Title Page

Protocol Title:		A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention
Short Protocol Title:		A Phase 2a Study of AMG 301 in Migraine Prevention
Protocol Number:		20150308
Investigational Product		AMG 301
Trade Name:		Not applicable.
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EudraCT Number:		2017-000630-57
NCT Number:		**NCT03238781**
Protocol Date:		**Document Version** / **Date** Original / 16 March 2017 Amendment 1 / 16 May 2017 **Amendment 2 / 17 October 2017**
Version/Date:		**Data Element Standards Version** / **Date** 5.0 / 20 Mar 2015

Confidentiality Notice

NCT Number: 03238781
This NCT number has been applied to the document
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Investigator's Agreement:

I have read the attached protocol entitled A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention, dated **17 October 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, 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) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 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)

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1. Protocol Synopsis

Protocol Title: A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention

Short Protocol Title: A Phase 2a Study of AMG 301 in Migraine Prevention

Study Phase: 2a

Indication: Migraine Prophylaxis in Subjects with Chronic Migraine (CM) or Episodic Migraine (EM)

Rationale

AMG 301 is an engineered human monoclonal immunoglobulin G1 (IgG1) antagonist to the pituitary adenylate cyclase-activating polypeptide type 1 receptor (PAC1). It is hypothesized that AMG 301 prevents migraine via inhibition of the trigeminal autonomic signaling through the blockade of the PAC1 receptor function. No clinical studies have investigated whether antagonism of the PAC1 pathway can be an effective means of migraine prevention. Two dose levels of AMG 301 (420 mg and 210 mg) were chosen for this phase 2a study to test proof of concept and aid in dose selection for future studies. The dose selection for this phase 2a study was based on preclinical and phase 1 safety data, as well as pharmacodynamic (PD) data obtained in humans.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days in subjects with migraine	• Change from the baseline period in monthly migraine days. The monthly migraine days will be calculated using the migraine days over the last 4 weeks of the 12-week double-blind treatment period
Secondary	
• To evaluate the effect of AMG 301 compared to placebo on the proportion of subjects with at least 50% reduction from the baseline period in monthly migraine days	• At least a 50% reduction from the baseline period in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly acute migraine-specific medication treatment days	• Change from the baseline period in monthly acute migraine-specific medication days in the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly physical impairment domain score as measured by the Migraine Physical Function Impact Diary (MPFID)	• Change from the baseline period in mean physical impairment domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly impact on everyday activities domain score as measured by the MPFID	• Change from the baseline period in mean impact on everyday activities domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the safety and tolerability of AMG 301	• Adverse events • Clinical laboratory values and vital signs

Hypotheses

In subjects with migraine, AMG 301 has a greater reduction from the baseline period in monthly migraine days, compared to placebo.

Overall Design

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel-group study of subjects with CM or EM.

Number of Subjects

Approximately 335 subjects will be randomized 4:3:3 to the following treatment groups: placebo for AMG 301, AMG 301 210 mg subcutaneous (SC) injections every 4 weeks (Q4W), or AMG 301 420 mg SC injections every 2 weeks (Q2W), respectively.

The anticipated number of subjects expected to be screened is 670 subjects with 503 enrolled into the baseline period, which is a 25% screen failure rate. From this, it is expected that approximately 35% of the subjects fail during the baseline period, such that 335 subjects are randomized into the study.

Summary of Subject Eligibility Criteria

Adults ≥ 18 to ≤ 60 years of age with history of migraine (with or without aura) for ≥ 12 months before screening and who experience ≥ 4 migraine days per month.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.4.

Treatments

Investigational product (ie, AMG 301 and/or placebo) will be dosed every 2 weeks (Q2W), SC during the double-blind treatment period. Subjects will be randomized 4:3:3 to placebo, AMG 301 210 mg Q4W, or AMG 301 420 mg Q2W, respectively.

During the 12-week double-blind treatment period, 6 SC injections will be administered at day 1, weeks 2, 4, 6, 8, and 10. All 6 SC injections are to be administered within 30 minutes. Subjects randomized to:

- AMG 301 420 mg Q2W will receive a total of 6 AMG 301 injections (70 mg/mL) at day 1, and weeks 2, 4, 6, 8, and 10.
- AMG 301 210 mg Q4W will receive a total of 3 AMG 301 injections (70 mg/mL) plus 3 matching placebo Q4W (day 1, weeks 4, and 8). Subjects randomized to AMG 301 210 mg Q4W will also receive 6 SC placebo injections on weeks 2, 6, and 10.
- Placebo will receive 6 SC placebo injections at day 1, and weeks 2, 4, 6, 8, and 10.

AMG 301 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL of AMG 301. Placebo will be presented in identical containers, stored/packaged the same as AMG 301.

Investigational product doses are fixed and will not be adjusted for individual subjects during the study. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen.

Procedures

After signing informed consent, subjects will enter the screening period. The screening period is up to 7 weeks and is composed of an initial screening phase (up to 3 weeks) followed by a 4-week baseline period. At the day 1 (postrandomization) visit, eligible subjects will be randomized into the 12-week double-blind treatment period and will begin to receive double-blind investigational product Q2W SC. A safety follow-up visit occurs 18 weeks after the last dose of investigational product. Subjects will use an electronic diary (eDiary) everyday throughout the baseline period, double-blind treatment period, and safety follow-up period to report information about their migraine and non-migraine headaches and acute medication use. Subjects will have scheduled in-clinic study visits throughout the study.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The primary analysis will be to test the primary efficacy endpoint once the primary completion milestone is achieved after the last subject reaches the last visit during the double-blind treatment period, and all data are collected for the primary endpoint. After about 50% of the subjects have been enrolled, the sponsor will perform multiple, independent unblinded interim analyses for administrative purposes for future study planning only.

Summary statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% confidence intervals of the means (confidence intervals will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

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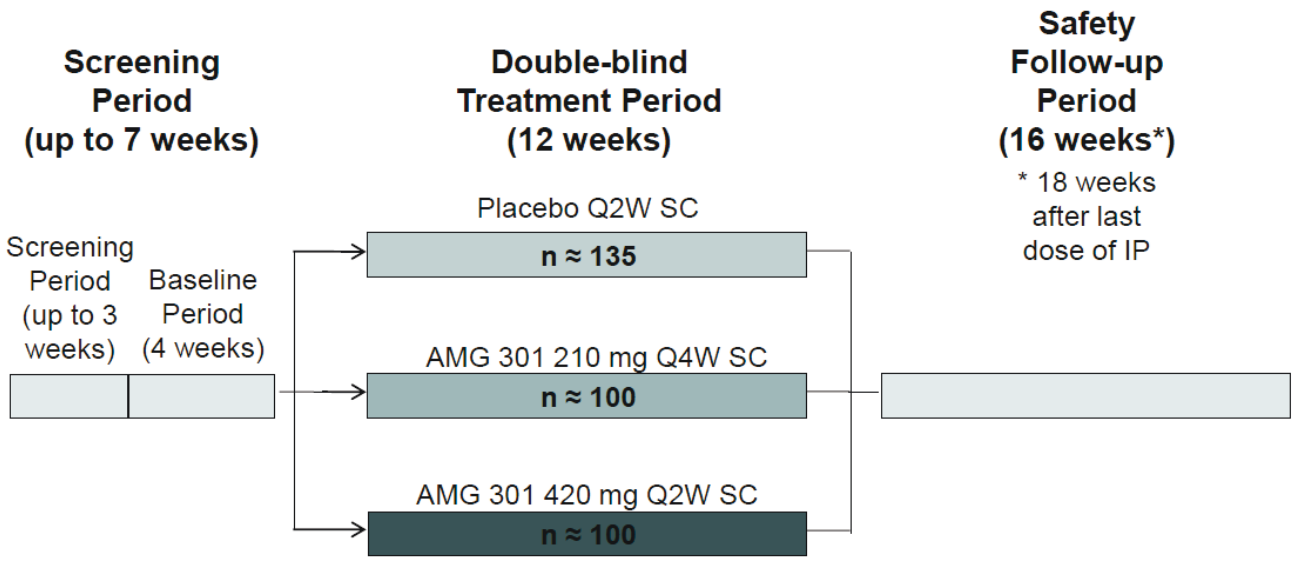
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



Abbreviations: IP = investigational product; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	Screening Period (Up to 7 weeks)			Double-Blind Treatment Period[a] (12 weeks) (± 2 days)									Safety Follow-up Period (16 weeks) (± 5 days)			
		Baseline Period[b]														
	Screening up to 3 weeks	-4 Weeks	Pre-rand (Day 1)	Day 1 (Post-rand)[c]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12/ET[d]	Wk 16	Wk 20	Wk 24	Wk 28/ET/ EOS[d]
GENERAL AND SAFETY ASSESSMENTS																
Informed consent	X															
Physical examination	X											X				X
Height and Weight[e]	X		X									X				X
Demographics[f]	X															
Vital signs[g]	X	X	X[h]	X[i]		X	X	X	X		X	X	X	X	X	X
Medical and Medication history[j]	X		X													
12-lead ECG	X			X					X			X		X		X
Adverse events[k]	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
Product Complaints Recording				X		X	X	X	X		X					
LABORATORY ASSESSMENTS																
Serum pregnancy test [l]	X															
Urine Pregnancy test[l]			X				X		X			X				X

Footnotes defined on last page of table

Table 2-1. Schedule of Activities

Procedure	Screening Period (Up to 7 weeks)			Double-Blind Treatment Period[a] (12 weeks) (± 2 days)									Safety Follow-up Period (16 weeks) (± 5 days)			
		Baseline Period[b]														
	Screening up to 3 weeks	-4 Weeks	Pre-rand (Day 1)	Day 1 (Post-rand)[c]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12/ET[d]	Wk 16	Wk 20	Wk 24	Wk 28/ET/ EOS[d]
Hepatitis B and Hepatitis C storage sample				X[m]												
Serum plasma glucose[n]	X															
HbA1c	X							X[o]				X[o]		X[o]		X[o]
Hematology, chemistry	X			X			X	X[o]				X[o]		X		X
Urinalysis	X											X				
Urine drug screen[p]	X															
RANDOMIZATION/INVESTIGATIONAL PRODUCT DOSING																
Call to IVR/IWR system[q]	X		X			X	X	X	X		X					X
Entry into the Baseline period		X														
Randomization			X													
Investigational Product				X[r]		X	X	X	X		X					
PK ASSESSMENTS																
PK Sampling **(serum)**[s]				X	X		X		X	X	X	X	X		X	X
BIOMARKER ASSESSMENTS																
Biomarker development				X								X[t]				X[t]
Anti-AMG 301 antibodies (serum)[s]				X					X			X	X		X	X

Footnotes defined on last page of table

Table 2-1. Schedule of Activities

Procedure	Screening Period (Up to 7 weeks)			Double-Blind Treatment Period[a] (12 weeks) (± 2 days)									Safety Follow-up Period (16 weeks) (± 5 days)			
		Baseline Period[b]														
	Screening up to 3 weeks	-4 Weeks	Pre-rand (Day 1)	Day 1 (Post-rand)[c]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12/ET[d]	Wk 16	Wk 20	Wk 24	Wk 28/ET/ EOS[d]
PHARMACOGNETIC ASSESSMENT																
Pharmacogenetic sample (Optional)[u]				X												
CLINICIAN ASSESSMENTS																
C-SSRS	X		X				X		X			X	X	X	X	X
CAPS Scale				X			X		X			X	X	X	X	X
SUBJECT COMPLETED ASSESSMENTS																
Modified MIDAS[v]		X		X			X		X			X	X	X	X	X
COAs[v]		X (daily)														
MPFID[v]		X (daily)														
BDI-II	X		X													
HIT-6[v]		X		X			X		X			X	X	X	X	X
Assign eDiary to Subject		X														
Subjects brings eDiary to study center for use during the study visit			X			X	X	X	X		X	X	X	X	X	X

