of IV PACAP-38 to be used in Part B of the study. The generation of headaches and migraine-like attacks (MLAs) are the pharmacodynamic (PD) effects desired to advance the study. The decision to proceed with Part B will be based on the objective of ensuring subject safety and ideally triggering headache in all subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort. However, the trigger of headaches in the majority of subjects within a given cohort and moderate to severe MLAs in the majority of subjects within the same cohort may be considered acceptable to advance to Part B of the study. In order to ensure the reliability of these subjective PD assessments, the sample size per cohort, has been increased to up to 5 subjects in Part A of the study.

The maximum dose of 115 pmol/kg was chosen because it provides a safety margin of approximately 10X (based on body weight) from the single-dose GLP IV rat study NOAEL. In this study, acute myocardial necrosis was observed at the mid and high doses. By day 15, repair of the myocardium at these doses was almost complete, with only scattered minimal to mild areas of immature connective tissue (fibroplasia) remaining. This is an anticipated pharmacologic effect of potent vasodilators in

nonclinical species: potent vasodilating drugs when administered at high doses to rats are known to produce necrosis and inflammation of the myocardium and cardiac arteries (Greaves, 2012). This is a rat-specific finding not known to translate to humans.

As the dose will be increased and the possible number of subjects exposed to PACAP-38 may also increase, additional risk mitigation steps have been added in order to ensure subject safety throughout the duration of the study. These include measurement of cardiac enzymes (Troponin T and CK-MB) pre-dose, and then at 2 hours, 4 hours, 8 hours and 24 hours after PACAP-38 dosing, and the addition of an ECG 48 hours after PACAP-38 dosing. Stopping rules have also been modified to include potential of PACAP-38 to decrease BP and are now as follows:

- Blood pressure:
  - Systolic BP > 150 mm Hg OR
  - Diastolic BP > 100 mm Hg OR
  - Decrease in SBP from baseline > 30 mm Hg OR
  - Decrease in DBP from baseline > 15 mm Hg and considered clinically relevant after consultation between the investigator and the medical monitor
- Mean heart rate increase of subjects in a given cohort is greater than 50% or greater than 20% decrease over baseline during a 2 hour period after dosing
- Changes in other vital signs or clinical laboratory results considered to pose a significant health risk to subjects

To date, IV PACAP-38 has been found to be safe and well tolerated with subjects experiencing the anticipated PD effects.

Safety: In the 3 cohorts dosed, the safety profile has been consistent with the exerted pharmacological effects of PACAP-38. Majority of reported events were CTCAE Grade 1.The following adverse events were assessed as being CTCAE Grade 2: feeling of pressure on the head (n=1), dry eyes (n=2), MLA (n=1), facial flushing (n=1), muscular tension in the face (n=1) and headache (n=2). Transient effects on blood pressure and heart rate were noted in subjects, however none met stopping criteria.

PD effect: In Cohort 1 (25 pmol/kg), both subjects experienced a mild headache. In Cohort 2 (50 pmol/kg, 1 subject experience a mild headache, and 2 subjects experienced a moderate MLA. However, in the most recent cohort (Cohort 3; 75 pmol/kg of IV PACAP-38), one subject did experience a moderate MLA, however the other subject did not experience either a headache or MLA.

In addition to the aforementioned updates, the amendment explicitly outlines the decision the Principal Investigator (PI), Global Safety Officer (GSO), and Medical Monitor (MM) may jointly make regarding whether the safety, tolerability, and pharmacodynamics effects of IV PACAP-38 observed in Part A of the study support advancing to Part B.

Lastly, clarification regarding the difference between a Safety Review Meeting and Dose Level Review Meeting (DLRM) has been added, along with more precise questions in the Headache Questionnaire. The criteria for post-menopausal status has been added. Administrative, typographical and formatting changes were also made throughout the protocol.

References

Greaves P. Cardiovascular system. In: Greaves P, ed. *Histopathology of Preclinical Toxicity Studies*. Amsterdam, The Netherlands: Academic Press; 2012;293-294.

Amendment 1

Protocol Title: Phase I, Randomized, Parallel-group, Double-Blind, Placebo-Controlled, Single Dose Study to Evaluate the Blockade of CGRP Receptor by AMG 334 in Preventing PACAP-38 Induced Migraine-like Attacks in Migraine Patients

Amgen Protocol Number AMG 334 20140207

Amendment Date: 26 June 2015

Rationale:

This amendment is designed to select a PACAP-38 dose that triggers migraine-like attacks, and to ensure subject safety with the fewest adverse events. Previous studies have shown that administration of pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) formulation will trigger migraine-like headaches in migraineurs (Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014). In these studies, 10 pmol/kg/min over 20 minutes (total dose 200 pmol/kg) was administered and 66% of migraineurs experienced migraine-like attacks with a median time of headache onset of 4 hours. As PACAP-38 is involved in various biological processes, including sensory processing, vasodilation, inflammation, and nociceptive transmission (Dickinson et al., 1999; Vaudry et al., 2000), both the healthy subjects and migraineurs also experienced the expected adverse events of flushing, heat sensation, along with a transient elevation in heart rate and systolic blood pressure (Birk et al, Regulatory Peptides 2007; Schytz et al, Brain 2009; Amin et al, Cephalagia 2011; Amin, Brain 2014).

The assay values observed during Amgen's replication testing of the PACAP-38 formulation used in the aforementioned published clinical studies, suggest that a significant amount of the PACAP-38 polypeptide binds to the product container surfaces. Although the data were variable, it is estimated that approximately 50% of the peptide may have been lost to surface binding. Amgen formulation modifications using human serum albumin and acetic acid have reduced this problem.

Therefore, in order to ensure subject safety and select the lowest PACAP-38 dose that will trigger moderate to severe migraine-like headaches, a sentinel dosing strategy, along with a Dose-Level Review Meeting (DLRM) has been implemented in this

amendment. The highest dose tested in the sentinel cohorts will be 50% lower than the dose used in the published studies. There will be a total of 3 sentinel cohorts each with a total of 2 subjects who both receive PACAP-38. The starting dose will be an infusion of 10 pmol/kg/min over 2.5 minutes (total dose 25 pmol/kg) for Cohort 1 and 10 pmol/kg/min over 5 minutes (total dose 50 pmol/kg) for Cohort 2 sentinel subjects. Cohort 3 may be enrolled following an informal safety meeting between the principal investigator (PI), medical monitor (MM), and global safety officer (GSO). At that time, available vital signs and adverse events occurring up to 24 hours following PACAP-38 dosing for Cohorts 1 and 2 will be reviewed. Cohort 3 will then receive 10 pmol/kg/min over 10 minutes (total dose 100 pmol/kg). Following Cohort 3, a Dose-Level-Review Meeting (DLRM) will occur to determine the dose of PACAP-38 to be used in the randomized portion of the study.

A high level summary of the adverse events observed in the published human PACAP-38 challenge studies is provided in the background section. Lastly, the eligibility criteria have been modified to ensure that only cardiovascularly healthy migraineurs are enrolled in the study.

Additional updates were made to be in alignment with the newly available protocol template language.

Minor administrative, typographical, and grammatical changes were made.