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Abbreviations: BDI-II = Beck Depression Inventory - II; CAPS = Cranial autonomic parasympathetic symptom; CM = chronic migraine; COAs = Clinical Outcome Assessments; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EM = episodic migraine; EOS = End of Study; ET = Early Termination; HbA1c = glycosylated hemoglobin; HIT-6 = Headache Impact Test; MIDAS = Migraine-specific and Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; Pre-rand = Pre-randomization; Post-rand = Post-randomization; PK = Pharmacokinetic; IVR/IWR = Interactive Voice Response/Interactive Web Response; WK = week

a. The day 1 visit (randomization day) window is +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 baseline period visit date. Each study visit during the double-blind treatment period has a window of ± 2 consecutive calendar days. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.
b. Entry into the baseline period must occur only after completion of the screening period procedures.
c. Randomization (day 1 pre-randomization) into the double-blind treatment phase using the IVR/IWR system must occur only after completion of all baseline period procedures and before the first dose of double-blind investigational product (randomization and administration of the first dose of investigational product should occur on day 1).
d. A subject who discontinues investigational product or the study during the double-blind treatment period will complete the week 12/ET visit. Subjects who discontinue after the double-blind treatment period (week 12) and before week 28 will complete the week 28/EOS/ET visit.
e. Height and weight will be measured without shoes. Height will be collected at the screening visit only.
f. Demographics will include sex, age, race and ethinicity.
g. **Vital signs will be assessed prior to investigational product administration, and** will include systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study.
h. **Vital signs will be assessed prior to subject registration using the IVR/IWR system.**
i. **Vital signs will be assessed approximately 30 to 60 minutes after investigational product administration.**
j. Medical history will include targeted cardiologic, neurologic, psychiatric, cardiovascular, and history of diabetes, including gestational diabetes and/or impaired glucose tolerance testing. A history of participation in prior Amgen studies will be included. Medication history to include prior migraine prophylactic treatment history within the 90 days before screening will be collected.
k. Serious adverse events are to be collected after signing of the informed consent through EOS (18 weeks after the last dose investigational product). Adverse events are to be collected after the first dose of investigational product through EOS (18 weeks after the last dose of investigational product). Disease related events are to be collected after the first dose of investigational product through 18 weeks after the last dose of investigational product (EOS).
l. Serum pregnancy test will be collected at screening and performed for all female subjects unless surgically sterile or ≥ 12 months postmenopausal. Urine pregnancy will be collected at all other visits. Additional pregnancy testing may be performed at the investigators' discretion or as required per local laws and regulations.
m. Collection only, no testing.
n. **Sites are encouraged to obtain a fasting glucose sample, if possible.**
o. A fasting blood glucose will be performed **at next visit** in cases where a serum glucose is ≥ 200 **mg/dL** or H**b**A1c is ≥ 5.7%.
p. Urine drug testing will be collected at screening and as needed throughout the study based on investigator's clinical suspicion.
q. Study centers are to call the IVR/IWR system for the following: to enter the subject into the screening period, to randomize an eligible subject into the double-blind treatment period, to obtain the investigational product assignment, to register the end of investigational product, and to register study ET or completion. Subject data will be collected in the IVR/IWR system including, but not limited to, CM versus EM, sex, and reason for screen fail (if applicable). Study centers to access the IVR/IWR system to obtain the investigational product assignment at day 1, and weeks 2, 4, 8, and 10.

r. **On day 1 post-randomization and week 2 visits,** study center staff are to observe the subject for at least 120 minutes after the last injection of investigational product. **On weeks 4, 6, 8, and 10 visits,** study center staff will observe the subject for at least 60 minutes after the last injection of investigational product. Investigators can retain subjects for longer if there is any sign of discomfort any time following AMG 301 administration.

s. PK sampl**es** will be collected at predose on day 1 and weeks 4, 8, and 10, and at postdose in weeks 1, 9, 12, 16, 24, and 28 or EOS. **On days that anti-AMG 301 antibodies are scheduled to be collected, they are to be collected following the predose/postdose PK sampling schedule.**

t. Biomarker may be collected if the subject ET occurs after the first dose of investigational product and before week 12.

u. For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample. Therefore, additional sampling is not required.

v. The COAs, modified MIDAS, MPFID, and HIT-6 are to be collected by subjects using eDiaries.

3. Introduction

3.1 Study Rationale

AMG 301 is an engineered human monoclonal immunoglobulin G1 (IgG1) antagonist to the pituitary adenylate cyclase-activating polypeptide type 1 receptor (PAC1). It is hypothesized that AMG 301 prevents migraine via inhibition of the trigeminal autonomic signaling through the blockade of the PAC1 receptor function. No clinical studies have investigated whether antagonism of the PAC1 pathway can be an effective means of migraine prevention. Two dose levels of AMG 301 (420 mg and 210 mg) were chosen for this phase 2a study to test proof of concept and aid in dose selection for future studies. The dose selection for this phase 2a study was based on preclinical and phase 1 safety data, as well as pharmacodynamic (PD) data obtained in humans.

3.2 Background

3.2.1 Disease

Migraine is a disabling disorder characterized by primary recurrent headaches lasting 4 to 72 hours (if not treated) with at least 2 of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia). Migraine has 2 major subtypes: migraine with aura (visual, sensory and/or speech symptoms that occur just before or at the onset of migraine headache) and migraine without aura per the International Headache Classification (ICHD)-III.

Migraine affects more than 10% of the world's population (Robbins and Lipton, 2010), and the prevalence of migraine is approximately 11.7% in the US, 14.6% in Canada, and 14.7% in Europe (Lipton et al, 2007; Stovner and Andree, 2010).

The patient burden and disability as well as the societal impact increases with higher attack frequency, which is why often the spectrum of migraine disorders is usually described according to frequency of migraine days per month. Episodic migraine (EM) is typically defined as 0 to 14 migraine days per month (Katsarava et al, 2012), though for clinical trial purposes, a lower limit of 4 migraine days per month is often chosen. Chronic migraine (CM) is defined as 15 or more headache days per months, at least 8 out of which have to be typical migraine days (Headache Classification Committee of the International Headache Society, 2013). Although EM and CM are somewhat arbitrarily distinguished based on migraine headache frequency, numerous lines of evidence support that they are a continuum of the same disorder. Not only are clinical

symptomologies and functional impairments very similar, but functional imaging results demonstrating that similar areas of the brain are involved support a common underlying pathophysiology (Aurora and Wilkinson, 2007; Afridi et al, 2005; Aurora et al, 2005; Welch et al, 2001).

Only approximately 12% of patients receive any preventive therapy due to limited efficacy and significant tolerability and safety issues with available preventive therapies. Migraine prophylaxis is an area of large unmet medical need.

Activation of the trigeminovascular system is associated with the onset of migraine headaches (Edvinsson, 2013; Goadsby et al, 2002). Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide expressed in the trigeminovascular system and has been proposed to play a role in migraine pathophysiology (Schytz et al, 2010).

PACAP belongs to the vasoactive intestinal polypeptide (VIP)/secretin/glucagon superfamily, with 2 forms, PACAP-38 and PACAP-27. The major form of PACAP in the human body is PACAP-38. Three PACAP receptors have been reported: 1 receptor that binds PACAP with high affinity and has a much lower affinity for VIP (PAC1 receptor), and 2 receptors that recognize PACAP and VIP equally well (vasoactive intestinal polypeptide receptor [VPAC1 and VPAC2 receptors] Vaudry et al, 2009).

3.2.1.1 Proposed Mechanism of Action and Nonclinical Evidence

Both calcitonin gene-related peptide (CGRP) and PACAP are expressed in the trigeminovascular system (Goadsby et al, 2002). In both rat and cynomolgus monkey tissue studies, PACAP is found to innervate the dura vessels in a way that is similar to CGRP (Amgen data). Follow-up immunohistochemistry studies in cynomolgus monkey mapped PACAP and PAC1 localization to the parasympathetic pathway through the sphenopalatine ganglion ([SPG]; also known as pterygopalatine ganglion), which also innervates the dura vasculature (Amgen data on file). While CGRP mainly functions as a neuropeptide in the sensory pathway, PACAP appears to be a neuropeptide in the parasympathetic pathway (Eftekhari et al, 2015).

Based on the different distribution pattern between CGRP and PACAP, it is conceivable that CGRP and PACAP may be working through distinct pathways. These are 2 major systems which innervate the dura vasculature and it is very likely both of them contribute to migraine pathology.

3.2.1.2 Clinical Evidence for Migraine Indication

Evidence supporting the role of the PAC1 receptor in migraine comes from human experimental migraine models using PACAP as a challenge agent. The group at the Danish Headache Center demonstrated, first in healthy subjects, then migraine patients that infusion of PACAP causes migraine-like headache in the tested populations (Schytz et al, 2009; Rahmann et al, 2008). In addition, the group tested VIP in the model and VIP did not cause migraine-like attacks. The lack of migraine induction from VIP infusion suggests that it is the PAC1 receptor, which is involved in migraine since VIP has a much lower affinity for this receptor. These data suggest that a selective PAC1 antagonist will have the potential to treat migraine.

3.2.2 Amgen Investigational Product Background: AMG 301

3.2.2.1 AMG 301

AMG 301 is a PAC1 receptor selective antagonist in the form of an antibody AMG 301 is an engineered human monoclonal antibody (mAB) that is expressed in a Chinese Hamster Ovary (CHO) cell line. The molecule is a heterotetramer consisting of 2 heavy chains of the lgG1 subclass and 2 light chains of the kappa subclass, which are covalently linked through disulfide bonds. AMG 301 is aglycosylated through heavy chain engineering. The heavy chain abrogates Fcγ receptor binding, avoiding any deleterious effects mediated through the Fc effector function (ie, antibody-dependent cellular cytotoxicity). AMG 301 contains 1326 amino acids. The molecular weight is approximately 145 kD. Refer to Investigator's Brochure for further details.

3.2.2.2 Pharmacodynamic Data

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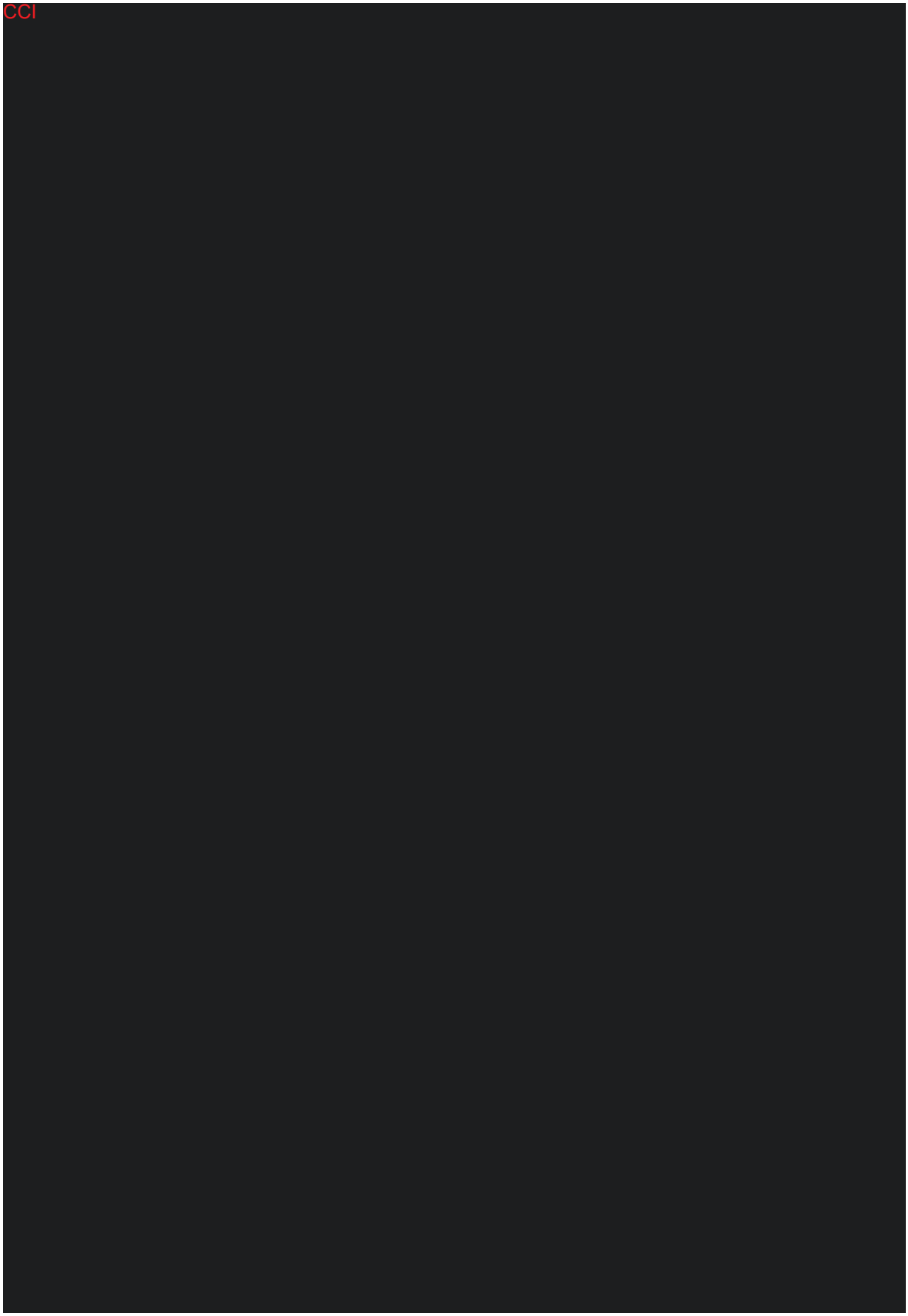

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3.2.2.5 Toxicology

The toxicity profile of AMG 301 has been characterized in cynomolgus monkeys following 1-month of weekly dosing (SC or IV up to 250 mg/kg per week). Furthermore, AMG 301 has also been evaluated with up to 6 months of weekly SC dosing in toxicology studies in cynomolgus monkeys. Four animals per sex were given doses of 0, 5, 50, or 250 mg/kg and 2 animals per sex in the 0 and 250 mg/kg dose groups were maintained for an additional 6 months of recovery following the last dose. AMG 301-related findings were limited to a non-adverse mild to moderate perivascular mononuclear cell infiltrates present in the skin of the SC administration site at ≥ 5 mg/kg. Based on the available results through the end of the dosing period, no observed adverse effect level was considered to be 250 mg/kg.

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A detailed description of the chemistry, PK, pharmacology, efficacy, and safety of AMG 301 is provided in the Investigator's Brochure.

3.2.3 Non-Amgen Investigational Product Background

Not applicable.

3.3 Benefit/Risk Assessment

Migraine prophylaxis remains an area of large unmet medical need. Topiramate is one of the most broadly used migraine prophylactics globally but approximately 50% of patients fail to respond. Topiramate is also poorly tolerated with common adverse events such as paresthesia, anorexia, cognitive impairment, somnolence, and fatigue, which frequently leads to discontinuation of treatment (Adelman et al, 2008; Brandes et al, 2004). Other pharmacological classes used for migraine prophylaxis (beta-blockers, tricyclic antidepressants, other anticonvulsants) also present significant tolerability issues with most patients stopping their migraine prophylactic in the first 3 months.

It is hypothesized that AMG 301 prevents migraine via inhibition of trigeminal autonomic signaling through blockade of the PAC1 receptor. No clinical studies have investigated whether antagonism of the PAC1 pathway can be an effective means of migraine prevention. Given that this study will be the first clinical study to determine whether blockade of the PAC1 receptor in the migraine population results efficacy, it is acknowledged that there may not be a direct benefit for the individual patients participating in this study. There is a potential indirect benefit to participants in this study since they will undergo numerous assessments related to their migraine care (eg, migraine specific patient reported outcomes, cranial autonomic parasympathetic symptom assessments, etc.) which may be informative to their treating physician, and patients are likely to receive additional monitoring beyond standard clinical practice. This phase 2a study provides important information that will guide future development of AMG 301, which has the potential to address a high unmet need.

PACAP is a vasoactive neuropeptide in the autonomic nervous system that is involved in various biological processes, including sensory processing, vasodilation, inflammation,

and nociceptive transmission (Vaudry et al, 2000; Dickinson and Fleetwood-Walker, 1999), as well as cardiovascular, pancreatic, central nervous system, and reproductive functions. PACAP binds to 3 different receptors with similar potency. AMG 301 (or Ab 1.8.1) only blocks the activity of PACAP at the pituitary adenylate cyclase-activating polypeptide type 1 receptor (PAC1R) and not at VIP/PACAP receptor 1 (VPAC1) or VPAC2. Thus, many of the pleiotropic activities reported in the literature may be due to the effect of PACAP at the 2 VPAC receptors. In addition, regarding PACAP's vasodilatory effects, there exist other vasodilatory mediators such as nitric oxide, substance P, and neurkinins (Burley et al, 2007), and in view of this redundancy, the relative importance of PACAP in vasodilation, as compared to other mediators, has not been established.

In AMG 301 nonclinical studies, there were no significant toxicology findings that would indicate a risk to human subjects and no immunogenicity findings that would impact the interpretation of the toxicology studies. AMG 301 administered to cynomolgus monkeys by SC injection at 5, 50, or 250 mg/kg weekly for 26 weeks was well tolerated. No AMG 301-related changes in clinical signs, body weight, food consumption, ophthalmology, electrocardiology (qualitative and quantitative), clinical pathology parameters (hematology, coagulation, clinical chemistry including glucose and insulin, and urinalysis), organ weights, and sperm count/motility/morphology were noted.

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As with any large molecule therapeutic agent, administration of AMG 301 may result in systemic reactions including immune mediated varieties of hypersensitivity. These may

include antibody mediated reactions, or those resulting from the release of cytokines (ie, cytokine release syndrome), generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea/vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can be severe or life threatening. Effects typically occur during or within several hours after drug administration, but they may be delayed. In general, all biologic molecules, including fully human proteins, have the potential to induce immunogenicity (the development of specific antidrug antibodies). In most cases however, antibodies developing against a biologic will be without clinical significance. In this study, AMG 301 will be administered SC by a qualified research staff member. Subjects will be monitored for systemic reactions during and after AMG 301 administration.

Based on the nonclinical toxicology and safety pharmacology studies, and upon review of available data in the ongoing clinical trial with AMG 301, there are no identified risks and no substantial risks can reasonably be anticipated. In conclusion, the overall risk and potential benefit to patients participating in this study is considered positive.

A comprehensive safety monitoring plan has also been included in this study in order to capture any possible risks. To assess potential impact on all body systems, all adverse events will be collected from the first dose through the end of study and various laboratory tests of blood (eg, red blood cells [RBC], white blood cells [WBC], liver function test, creatinine phosphokinase [CPK], cholesterol, potassium, HbA1C, glucose) and urine (eg, blood, bilirubin, WBC, RBC, protein) (Table 12-1) will be conducted to provide additional clinical data. In addition, to assess potential impact on the central nervous system, physical examination, including neurological examination and suicidal risk monitoring by Columbia Suicide Severity Rating Scale (C-SSRS) will be implemented throughout the double-blind and safety follow-up period. To assess potential impact on the respiratory and cardiovascular system, vital signs including systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature will be assessed during every visit when the investigational product is administered and electrocardiograms will be assessed on day 1, week 8, week 12, week 20, and week 28. Energy metabolism will be assessed through repeated HbA1C and fasting glucose tests as well as body weight monitoring. Homeostatic control is closely monitored through vital sign assessment (eg, body temperature) and various lab tests (eg, blood sodium, potassium, calcium and glucose levels; urine pH and glucose level). Furthermore,

appropriate inclusion/exclusion criteria and precautionary measures have been implemented within the study protocol to ensure subject safety remains paramount.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days in subjects with migraine	• Change from the baseline period in monthly migraine days. The monthly migraine days will be calculated using the migraine days over the last 4 weeks of the 12-week double-blind treatment period
Secondary	
• To evaluate the effect of AMG 301 compared to placebo on the proportion of subjects with at least 50% reduction from the baseline period in monthly migraine days	• At least a 50% reduction from the baseline period in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly acute migraine-specific medication treatment days	• Change from the baseline period in monthly acute migraine-specific medication days in the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly physical impairment domain score as measured by the Migraine Physical Function Impact Diary (MPFID)	• Change from the baseline period in mean physical impairment domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period

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Objectives	Endpoints
• To evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly impact on everyday activities domain score as measured by the MPFID	• Change from the baseline period in mean impact on everyday activities domain scores as measured by the MPFID over the last 4 weeks of the 12-week double-blind treatment period
• To evaluate the safety and tolerability of AMG 301	• Adverse events • Clinical laboratory values and vital signs

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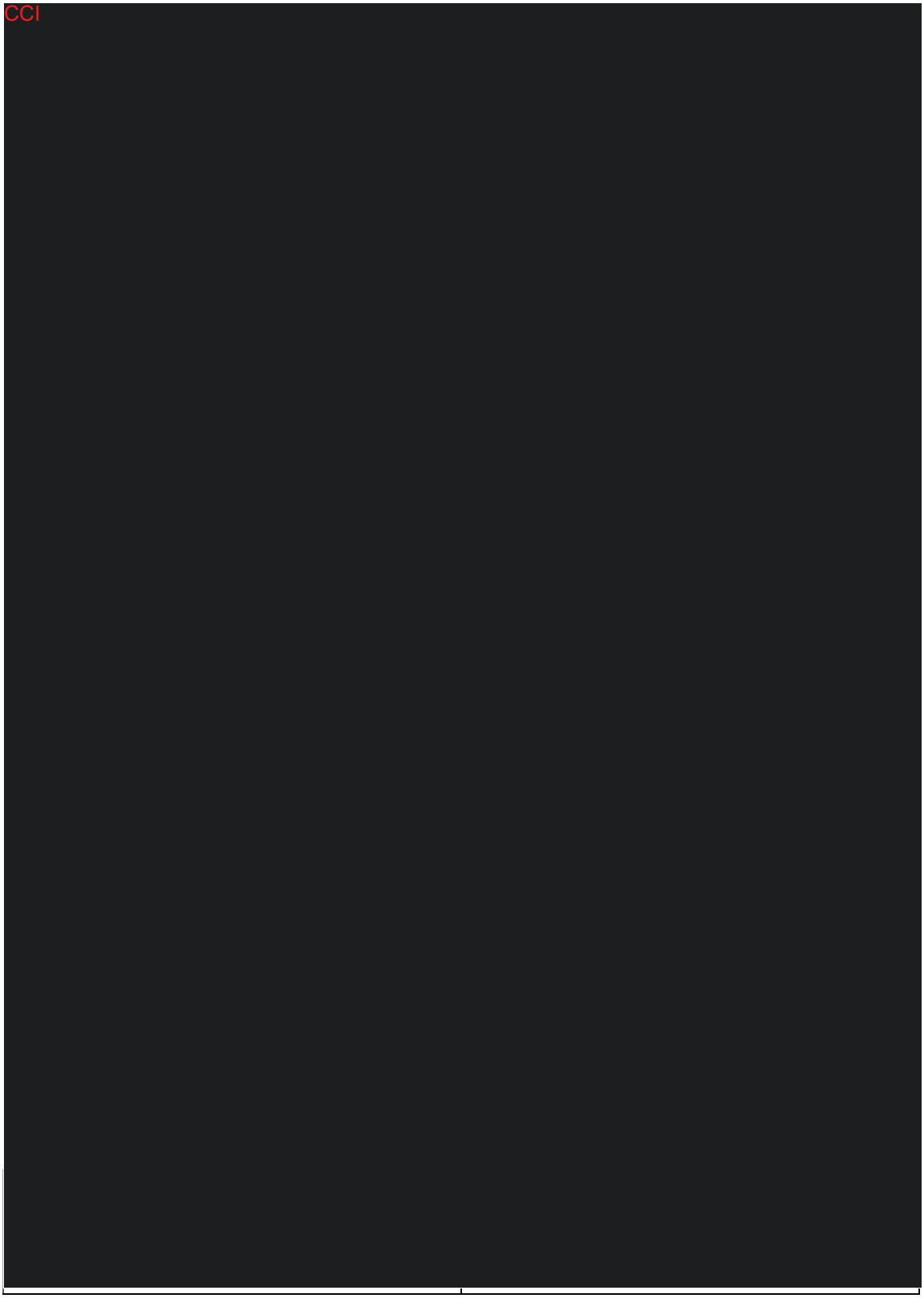

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4.2 Hypotheses

In subjects with migraine, AMG 301 has a greater reduction from the baseline period in monthly migraine days, compared to placebo.

5. Study Design

5.1 Overall Design

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled, 3-arm parallel-group study of subjects with CM or EM. Approximately 335 subjects will be randomized in a 4:3:3 to the following treatment groups: placebo for AMG 301, AMG 301 210 mg via SC injections Q4W, or AMG 301 420 mg via SC injections Q2W, respectively. The randomization will have 2 stratification factors: baseline migraine frequency (CM versus EM) and region (North America versus Rest of World).

Interactive Voice Response (IVR)/Interactive Web Response (IWR) system will be used to facilitate randomization, stratification, and investigational product assignment.

Stratification at Randomization:

Baseline migraine frequency (CM versus EM; limit both CM and EM randomization to approximately 50% of total sample size) and Region (North America versus Rest of World; limit each region to approximately 60%, and limit the other region to approximately 40%).

CM is defined as:

- ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline period based on the electronic diary (eDiary) calculations

EM is defined as:

- < 15 headache days of which at least 4 or more headache days meet criteria as migraine days during the baseline period based on the eDiary calculations

After signing the informed consent form, subjects will enter the screening period. The screening period includes a screening period (up to 3 weeks) followed by a 4-week baseline period. At the day 1 visit (window is +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 baseline period visit date), eligible subjects will be randomized into the 12-week double-blind treatment period and will begin to receive double-blind investigational product. At the week 10 visit, subjects will receive the last dose of treatment with investigational product. At the week 12 visit, subjects will end the double-blind treatment period. A safety follow-up period will be conducted 18 weeks after the last dose of investigational product (16 weeks after the end of the double-blind treatment period). Subjects will use an eDiary every day throughout the baseline period, double-blind treatment period, and safety follow-up period to report information about the migraine and non-migraine headaches and acute medication use. Subjects will have in-clinic study visits Q2W after day 1 through to the week 12 visit and then Q4W.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 335 subjects will be randomized in a 4:3:3 to the following treatment groups: placebo for AMG 301, AMG 301 210 mg SC Q4W, or AMG 301 420 mg SC Q2W.

Assuming a 25% screen failure rate, approximately 670 subjects will be screened, of which approximately 503 will enter the baseline period. From this, it is expected that approximately 35% will fail in the baseline period.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 50 sites will be included. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint, for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for the week 12 assessment or is discontinued from the study.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined when the last subject across all sites 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 18 weeks after the last dose of investigational product, or is discontinued from the study).

5.3.2 Study Duration for Subjects

The planned length of participation for subjects receiving investigational product is approximately 35 weeks, which includes up to a 7-week screening period (up to 3 weeks for screening, 4 weeks for the baseline period), followed by a 12-week double-blind treatment period, and a 16-week safety follow-up period (18 weeks after last dose of investigational product).

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Refer to the AMG 301 Investigator's Brochure for details.

6. Study Population

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). This log may be completed and updated via an IVR/IWR.

Part 1: Eligibility criteria will be evaluated during screening. Subjects must meet Part 1 eligibility criteria to enter the baseline period of screening and a subject is considered enrolled when the investigator decides that the subject has met all Part 1 and Part 2 eligibility criteria. Part 2: Eligibility criteria will be assessed during the baseline period and confirmed before randomizing the subject into the double-blind treatment period.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria Part 1

Subjects are eligible to be included in the baseline period of the study only if all of the following criteria apply:

101 Subject has provided informed consent prior to any study-specific activities/procedures being initiated.

102 Adults ≥ 18 to ≤ 60 years of age at the time of signing the informed consent form.

103 History of migraine (with or without aura) for ≥ 12 months before screening according to the International Headache Society (IHS) Classification ICHD-III (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or patient self-report.

104 Migraine frequency: ≥ 4 migraine days per month on average across the 3 months before screening (refer to Appendix 1 for definition of migraine day)

105 Failed at least 1 medication for prophylactic treatment of migraine due to tolerability or lack of efficacy as determined by the investigator, after an adequate

therapeutic trial at a dose that is used in the prevention of migraine (Refer to Section 7.1.7 for the list of medications used for migraine prophylaxis).

106 Must meet 1 of the following acute migraine-specific treatment criteria:

1. currently taking triptans or ergotamines as acute migraine treatment (within the last month)
2. had previously responded to triptans or ergotamines but had to discontinue due to intolerance
3. unable to take triptans or ergotamines as acute migraine treatments due to contraindications

6.2 Exclusion Criteria Part 1

Subjects are excluded from the study and the baseline period if any of the following criteria apply:

Disease Related

201 Older than 50 years of age at migraine onset.

202 History of cluster headache, hemiplegic migraine headache

203 Unable to differentiate migraine from other headaches

204 Migraine with continuous pain, in which the subject does not experience any pain-free periods (of any duration) during the 1 month before the screening period

Other Medical Conditions

205 Currently diagnosed with chronic pain syndromes (eg, fibromyalgia, chronic back pain, chronic pelvic pain)

206 History of major psychiatric disorder, (such as schizophrenia and bipolar disorder), or current evidence of depression based on a Beck Depression Inventory II (BDI-II) total score > 19 at screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if the investigator considers the subject to be stable (with BDI-II ≤ 19) and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 2 months before the start of the baseline period.

207 History of seizure disorder or other significant neurological conditions other than migraine. Note: A single childhood febrile seizure is not exclusionary.

208 Malignancy within the 5 years before screening, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ.

209 Known human immunodeficiency virus infection by history

210 Hepatic disease by history or total bilirubin ≥ 1.5 x upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.0 x ULN, as assessed by the central laboratory at screening.

211 Glycosylated hemoglobin (HbA1c) ≥ **6.0**% at screening

212 **Serum plasma** glucose **level** ≥ 100 mg/dL at screening**; ideally performed while fasting**

213 History of diabetes mellitus or history of impaired fasting glucose

214 Body mass index (BMI) ≤ 18.0 or ≥ 40 at screening

215 Poorly controlled hypertension (systolic blood pressure 150 mmHg and/or diastolic blood pressure 90 mmHg or greater)

216 Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months before screening

217 History or evidence of any other unstable or clinically significant medical condition that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

218 Subject has any clinically significant vital sign, laboratory, or electrocardiogram (ECG) abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation

219 Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening.

220 Evidence of drug or alcohol abuse or dependence within 12 months before screening, based on medical records, subject self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids, **or** barbiturates).

Prior/Concomitant Therapy

221 No therapeutic response with > 3 of the following 8 medication categories for prophylactic treatment of migraine after adequate therapeutic trial. These medication categories are:

- Category 1: Divalproex sodium, sodium valproate
- Category 2: Topiramate
- Category 3: Beta blockers (eg, atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Category 4: Tricyclic antidepressants (eg, amitriptyline, nortriptyline, protriptyline)
- Category 5: Serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 6: Flunarizine, verapamil
- Category 7: Lisinopril, candesartan
- Category 8: OnabotulinumtoxinA

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment.

The following scenarios do not constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

222 Used a prohibited medication, device or procedure before the start of the baseline period (Refer to Section 7.1.7 for the list of these excluded treatments and the timeframes before the start of the baseline period)

223 Taken opioid (including codeine) or butalbital-containing analgesics or other narcotics (including tramadol, Fiorinal, Fioricet) on ≥ 4 days per month for any indication in any month during the 2 months before the start of the baseline period

224 Anticipated to require any excluded medication, device or procedure during the study (Refer to Section 7.1.7 for the lists of these medications, devices and procedures)

225 Subjects **taking** medications listed in Section 7.1.7 for at least 2 months before the start of the baseline period (at least 4 months before baseline for botulinum toxin [head and/or neck region] and mABs targeting CGRP).

Prior/Concurrent Clinical Study Experience

226 Currently receiving treatment in another investigational device or drug study, or less than 90 days before screening since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

227 Pregnant or breastfeeding, or is a female expecting to conceive during the study, through 18 weeks after the last dose of investigational product

228 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with AMG 301 through 18 weeks after the last dose of investigational product.

Refer to Appendix 5 for additional contraceptive information.

229 Subject has known sensitivity to any of the products or components to be administered during dosing (refer to Investigational Product Instruction Manual [IPIM] for details).

230 Previously randomized in an AMG 301 study

231 Member of investigational study center staff or relatives of the investigator

232 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, independent completion of eDiary items) to the best of the subject and investigator's knowledge.

233 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Inclusion Criteria Part 2

Subjects are eligible to be included in the study only if all of the following criteria apply:

107 Must meet the one of the following migraine criteria:

CM is defined as:

- ≥ 15 headache days of which ≥ 8 headache days meet criteria as migraine days during the baseline period based on the electronic diary (eDiary) calculations

EM is defined as:

- < 15 headache days of which at least 4 or more headache days meet criteria as migraine days during the baseline period based on the eDiary calculations

108 Demonstrated at least 80% compliance with the eDiary (for example, completing eDiary items for at least 23 out of 28 days during the baseline period)

6.4 Exclusion Criteria Part 2

Subjects are excluded from the study if any of the following criteria apply:

234. Used a prohibited medication, device or procedure during the baseline period (Refer to Section 7.1.7 for the list of these excluded treatments and the timeframes)

235. Received botulinum toxin in the head and/or neck region during the baseline period

236. Taken opioid- or butalbital-containing analgesics or other narcotics (including tramadol, Fiorinal, Fioricet) on ≥ 4 days per month for any indication in any month during the baseline period

237. Subject has a history or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behavior based on an assessment with the C-SSRS at baseline

6.5 Lifestyle Restrictions

6.5.1 Meals and Dietary Restrictions

Not applicable.

6.5.2 Caffeine, Alcohol, and Tobacco

Not applicable.

6.5.3 Activity

Not applicable.

6.6 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, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered eligible for participation in the baseline period if the subject meets all screening eligibility criteria (Part 1).

Upon completion of the baseline period procedures, the subject is evaluated by the investigator, and if the subject meets all Part 2 eligibility criteria the subject is subsequently randomized to a treatment regimen.

A subject is considered enrolled when the investigator decides that the subject has met all Part 1 and Part 2 eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (screening period starts when the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IVR/IWR. 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.

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.

The screening period must not exceed 7 weeks (screening up to 3 weeks followed by a 4-week baseline period), except after consultation with and approval by Amgen. Amgen may grant such approval in cases for which additional time is required to confirm eligibility.

A subject who is determined to be ineligible must be registered as a screen fail in the IVR/IWR System.

6.7 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Investigators may re-screen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved before or during a repeat screening attempt. Reasons to re-screen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically-appropriate supplementation. (Note: Before screen failing and then re-screening the subject, efforts should be made to repeat the laboratory assessment(s) during the original screening period);
- The subject has a medical condition that can be stabilized or resolved before the repeat screening attempt;

  OR
- Additional time is required after the subject's last dose of an excluded medication.

Investigators are encouraged to consult with Amgen before re-screening subjects for other reasons.

A subject must provide informed consent before the initiation of any re-screening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. The subject is entered into re-screening in the IVR/IWR System, and all screening procedures must be repeated except as noted in the inclusion/exclusion criteria. A subject may be screened up to 2 times (ie, no more than 1 re-screen).

Near to the end of randomization, study centers may be notified when no additional subjects will be screened or re-screened.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 301	Placebo
Dosage Formulation	AMG 301 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL of AMG 301. AMG 301 is formulated with C mM sodium acetate, C % (w/v) sucrose, CCI % polysorbate 80, at pH CC.	Placebo will be presented in identical containers, stored/packaged the same as AMG 301. Placebo is composed of C mM sodium acetate, CC% (w/v) sucrose, CCI % polysorbate 20, at pH CC.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	• AMG 301 420 mg Q2W will receive a total of 6 AMG 301 injections (70 mg/mL) at day 1, and weeks 2, 4, 6, 8, and 10. • AMG 301 210 mg Q4W will receive a total of 3 AMG 301 injections (70 mg/mL) plus 3 matching placebo Q4W (day 1, weeks 4, and 8). Subjects randomized to AMG 301 210 mg Q4W will also receive 6 SC placebo injections on weeks 2, 6, and 10.	Placebo will receive 6 SC placebo injections at day 1, and weeks 2, 4, 6, 8, and 10.
Route of Administration	SC injections administered within 30 minutes. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Refer to the IPIM for investigational product administration details.	
Accountability	The quantity, start date, start time, injection site, and box number(s) of investigational product are to be recorded on each subject's CRF.	
Dosing Instructions	On days where the first and second dose are administered, study center staff are to observe the subject for at least 120 minutes after the last injection of investigational product. On later days, when dose is administered, study center staff are to observe the subject for at least 60 minutes after the last injection of investigational product. Investigators can retain subjects for longer if there is any sign of discomfort any time following AMG 301 administration.	

Abbreviations: IPIM = Investigational Product Instruction Manual; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous
[a] AMG 301 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

AMG 301 and placebo will be considered as Amgen investigational product.

The investigational product doses are fixed and will not be adjusted for individual subjects during the study.

During the double-blind treatment period, 6 SC injections will be administered at day 1, weeks 2, 4, 6, 8, and 10. All 6 SC injections are to be administered within 30 minutes. Subjects randomized to:

- AMG 301 420 mg Q2W will receive a total of 6 AMG 301 injections (70 mg/mL) at day 1, and weeks 2, 4, 6, 8, and 10.
- AMG 301 210 mg Q4W will receive a total of 3 AMG 301 injections (70 mg/mL) plus 3 matching placebo Q4W (day 1, weeks 4, and 8). Subjects randomized to AMG 301 210 mg Q4W will also receive 6 SC placebo injections on weeks 2, 6, and 10.
- Placebo will receive 6 SC placebo injections at day 1, and weeks 2, 4, 6, 8, and 10.

On days where the first and second dose are administered, study center staff are to observe the subject for at least 120 minutes after the last injection of investigational product. On later days when dose is administered, study center staff are to observe the subject for at least 60 minutes after the last injection of investigational product. Investigators can retain subjects for longer if there is any sign of discomfort any time following AMG 301 administration. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Refer to the IPIM for administration details.

Only authorized investigational study center study staff members are to administer Amgen investigational product.

7.1.2 Non-investigational Products

Not applicable.

7.1.3 Medical Devices

Sterile syringes will be used in this study. Authorized study staff will use the syringes to pull out investigational product from the vials in the subject's assigned kit and administer the investigational product to the subject. Refer to the IPIM for syringe details.

Medical devices (eg, syringes, alcohol prep pads) that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

7.1.4 Other Protocol-required Therapies

Not applicable.

7.1.5 Other Treatment Procedures

Not applicable.

7.1.6 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(s) or device(s) 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(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following medications are excluded throughout the study:

- divalproex sodium, sodium valproate, topiramate, carbamazepine, or gabapentin
- all beta blockers (eg, metoprolol, propranolol, timolol, atenolol, nadolol, nebivolol, pindolol, bisoprolol)
- all tricyclic antidepressants (eg, amitriptyline, nortriptyline, protriptyline)
- flunarizine or verapamil
- serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine, duloxetine or milnacipran)
- OnabotulinumtoxinA (injected in the head and/or neck region)
- lisinopril
- candesartan

- clonidine or guanfacine
- cyproheptadine
- methysergide
- pizotifen
- butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- monoclonal antibodies targeting CGRP or CGRP receptor
- **cannabinoids**

Subjects also must have been free from these medications for at least 2 months before the start of the baseline period (at least 4 months before screening for botulinum toxin and monoclonal antibodies targeting the CGRP system).

The following medications are excluded only if used daily throughout the month for migraine prophylaxis:

- fluoxetine, fluvoxamine
- acetazolamide
- picotamide
- cyclandelate
- ergot-derivatives, steroids, triptans
- nicardipine, nifedipine, nimodipine

If the above medications are used daily for migraine prophylaxis, subjects must have been free from these medications for at least 2 months before the start of the baseline period and throughout the study.

Investigational drugs, devices, or procedures (eg, acupuncture, occipital stimulator, and transcranial magnetic stimulation) are excluded throughout the study.

7.2 Method of Treatment Assignment

Eligible subjects will be randomized in a 4:3:3 allocation to 1 of 3 treatment groups: placebo for AMG 301, AMG 301 210 mg SC injections Q4W, or AMG 301 420 mg SC injections Q2W, respectively. The randomization will be stratified by CM versus EM and North America versus Rest of World.

Randomization will be based on a generated by Amgen before the start of the study and will be centrally executed using the IVR/IWR System. The subject, study center personnel, and Amgen study personnel and designees will be blinded to the randomization treatment group assignment.

7.3 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation, as applicable.

7.3.2 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 is not to 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 7.3.1). However, the external team members outside of the study team will be unblinded to conduct interim analyses (refer to Section 10.4.1.1). Otherwise, if unblinding occurs, only the subject and investigators will have access to what investigational product treatment was received and Amgen will not have access to this information.

Individual subject treatment assignments will be maintained by the IVR/IWR System. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

Staff from Clinical Supply Chain, Biological Sample Management, PK and Drug Metabolism, Clinical Immunology, Department of Molecular Sciences and Computational Biology, Safety, internal team, and Global Biostatistical Science departments who are responsible for tracking, assaying, or analyzing biological samples during the conduct of this study are considered to be unblinded to the treatment assignments in this study. These individuals will not have access to subject level clinical data apart from the samples they are assaying and analyzing during the course of the study.

7.4 Dose Modification

7.4.1 Hepatotoxicity Stopping Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.4.2 Dose-cohort Study Escalation/De-escalation and Stopping Rules

Not applicable.

7.4.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.3.1 Amgen Investigational Product: AMG 301

At any time during the study, the investigator may discontinue investigational product administration for any subject who experiences a severe or life-threatening adverse event reported by the investigator to be related to investigational product. Refer to Section 9.2.3.1 for details regarding adverse event reporting.

Subjects who discontinue investigational product during the double-blind treatment period are to continue to fill out the daily eDiary and to return for all other study procedures and measurements until the end of the double-blind treatment period.

End of investigational product and early discontinuation from investigational product are to be registered in the IVR/IWR System.

The reason for dose change of AMG 301 is to be recorded on each subject's CRF(s).

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

7.6 Treatment Compliance

Administration of investigational product will be conducted at sites during scheduled visits.

7.7 Treatment of Overdose

Overdose with this product has not been reported.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 90 days before the start of the baseline period through the baseline will be collected. In addition to this, the complete history of the subject's migraine prophylactic medication and acute migraine-specific medications

(triptans and ergotamine-derivatives, alone or in combination) will be collected along with the determination of adequate therapeutic trial and the reason for discontinuation.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from signing the informed consent through the end of safety follow-up period.

During the screening period, the subject and investigator are to agree on the acute headache medications and the appropriate dose(s) that the subject may take on an as-needed basis throughout the study. To avoid confounding the study results, efforts should be made to not introduce new acute migraine medications during the study.

Acute medications taken during aura or to treat headache will be collected in the eDiary, and data will include the medication name, date of administration, time of administration, dose, and route of administration. The acute headache medications reported in the eDiary will also be collected in the CRF, but data will include only the drug name, indication, and start and stop dates as-needed use (not the individual administration dates). Other concomitant therapies will be collected in the CRF, and data will include the generic drug name/treatment, indication, and dates of administration.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for

continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

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 Appendix 3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request

8.2 Discontinuation From the Study

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, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for

data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor (other than subject request, safety concern, lost to follow-up)
- Withdrawal of consent from study
- Death
- Lost to follow-up
- Safety concern

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1). All study procedures for a given study visit are to be completed on the same day.

As protocol waivers or exemptions for inclusion/exclusion are not allowed, if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

9.1.1.1 Screening Period and Baseline Period

9.1.1.1.1 Screening Period

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IVR/IWR and screen the subject in order to assess eligibility for participation. The screening period is up to 7 weeks, which consists of an initial screening period of up to 3 weeks and a baseline period of 4 weeks.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IVR/IWR and subsequently registered as rescreens. Once the subject is registered as rescreened, a new day/week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

9.1.1.1.2 Baseline Period

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to Section 6.1) and is entered in the baseline period (refer to Section 6.6) and ends when the subject is considered a screen failure (discontinuation before randomization and/or subject does not meet all baseline eligibility criteria, refer to Section 6.3) or randomized.

9.1.1.2 Randomization

After meeting all Part 1 and Part 2 eligibility criteria, a subject will be randomized to treatment assignment and is eligible for participation in the double-blind treatment period if the subject meets baseline eligibility criteria. The day 1 visit (randomization day) window is +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 baseline period visit date.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 2 days. The date of the first dose of protocol-required therapy is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date and will occur Q2W or Q4W.

During the double-blind treatment period, 6 SC injections will be administered at day 1, weeks 2, 4, 6, 8, and 10. All 6 SC injections are to be administered within 30 minutes during each visit that it is required. Subjects randomized to:

- AMG 301 420 mg Q2W will receive of a total of 6 AMG 301 injections (70 mg/mL) at day 1, and weeks 2, 4, 6, 8, and 10
- AMG 301 210 mg Q4W will receive a total of 3 AMG 301 injections (70 mg/mL) plus 3 matching placebo Q4W (day 1, weeks 4, and 8). Subjects randomized to AMG 301 210 mg Q4W will also receive 6 SC placebo injections on weeks 2, 6, and 10
- Placebo will receive 6 SC placebo injections at day 1, and weeks 2, 4, 6, 8, and 10.

9.1.3 Safety Follow-up

A safety follow-up period will be conducted 18 weeks after the last dose of investigational product (16 weeks after the end of the double-blind treatment period).

Upon early discontinuation from study treatment for any reason, a general safety follow-up visit will be performed approximately 30 (± 5) days after the end of the last dosing interval of investigational product.

9.1.4 Long-term Follow-up

Not applicable.

9.1.5 Early Termination

Subjects who early terminate the study before week 12 should complete the week 12/early termination (ET) assessments (Table 2-1).

Subjects who early terminate the study after week 12 and before week 28 should complete the week 28/end-of-study (EOS)/ET assessments (Table 2-1).

9.1.6 End of Study

Subjects who reach week 28 will end the study and complete all week 28 EOS/ET assessments according to Table 2-1.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex (male, female), age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study biomarkers, variability, and PK of the investigational product.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical history including targeted medical cardiologic, neurologic, psychiatric, cardiovascular, history of diabetes, including gestational diabetes and/or impaired glucose tolerance testing, and reproductive status. For female subjects who are premenopausal, start date of menses for each month should be collected. The current Common Terminology Criteria for Adverse Events (CTCAE) will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

Physical examination (including neurologic exam) will be performed as per standard of care. Physical examination findings should be recorded (eg, medical history, event).

Any clinically significant anomalies noted during the screening period are to be detailed in Medical History. Investigators are to check for any findings that would constitute study exclusion.

9.2.1.5 Physical Measurements

Height (screening only) and weight should be measured without shoes.

Body Mass Index should be calculated using the following formula:
BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol and tobacco.

9.2.1.7 Performance Status

Not applicable.

9.2.1.8 Clinician Assessments

9.2.1.8.1 Cranial Autonomic Parasympathetic Symptom Scale

The CAPS Scale is a 5-item questionnaire that assesses whether migraine subjects experience each of the following 5 CAPS based on the ICHD, third edition beta (ICHD-IIIb), with headaches. These CAPS consist of the following items; 1) lacrimation, 2) conjunctival injection, 3) eyelid edema, 4) sensation of fullness in the ear and 5) nasal congestion and/or rhinorrhea. Each CAPS (eg, consider all headaches experienced over the past 4 weeks) is graded as either 0 (absent), 1 (present but mild) or 2 (present and conspicuous). The score in this CAPS scale ranges from 0 to 10 points (Riesco et al, 2016).

The CAPS scale will be administered by **a clinician (ie, primary investigator or delegate)** as described in Table 2-1.

9.2.1.9 Subject Completed Assessments

9.2.1.9.1 Modified Migraine Disability Assessment Questionnaire

The modified MIDAS Questionnaire is a 5-item self-administered questionnaire that sums the number of productive days lost over the past month in 2 settings: the workplace and the home. The MIDAS also assesses disability in family, social, and leisure activities. The MIDAS score is the sum of missed days due to a headache from paid work, housework, and non-work (family, social, leisure) activities; and days at paid work or housework where productivity was reduced by at least half.

The score is categorized into 4 severity grades: Grade I = 0 to 5 (defined as minimal or infrequent disability), Grade II = 6 to 10 (mild or infrequent disability), Grade III = 11 to 20

(moderate disability), and Grade IV = 21 and over (severe disability). Two other questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain intensity.

The recall period is the past 1 month.

Subjects will complete the MIDAS using the eDiary at the clinical assessment visit.

9.2.1.10 Beck Depression Inventory-II

The BDI-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: Minimal depression (0 to 13), mild depression (14 to 19), moderate depression (20 to 28), and severe depression (29 to 63).

Subjects will complete the BDI-II using a paper form.

9.2.1.11 Headache Impact Test

The HIT-6 is a short-form self-administered questionnaire based on the Internet-HIT-6 question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a subject's clinical status over a short period of time. Six questions cover severe pain, limitation of daily activity (household, work, school and social), wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling "fed up" or irritated because of headache, and headache limiting ability to concentrate or work on daily activities. Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always."

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores are categorized into 4 grades, representing little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78) due to headache. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.

Subjects will complete the HIT-6 using the eDiary at the clinical assessment visit.

9.2.2 Efficacy Assessments

9.2.2.1 Clinical Outcomes Assessments and Electronic Diaries (eDiaries)

The **Clinical Outcome Assessments (**COAs**)** will be collected by subjects using a handheld eDiary at various frequencies. The eDiary will collect the following COAs daily at home:

- date and time of start of headache (ie, migraine or non-migraine headache)
- date and time of end of each headache
- worst pain severity per headache
- pain features (eg, 1-sided, throbbing, worsens with exercise/physical activity)
- symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute medications (medication name [from pre-entered list] date of dosing, number of times taken of each date, number of units taken)

Study center staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's eligibility to enter the baseline period). The study center staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit. At the day 1 study visit the investigator will use the subject's eDiary to review all data entered during the baseline period and confirm the relevant inclusion and exclusion criteria.

The subject's eDiary will also be used for the completion of the following patient-reported outcomes (PROs) measures:

- MPFID, daily at home
- HIT-6, monthly in clinic
- Modified MIDAS questionnaire, monthly in clinic

Refer to the eDiary manual for details.

9.2.2.2 Migraine Physical Function Impact Diary

The MPFID has 2 domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and 1 stand-alone global question that provides an assessment of the overall impact of migraine on subjects' everyday activities. The recall period for each item is the past 24 hours.

A subjects' response to the difficulty of an item is measured using a 5-point scale, with difficulty measurements ranging from without any difficulty (1) to unable to do (5).

Response to the frequency with which items occur ranges from none of the time (1) to all of the time (5). For each domain, the scores will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 100 scale, with higher scores representing greater impact of migraine (ie, higher burden). There will be a score for each of the 2 domains and a third score for the stand-alone item.

Subjects will complete the MPFID every day using the eDiary.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Table 2-1.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Migraine and headache are study disease-related events and thus should not be routinely reported as (serious) adverse events unless assessed to be more severe than expected for the subject. Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through 18 weeks after the last dose of investigational product (EOS) are reported using the Event CRF.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

Disease-related events pre-defined for this study include: migraine and headache and should not be routinely reported as (serious) adverse events unless assessed to be more severe than expected for the subject.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE Version 4.0 or the Amgen Adverse Event Grading Scale and is described in Appendix 4.

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

9.2.3.1.1.3 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 the end of the safety follow-up visit (18 weeks after last dose of investigational product or EOS) are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 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. Per local requirements in some countries, 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 and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.1.5 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (eg, adverse events, clinical laboratory values, and vital signs) that are study endpoints are reported on the Event CRF.

9.2.3.1.1.6 Serious Adverse Events That Are Not to be Reported by the Sponsor to Regulatory Agencies in an Expedited Manner

Not applicable.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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. Aggregate analyses may also be unblinded by the Safety Assessment Team (SAT) as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and until 18 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.2 Vital Signs

The following measurements must be performed: Systolic/Diastolic Blood Pressure, Heart Rate, Respiratory Rate, and Temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

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. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. Study centers will use ECG equipment supplied by the central vendor. It is the responsibility of the investigator to determine if the ECG tracings are consistent with a

subject's safe participation in the study. The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. The central reader will review all ECGs. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

Any ECG abnormality noted by the central reader must be evaluated by the investigator and discussed with the Amgen Medical Monitor as deemed necessary to determine if the ECG finding is representative of an unstable or clinically significant medical condition.

Refer to the central ECG reader manual for details.

9.2.3.4 Vital Status

Not applicable.

9.2.3.5 Suicidal Risk Monitoring

9.2.3.5.1 Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items, which defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered to study subjects at time points specified in Table 2-1 possible suicidal ideation and behavior. Reports of suicidal ideation with intent to act (severity of 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.

9.2.3.6 Other Safety

Not applicable.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

Laboratory assessments listed in Appendix 7 will be performed by the local laboratory.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine 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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

9.2.4.1 Pregnancy Testing

A high sensitivity (serum) pregnancy test should be completed at screening and a urine pregnancy test at pre-randomization on day 1 prior to the initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

Additional pregnancy testing should be performed per Table 2-1 and at the end of study or early termination.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.4.2 Prespecified Biomarker Assessments

Not applicable.

9.2.4.3 Hepatitis Assessment

If a hepatic event is suspected during the study, hepatitis testing will be performed on a blood sample collected and stored during screening and a blood sample collected during the event (refer to Appendix 7). Hepatitis testing will be performed by the central laboratory.

The following laboratory testing will be performed:

- Hepatitis B surface antigen (HepBsAg) and total hepatitis B core antibody (HepBcAb)
- hepatitis B Virus DNA Real-Time polymerase chain reaction will be only performed if total HepBcAb is positive and HepBsAg is negative
- hepatitis C virus antibody
- hepatitis C Virus RNA Real-Time polymerase chain reaction will be only performed if hepatitis C virus antibody is positive

9.2.5 Pharmacokinetic Assessments

During the study visits at which investigational product is administered, the investigator will administer the investigational product to the subject after the PK sample has been collected.

All subjects randomized, enrolled to the double-blind treatment will have PK samples assessed.

Serum samples of approximately 1 mL will be collected for measurement of serum concentrations as specified in the Schedule of Activities (Table 2-1). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.2.6 Pharmacodynamic Assessments

Not applicable.

9.2.7 Pharmacogenetic Assessments

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, migraine), neurological diseases, and/or AMG 301 immunogenicity, and/or in the identification of subjects who may have positive or negative responses to AMG 301. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

The final disposition of samples will be described in Appendix 6.

9.2.8 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Table 2-1) for the measurement of anti-AMG 301 binding antibodies. Samples testing positive for binding antibodies may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained to evaluate any anti-AMG 301 antibody mediated impact on safety, PK and/or PD, and efficacy during the study. Subjects who test positive for binding antibodies and have clinical sequelae that are considered

potentially related to an anti-AMG 301 antibody response may be asked to return for additional follow-up testing.

9.2.9 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 301 to investigate and further understand the CM or EM.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (Table 2-1).

9.2.10 Clinical Outcome Assessments

Refer to Section 9.2.2.1 for COAs details.

9.2.11 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9.2.12 Optional Substudies

Not applicable.

9.2.13 Other Assessments

Not applicable.

10. Statistical Considerations

10.1 Sample Size Determination

CCI

[redacted]

CCI

[redacted]

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Full Analysis Set

The Full Analysis Set (FAS) consists of all subjects who were enrolled in the study. The FAS will be used to tabulate subject disposition, demographic data, baseline disease characteristics, and important protocol deviations for all enrolled subjects.

10.2.1.2 Primary Analysis Set

The Primary Analysis Set (PAS), also known as the efficacy analysis set, will be used to carry out the primary analyses of the efficacy endpoints. It consists of all subjects who were enrolled, randomized, received at least 1 dose of investigational product, and have at least 1 postbaseline monthly eDiary measurement. Subjects will be analyzed according to their randomized treatment group, regardless of treatment received. The PAS will be used to analyze all efficacy and PRO endpoints.

10.2.1.3 Safety Analysis Set

The Safety Analysis Set (SAS) consists of all enrolled subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire double-blind treatment period. Analyses for safety endpoints and summary of investigational product administration will use this analysis set.

10.2.2 Covariates

The baseline covariates are:

- age (categorical: < median, ≥ median)
- region (categorical: North America, Rest of World)
- race (categorical: white, other)
- sex (categorical: female, male)
- acute medication overuse (categorical: yes, no)
- baseline period monthly migraine days (continuous, days)
- baseline period monthly migraine attacks (continuous, number)
- baseline period monthly headache days (continuous, days)
- acute migraine medications selected for on-study use (categorical: yes, no)
- treatment with migraine prophylactic medication(s) before entry into screening (categorical: yes, no)
- duration of disease (continuous, years)

Other covariates may be evaluated as necessary.

For monthly migraine and non-migraine headache related variables, the subject baseline values will be summarized from the entire baseline period. For the rest of the variables, the baseline value is the last non-missing assessment taken before the first investigational product administration.

Region (North America versus Rest of World) and baseline migraine frequency (CM versus EM) will be included in the models as stratification factors.

The impact of the baseline covariates on the treatment effect may be explored and adjusted in the model for the primary and secondary endpoints as deemed necessary as a secondary analysis.

10.2.3 Subgroups

The primary and secondary endpoints may also be explored using subgroup analyses of age (< median age, ≥ median age), sex (female, male), race (White, Other), and region (North America, Rest of World), medication overuse (Yes, No), prior migraine prophylactic treatments and other subgroup variables (EM versus CM) as deemed appropriate.

Stratification at Randomization:

Baseline Migraine Frequency (CM versus EM; limit EM randomization to approximately 50% of total sample size) and Region (North America versus Rest of World, limit each

region to approximately 60% and limit the other region to approximately 40% of total sample size).

10.2.4 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, most of the efficacy endpoint will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe what will be done when a data point is missing.

In general, the PAS will be used without any imputation for missing data for the primary and secondary endpoints, except for proration performed for the eDiary measurements, as described below. The sensitivity analyses for both primary and secondary analyses will use non-responder imputation for categorical endpoints and last observation carried forward analyses for the continuous endpoint.

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches and missing daily scores of impairment day based on MPFID will be handled based on the degree of completion during the month.

For the eDiary, if at least 14 out of 28 monthly days are not missing, then the monthly frequency measurements (eg, migraine days, headache days, migraine attacks) will be prorated based on the number of days with available information using the following formula:

Number of observed migraine days *28/Number of information days in interval, where an information day is a diary day or headache day.

For each MPFID daily diary domain, if greater than 50% of the items within a domain are not missing, the mean of the item scores that are present for that day will be used to impute a score for the missing item(s). Otherwise, no domain score will be calculated; the domain score will be considered missing.

Missing COAs and subject-completed assessments (eg, HIT-6, MIDAS) scheduled to be collected at office visit at certain assessment will not be imputed.

Missing safety endpoints and antibody data will not be imputed, except for adverse event dates as described in Section 10.2.4.1.

10.2.4.1 Missing and Incomplete Dates

Missing or incomplete dates will be listed unless imputed as follows:

Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

	Missing	Imputation	Exception
Start date (Adverse event, concomitant medication)	Day	01	Default to Study Day 1 if an adverse event starts the same year and month as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month	01 JAN	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month/Year	No imputation	

10.3 Adaptive Design

Not applicable.

10.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.4.1 Planned Analyses

10.4.1.1 Interim Analysis

After about 50% of the subjects have been enrolled into the double-blind treatment period, multiple independent, unblinded interim analyses will be performed for administrative purposes for future study planning and development based on the interim effect size results for the primary endpoint. This study will not be modified based on the interim effect size results. The maximum number of interim analyses will be no more than 5.

The administrative analysis will be conducted by an independent group that is internal to Amgen (eg, Global Development Lead/Clinical Therapeutic Area Head and 2 statisticians) and separate from the study team; the study team will remain blinded to the specific results. Subject level treatment group assignment will only be available to Amgen personnel who comprise the external team until the study has been unblinded for primary analysis.

The primary endpoint (ie, change from baseline period in monthly migraine days) and the following secondary endpoints will be included: 50% reduction in monthly migraine days and change from baseline period in monthly acute migraine-specific medication days.

10.4.1.2 Primary Analysis

The objective of the primary analysis will be to test the primary efficacy endpoint once the primary completion milestone is achieved after the last subject reaches the last visit in the double-blind period, and all data are collected for the primary endpoint. At this time, the study will be unblinded and all efficacy and safety analyses will be conducted and reported by treatment group.

The primary analysis will also be conducted to evaluate the efficacy and safety of AMG 301 in subjects with CM or EM, compared to placebo. The following hypothesis for the primary endpoint will be tested for each AMG 301 treatment group (420 mg SC injections Q2W, 210 mg SC injections Q4W) compared to placebo using the generalized linear mixed effects model:

- Clinical Hypothesis: In subjects with CM or EM, AMG 301 reduces from the baseline period the monthly migraine days, compared to placebo

To maintain a family-wise type I error at 0.10 for the testing of the primary endpoint, the pair-wise comparison will be tested for both (1) AMG 301 420 mg SC injections Q2W versus placebo and (2) AMG 301 210 mg SC injections Q4W versus placebo, each at an alpha of 0.05.

10.4.1.3 Final Analysis

The final analysis will be completed after study completion is reached, after the last subject reaches the last visit during the safety follow-up period, and all data are collected for the study.

10.4.2 Data Review Team (DRT)

An independent Data Review Team (DRT) will review and make recommendations regarding the safety of the study participants throughout the double-blind treatment phase and until treatment assignment is unblinded to the study team. The DRT will be composed of Amgen staff that are external to the study team and will include a clinician, a safety physician, and a biostatistician. Summaries of data at the treatment group level will be prepared and presented by an independent biostatistician at the DRT meeting. A study DRT charter will be developed to guide membership, procedures, and meeting timing.

10.4.3 Methods of Analyses

10.4.3.1 General Considerations

The primary objective of this study is to evaluate the effect of AMG 301 compared to placebo on the change from the baseline period in monthly migraine days, in subjects with CM or EM.

Summary statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% confidence intervals of the means (confidence intervals will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

Details of all statistical methods will be provided in the Statistical Analysis Plan.

10.4.3.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, change in monthly migraine days from the baseline period to the last 4 weeks of the 12-week double-blind treatment period, will be analyzed using the generalized linear mixed effects model, adjusting for baseline values and stratification factors using the PAS without any imputation for missing data. The primary endpoint will be tested for each AMG 301 treatment group (AMG 301 420 mg SC injections Q2W and AMG 301 210 mg SC injections Q4W) compared to the placebo group using appropriate contrasts for pairwise comparisons. Each AMG 301 dose will be compared to placebo at an alpha of 0.05 to maintain the family-wise type I error at 0.10. The mean change from the baseline period for each treatment group, and the treatment difference, 95% confidence intervals, and p-values will be reported. Sensitivity analyses for the primary endpoint include subgroup analyses and an analysis of covariance model using data through week 12 data, in which missing values will be imputed by the last observation carried forward up to week 12.
Secondary	• At least a 50% reduction from the baseline period in monthly migraine days in the last 4 weeks of the 12-week double-blind treatment period: Comparison between treatment arms will be performed using a generalized linear mixed effects model on observed data, adjusting for baseline values and stratification factors with appropriate contrasts for pairwise comparisons. The odds ratio for each AMG 301 treatment group versus placebo group, associated 95% confidence intervals, and nominal p-values will be reported. Sensitivity analyses for response include: a logistic regression model using data through week 12, adjusting for baseline values where missing values will be imputed as non-responders. • Change from the baseline period on monthly acute migraine-specific medication days in the last 4 weeks of the 12-week double-blind treatment period: The same analysis methods will be used as for the primary endpoint.
CCI	[redacted]

10.4.3.3 Safety Analyses

10.4.3.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	For safety endpoints, data for all enrolled subjects who received at least 1 dose of investigational product (ie, SAS) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose the entire period of interest (period or study). The Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later will be used to code all adverse events to a system organ class and a preferred term. All adverse events will be graded using the CTCAE Version 4 or the Amgen Adverse Event Grading Scale and is described in Appendix 4. All adverse event tables will be summarized by treatment group. Subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events. Adverse events will be tabulated by system organ class and preferred term in alphabetical order. In addition, subject incidence of all treatment-emergent adverse events and serious adverse events will be tabulated by system organ class, preferred term and CTCAE grade in alphabetical order. Subject incidence of all treatment-emergent adverse events and serious adverse events will also be tabulated by preferred term in descending order of frequency. No statistical testing comparing treatment groups will be performed for the safety analyses. Descriptive statistics will be provided for all safety endpoints.

10.4.3.3.2 Adverse Events and Disease-related Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided. Subject incidence of disease-related events, fatal disease-related events, and device-related events, if applicable, will be tabulated by system organ class and preferred term.

10.4.3.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group. Shifts in grades of safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group.

10.4.3.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group. Shifts in vital sign values between the baseline and the worst on-study value will be tabulated by treatment group.

10.4.3.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics over time by treatment group.

10.4.3.3.6 Electrocardiogram

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other studies.

10.4.3.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 301 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

10.4.3.3.8 Exposure to Investigational Product

The total dose of investigational product and the proportion of subjects receiving each dose level will be summarized using descriptive statistics.

10.4.3.3.9 Exposure to Other Protocol-required Therapy

Not applicable.

10.4.3.3.10 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest (eg, triptan and ergotamine use) will be summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug dictionary.

10.4.3.4 Other Analyses

Not applicable.

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12. Appendices

Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
AST	aspartate aminotransferase
BDI-II	Beck Depression Inventory - II
BMI	body mass index
cAMP	Cyclic Adenosine Monophosphate
CAPS	Cranial Autonomic Parasympathetic Symptom
CFR	Code of Federal Regulations
CGRP	Calcitonin gene-related peptide
CHO	Chinese Hamster Ovary
CIOMS	Council for International Organizations of Medical Sciences
CM	chronic migraine
COAs	Clinical Outcome Assessments
CPK	Creatine phosphokinase
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBF	Dermal blood flow
DILI	drug-induced liver injury
DRT	Data Review Team
ECG	electrocardiogram
EDC	Electronic data capture
eDiary	Electronic diary
EM	episodic migraine
End of Study (end of trial)	defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Enrollment	when the investigator decides that the subject has met all Part 1 and Part 2 eligibility criteria
EOS	end of study
ET	Early termination
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbA1c	glycosylated hemoglobin

Abbreviation or Term	Definition/Explanation
Headache Day	A headache day is defined as any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as: • a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or • a qualified non-migraine headache, which is a headache that lasts ≥ 4 hours and is not a qualified migraine headache, or • a headache of any duration for which acute headache treatment is administered
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test-6
HRT	hormonal replacement therapy
IC_{50}	half maximum inhibitory concentration
ICH	International Council for Harmonisation
ICHD	International Headache Classification
ICHD-IIIb	ICHD, third edition beta
ICMJE	International Committee of Medical Journal Editors
IgG1	Immunoglobulin G1
IHS	International Headache Society
IHS	International Headache Society
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IUD	Intrauterine device
IUS	Intrauterine hormonal-releasing system
IV	Intravenous
IVR	Interactive Voice Response
IWR	Interactive Web Response
Ki	Equilibrium inhibition constant
LDH	lactate dehydrogenase
LDI	Laser Doppler Imaging
mAB	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine-specific and Migraine Disability Assessment
Migraine Day	A migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 4 hours, and meeting at least 1 of the following criteria (a and/or b): a. ≥ 2 of the following pain features: • unilateral • throbbing • moderate to severe • exacerbated with exercise/physical activity

Abbreviation or Term	Definition/Explanation
	b. ≥ 1 of the following associated symptoms: •nausea and/or vomiting •photophobia and phonophobia If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
MPFID	Migraine Physical Function Impact Diary
NASH	Nonalcoholic fatty liver disease including steatohepatitis
NOAEL	no observed adverse effect level
oGTT	oral glucose tolerance test
PAC1R	pituitary adenylate cyclase-activating polypeptide type 1 receptor
PACAP	Pituitary adenylate cyclase-activating polypeptide
PAS	Primary Analysis Set
PD	pharmacodynamic
PK	Pharmacokinetics
POR	Proof of Receipts
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Randomization	A subject will be randomized to treatment assignment
SAS	safety analysis set
SAT	Safety Assessment Team
SC	Subcutaneous
SEC	Self-Evident Corrections
SEFL	Stable Effector Function Less
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
SPG	sphenopalatine ganglion
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal
VIP	vasoactive intestinal polypeptide
VPAC	Vasoactive intestinal polypeptide receptor

Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory and/or by the local laboratory, except for urine pregnancy tests.

Laboratory assessments listed in Appendix 7 will be performed by the local laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.4 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Central Laboratory Chemistry	Central Laboratory Urinalysis	Central Laboratory Hematology	Central Laboratory Other Labs	Local Laboratory Other Labs
Sodium	Specific gravity	RBC	Pregnancy testing- serum	Urine pregnancy test (Local)
Potassium	pH	Hemoglobin	HepBsAg	
Chloride	Blood	Hematocrit	Total HepBcAb	
Bicarbonate	Protein	MCV	HCV	
Total protein	Glucose	MCH	Urine drug screening[b]	
Albumin	Bilirubin	MCHC	PK	
Calcium	WBC	RDW	Anti-AMG 301 antibodies	
Magnesium	RBC	Reticulocytes	Biomarker development	
Phosphorus	Epithelial cells	Platelets	Pharmacogenetic studies *(optional)*	
Glucose		WBC		
HbA1c				
FPG[a]	Bacteria	WBC Differential		
BUN or Urea	Casts	• Bands/stabs		
Creatinine	Crystals	• Eosinophils		
eGFR MDRD		• Basophils		
Uric acid				
Total bilirubin		• Lymphocytes		
CPK		• Neutrophils		
Direct bilirubin		• Monocytes		
ALP		• Myeloblasts		
AST (SGOT)		• Promyelocytes		
ALT (SGPT)		• Myelocytes		
Cholesterol		• Metamyelocytes		
HDL				
LDL				
Triglycerides		Nucleated RBC		
TSH				

Abbreviations: ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = Blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimating glomerular filtration rate; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; HCV = hepatitis C vaccine; HDL = high-density lipoprotein; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MDRD = Modification of Diet in Renal Disease; PK = pharmacokinetics; RBC = red blood cell; RDW = red (cell) distribution width; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TSH = thyroid-stimulating hormone; WBC = white blood cell

[a] Subjects are to fast for at least 8 hours before blood draw. Study center staff is to confirm the subjects fasting status. If a subject has a HbA1c ≥ 5.7% from week 6 and beyond a fasting glucose will be assessed at the next visit.

[b] Subjects will be tested for substances of abuse at screening to confirm subject eligibility. During the study, urine drug tests can also be performed at the investigator's discretion based on clinical suspicion. Urine samples will be analyzed by the central laboratory. For a subject with a positive urine drug screen during the study (except for certain prescribed medications), the investigator should consider discontinuing the subject from investigational product.

Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC. 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.

Amgen, as the sponsor, will submit and obtain competent authority approval in the European Union (EU) for any amendments which are determined to be substantial. Similarly, Amgen will submit and obtain regulatory approval in other regions, where necessary, when making significant changes to the study.

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the 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 IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB 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 IEC approval throughout the duration of the study. Copies of the investigator's reports and the IEC continuance of approval must be sent to Amgen.

Informed Consent Process

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 sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative (a physician) will explain to the subject the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

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 unless it is a local requirement. The

investigator shall then inform the primary care physician. 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 and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

A subject must provide informed consent prior to the initiation of any re-screening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent.

CCI

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at 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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental 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 such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate 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 (ICMJE) Recommendations for the

Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to 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; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or

adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit 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.

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

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee)

include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the Interactive Voice Response (IVR)/Interactive Web Response (IWR) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 CRFs, 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
- Medical device (ie, syringes) documentation, as applicable

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. 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(s) 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 the product(s) is/are available commercially.

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.

Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  ○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition 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.
• Disease-related events that do not qualify as adverse events or 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.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an

adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

  OR

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:

- **Results in death (fatal)**

- **Immediately life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria,

the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
• **Results in persistent or significant disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Other medically important serious event** Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all medical devices provided for use in the study (see Section 7.1.3 for the list of medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

- If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF
- When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event case report form (CRF).
  - Additionally, the investigator is required to report a fatal disease-related event on the 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 (or toxicity defined below);
  - Assessment of relatedness to investigational product, or devices; and
  - Action taken.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The **Common Terminology Criteria for Adverse Events (CTCAE)**, version 4.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an Serious Adverse Event Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1).

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial 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.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

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 serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious 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 (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and 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 – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   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.**

   - 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 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.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

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.

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 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 # 20150308
AMG 301

Electronic Serious 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

<<For completion by COM 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	Race	If applicable, provide End of Study date
		☐F ☐M		

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. SERIOUS ADVERSE EVENT

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

Serious 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	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						IP		<Device>		<Device>		<Device>			
						No	Yes	No	Yes	No	Yes	No	Yes		
				☐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

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

IP/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 #
AMG 301/Placebo	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20150308 AMG 301	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

AMGEN Study # 20150308 AMG 301	Electronic Serious 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 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 18 weeks after the last dose of protocol-required therapies.

If subjects may receive additional drugs during the study that are not required as part of the protocol, include the following language: Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhoea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 18 weeks after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not

required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws.)

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 18 weeks after the last dose of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.2.2 for details).

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 18 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 228.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through the last dose of investigational product after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

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:** _____

****

Effective Date: March 27, 2011

Page 1 of 1

Print Form

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:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix 6. Sample Storage and Destruction

Any blood (eg, biomarker, PK) sample collected according to the Schedule of Activities (Table 2-1) 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 the study indications (eg, migraine), neurological diseases, and/or AMG 301 immunogenicity, and/or in the identification of subjects who may have positive or negative responses to AMG 301, 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.

CCI

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 [sample types (eg, blood, tumor)] 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 Appendix 3 for subject confidentiality.

Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or 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 (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible DILI according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and 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 the above, 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, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to 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 Appendix 4.

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 Table 12-2) or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug 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. The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- 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
- Viral serologies
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. 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 the corresponding CRFs.

Amendment 2

Protocol Title: A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention

Amgen Protocol Number AMG 301 20150308

EudraCT Number: 2017-000630-57

NCT03238781

Amendment Date: 17 October 2017

Rationale:

This protocol is being amended for the following reasons:

- Update schedule of activities and footnotes to maintain consistency with the protocol.
- Update the exclusion screening criterion to maintain accordance with the World Health Organization's guidelines of assessing impaired glucose regulation/ prediabetes with glycosylated hemoglobin (HbA1c) values.
- Make minor corrections and clarifications throughout the document, including administrative, typographical, and formatting errors.

Description of Changes:

Section: Global

Change: Update protocol amendment dates throughout document from 16 May 2017 to **17 October 2017**

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title page

Replace:

NCT Number:	Not applicable

With:

NCT Number:	**NCT03238781**

Section: Title page

Add:

Protocol Date:	Document Version	Date
	Original	16 March 2017
	Amendment 1	16 May 2017
	Amendment 2	**17 October 2017**

Section: 2.2. Schedule of Activities, Table 2-1

Replace:

Procedure	Screening Period (Up to 7 weeks)			Double-Blind Treatment Period[a] (12 weeks) (± 2 days)									Safety Follow-up Period (16 weeks) (± 5 days)			
	Screening up to 3 weeks	Baseline Period[b]		Day 1 (Post-rand)[c]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12/ET[d]	Wk 16	Wk 20	Wk 24	Wk 28/ET/ EOS[d]
		-4 Weeks	Pre-rand (Day 1)													
Vital signs[g]	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
Hepatitis B and Hepatitis C storage sample			X[p]													
Fasting plasma glucose	X															
PK Sampling[m]				X	X		X		X	X	X	X	X		X	X
Anti-AMG 301 antibodies (serum)				X					X			X	X		X	X

With:

Procedure	Screening Period (Up to 7 weeks)			Double-Blind Treatment Period[a] (12 weeks) (± 2 days)									Safety Follow-up Period (16 weeks) (± 5 days)			
	Screening up to 3 weeks	Baseline Period[b]		Day 1 (Post-rand)[c]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 9	Wk 10	Wk 12/ET[d]	Wk 16	Wk 20	Wk 24	Wk 28/ET/ EOS[d]
		-4 Weeks	Pre-rand (Day 1)													
Vital signs[g]	X	X	X[h]	X[i]		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
Hepatitis B and Hepatitis C storage sample				**X[m]**												
Serum plasma glucose[n]	X															
PK Sampling **(serum)**[s]				X	X		X		X	X	X	X	X		X	X
Anti-AMG 301 antibodies (serum)[s]				X					X			X	X		X	X

Section: 2.2. Schedule of Activities, Table 2.1, Footnotes h, i, and n

Add:

h. **Vital signs will be assessed prior to subject registration using the IVR/IWR system.**

i. **Vital signs will be assessed approximately 30 to 60 minutes after investigational product administration.**

n. **Sites are encouraged to obtain a fasting glucose sample, if possible.**

Section: 2.2. Schedule of Activities, Table 2.1, Footnote g

Replace:

g Vital signs will include systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study.

With:

g **Vital signs will be assessed prior to investigational product administration, and** will include systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study.

Section: 2.2. Schedule of Activities, Table 2.1, Footnote o (formally q and r)

Replace:

q. Fasting blood glucose will be assessed at next visit if a subject has an HbA1c ≥ 5.7% from week 6 and beyond.

r. A fasting blood glucose will be performed in cases where a serum glucose is ≥ 200 or HgA1c is ≥ 5.7%.

With:

o. A fasting blood glucose will be performed **at next visit** in cases where a serum glucose is ≥ 200 **mg/dL** or H**b**A1c is ≥ 5.7%.

Section: 2.2. Schedule of Activities, Table 2.1, Footnote s (formally m)

Replace:

m. PK sampling will be serum and collected at predose on day 1 and weeks 4, 8, and 10, and at postdose in weeks 1, 9, 12, 16, 24, and 28 or EOS.

With:

s. PK sampl**es** will be collected at predose on day 1 and weeks 4, 8, and 10, and at postdose in weeks 1, 9, 12, 16, 24, and 28 or EOS. **On days that anti-AMG 301 antibodies are scheduled to be collected, they are to be collected following the predose/postdose PK sampling schedule.**

Section: 2.2. Schedule of Activities, Table 2.1, Footnote r (formally s)

Replace:

s. On days where the first and second dose are administered, study center staff are to observe the subject for at least 120 minutes after the last injection of investigational product. On later days when dose is administered, study center staff will observe the subject for at least 60 minutes after the last injection of investigational product. Investigators can retain subjects for longer if there is any sign of discomfort any time following AMG 301 administration.

With:

r. **On day 1 post-randomization and week 2 visits,** study center staff are to observe the subject for at least 120 minutes after the last injection of investigational product. **On weeks 4, 6, 8, and 10 visits,** study center staff will observe the subject for at least 60 minutes after the last injection of investigational product. Investigators can retain subjects for longer if there is any sign of discomfort any time following AMG 301 administration.

Section: 2.2. Schedule of Activities, Table 2.1, Footnotes j and q (formally h and l)

Delete:

j. Medical history will include targeted cardiologic, neurologic, psychiatric, cardiovascular, and history of diabetes, including gestational diabetes and/or impaired glucose tolerance testing. A history of participation in prior Amgen studies will be included. Medication history to include ~~targeted~~ prior migraine prophylactic treatment history within the 90 days before screening will be collected.

q. Study centers are to call the IVR/IWR system for the following: to enter the subject into the screening period, to randomize an eligible subject into the double blind treatment period~~, to re-randomize a subject into the double-blind treatment period~~, to obtain the investigational product assignment, to register the end of investigational product, and to register study ET or completion. Subject data will be collected in the IVR/IWR system including, but not limited to, CM versus EM, sex, and reason for screen fail (if applicable). Study centers to access the IVR/IWR system to obtain the investigational product assignment at day 1, and weeks 2, 4, 8, and 10.

Section: 6.2 Exclusion Criteria Part 1

Replace:

211 Glycosylated hemoglobin (HbA1c) ≥ 5.7% at screening

212 Impaired glucose metabolism: defined as plasma glucose (fasting or otherwise) ≥ 100 mg/dL at screening

220 Evidence of drug or alcohol abuse or dependence within 12 months before screening, based on medical records, subject self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids, barbiturates, or cannabinoids).

225 Subjects must have been free of medications listed in Section 7.1.7 for at least 2 months before the start of the baseline period (at least 4 months before baseline for botulinum toxin [head and/or neck region] and mABs targeting CGRP).

228 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with AMG 301 through 18 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 [periodic abstinence, eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception), 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 2 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 and no spontaneous menses for at least 12 months and with a follicle-stimulating hormone level > 40 IU/L or according to the definition of “postmenopausal range” for the laboratory involved

  OR

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

Refer to Appendix 5 for additional contraceptive information.

With:

211 Glycosylated hemoglobin (HbA1c) ≥ **6.0**% at screening

212 **Serum plasma** glucose **level** ≥ 100 mg/dL at screening**; ideally performed while fasting**

220 Evidence of drug or alcohol abuse or dependence within 12 months before screening, based on medical records, subject self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids, **or** barbiturates).

225 Subjects **taking** medications listed in Section 7.1.7 for at least 2 months before the start of the baseline period (at least 4 months before baseline for botulinum toxin [head and/or neck region] and mABs targeting CGRP).

228 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with AMG 301 through 18 weeks after the last dose of investigational product.

Refer to Appendix 5 for additional contraceptive information.

Section: 6.4 Exclusion Criteria Part 2

Delete:

234. Used a prohibited medication, device or procedure ~~before~~ during the baseline period (Refer to Section 7.1.7 for the list of these excluded treatments and the timeframes)

Section: 6.7. Screen Failures, Paragraph 1

Delete:

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, ~~medical history, prior therapies, Clinical Outcome Assessments (COAs), C-SSRS, BDI-II, laboratory assessments~~ and any serious adverse events.

Section: 7.1.3. Medical Devices, Paragraph 1

Replace:

One mL sterile syringes will be used in this study.

With:

Sterile syringes will be used in this study.

Section: 7.1.7. Excluded Treatments, Medical Devices, and/or Procedures During Study Period, Bullet point 15

Add:

- **cannabinoids**

Section: 9.2.1.8.1. Cranial Autonomic Parasympathetic Symptom Scale

Replace:

The CAPS scale will be administered by clinical study center staff as described in Table 2-1.

With:

The CAPS scale will be administered by **a clinician (ie, primary investigator or delegate)** as described in Table 2-1.

Section: 9.2.3.1.1.2. Adverse Events, Paragraph 1

Delete:

~~Adverse Events will be reported from the first dose of investigational product through the EOS.~~

Section: 9.2.3.1.1.3. Serious Adverse Events, Paragraphs 1 and 2 (text rearranged)

Replace:

Serious Adverse Events will be collected from signing of Informed Consent Form through the end of the safety follow-up visit (18 weeks after last dose of investigational product or EOS).

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 end of study are reported using the Event CRF.

With:

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 the end of the safety follow-up visit (18 weeks after last dose of investigational product or EOS) are reported using the Event CRF.

Section: 9.2.3.3. Electrocardiograms (ECGs), Paragraph 1, Sentence 6

Delete:

The ~~primary~~ investigator will review all ECGs.

Section: Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting, Reporting of Serious Adverse Event, Figure 12-1

Replace:

Figure 12-1. Sample Electronic Serious Adverse Event Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial 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.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

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 serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious 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 (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and 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 – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   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.**
   - 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 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.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

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.

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 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 # 20150308 AMG 301	**Electronic Serious 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

<<For completion by COM 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	Race	If applicable, provide End of Study date
		☐F ☐M		

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. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month_____ Year_____

Serious 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 eeath. 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	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						<Ptdevice> No✓	<Ptdevice> Yes✓	<Ptdevice> No✓	<Ptdevice> Yes✓	<Ptdevice> No✓	<Ptdevice> Yes✓	<Ptdevice> No✓	<Ptdevice> Yes✓		
				☐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

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

IP/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 #**
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20150308 AMG 301	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

AMGEN Study # 20150308 AMG 301	**Electronic Serious 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

With:

Figure 12-1. Sample Electronic Serious Adverse Event **Contingency** Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial 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.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

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 serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious 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 (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and 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 – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   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.**
   - 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 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.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

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.

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 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 # 20150308 AMG 301	Electronic Serious 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

<<For completion by COM 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	Race	If applicable, provide End of Study date
		☐F ☐M		

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. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious 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	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? IP: No / Yes <Device>: No / Yes <Device>: No / Yes <Device>: No / Yes	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria:			
	01 Fatal	03 Required/prolonged hospitalization	05 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	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

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

		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 #
IP/Amgen Device:								
AMG 301/Placebo	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20150308 AMG 301	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

AMGEN Study # 20150308 AMG 301	Electronic Serious 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

Section: Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Definition of Females of Childbearing Potential, Paragraph 2, Bullet point (level 1) 3

Delete:

- Postmenopausal female ~~(refer to Exclusion Criteria 229 above)~~

Amendment 1

Protocol Title: A Phase 2a Randomized Double-blind Placebo Controlled Study to Evaluate the Efficacy and Safety of AMG 301 in Migraine Prevention

Amgen Protocol Number 20150308

EudraCT Number 2017-000630-57

Amendment Date: 16 May 2017

Rationale:

The original protocol was submitted to regulatory authorities in the EU via the Voluntary Harmonisation Procedure (VHP). During review the VHP revisions were requested to the study protocol. In addition, the Sponsor took the opportunity to make corrections and administrative updates.

In addition, the following were clarified to ensure alignment with study procedures:

- Clarify the number of subjects that will be screened and enter baseline in order to achieve the target randomization
- Clarify when vital signs, pharmacokinetic sampling, and Headache Impact Test will be collected during the study
- Clarify the risks and benefits of the study
- Removal of legally acceptable representative from the study
- Clarify that upon early discontinuation, a safety follow-up visit will be performed approximately 30 (± 5) days after the last dosing interval of investigation product
- Add additional information for sample size calculation for each AMG 301 group versus placebo
- Clarify that the primary analysis set is also known as the efficacy analysis set
- Clarify which primary and secondary endpoints will be included in the interim analysis
- Add the responsibilities of the Data Review Team during the double-blind treatment phase
- Clarify Amgen's regulatory responsibilities when an amendment is determined to substantial
- Administrative, typographical, and formatting changes were made throughout the protocol