Title: An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334

Amgen Protocol Number AMG 334 20130255
EudraCT number 2013-005311-27

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Date:	12 December 2013
Superseding Date:	30 January 2014
Amendment 1:	25 January 2015
Amendment 2	14 October 2015
Amendment 3	**31 March 2016**

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I have read the attached protocol entitled An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334, dated **31 March 2016**, and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334

Study Phase: Open-label extension

Indication: Prevention of chronic migraine

Primary Objective: To characterize the safety and tolerability of long-term administration of AMG 334

- Primary Objective of Clinical Home Use (CHU) Substudy: To assess users' ability to administer a full dose of AMG 334 in home-use, using either two prefilled syringes (PFS) or two prefilled autoinjector/pens (AI/pen).

Secondary Objectives:

- To characterize the efficacy of long-term administration of AMG 334 as assessed by:
- Change from baseline in monthly migraine days
- Proportion of subjects with at least 50% reduction from baseline in monthly migraine days
- Change from baseline in monthly acute migraine-specific medication treatment days
- Change from baseline in monthly cumulative hours of headache
- Secondary Objective of CHU Substudy: To assess the safety and tolerability of AMG 334 administered using two 1-mL PFS or two 1-mL AI/pens

For the purpose of primary analysis for secondary and exploratory endpoints in the 20130255 open-label extension (OLE) study, baseline is defined as baseline of the AMG 334 20120295 parent study (from the first day subject used eDiary in baseline at week -4 study visit through the day prior to study day 1). However, change from week 8 through 12 data of the parent study (hereafter referred to as parent study Month 3 data) will also be evaluated.

Hypotheses: The clinical hypothesis is that long-term exposure of AMG 334 will be safe and well tolerated in subjects with chronic migraine

Primary Endpoint: Subject incidence of adverse events

Secondary Endpoints:

- Change from baseline in monthly migraine days at assessment timepoints
- Achievement of at least a 50% reduction from baseline in monthly migraine days at assessment timepoints
- Change from baseline in monthly migraine-specific medication treatment days at assessment timepoints
- Change from baseline in cumulative monthly headache hours at assessment timepoints

Study Design: This is a multicenter, open-label study designed to assess the long-term safety and efficacy of AMG 334. Subjects who complete the 12-week double-blind treatment phase of the AMG 334 20120295 parent study and meet all AMG 334 20130255 eligibility criteria will be enrolled into the study. Enrollment should occur within 14 days of the week 12 visit of the AMG 334 20120295 parent study. Subjects who enroll in the AMG 334 20130255 study will end the AMG 334 20120295 study and will not participate in the parent study safety follow-up visit. Subjects may also elect to participate in a Novel Patient-reported Outcome Substudy in addition to a CHU substudy.

All subjects who have not yet enrolled in the study will receive open-label AMG 334 140 mg every month (QM) subcutaneous (SC) for 13 months. Subjects who are already enrolled in the 20130255 study will increase the open-label dose from 70 mg QM to 140 mg QM at the first available opportunity at either week 4, 8, 12, 16, 20, 24, or 28 visits. Subjects who have already

completed the week 28 visit will continue to receive 70 mg QM. Subjects will not have the option to decrease open-label AMG 334 from 140 mg QM to 70 mg QM. The 13-month open-label AMG 334 treatment phase will be followed by a 12-week safety follow-up visit (16 weeks after last dose of investigational product).

Sample Size: All subjects who completed the 12-week double-blind treatment phase of the AMG 334 20120295 parent study, meet the inclusion and exclusion criteria for the AMG 334 20130255 OLE study will be eligible to be enrolled. Up to 651 subjects may participate in the study.

Summary of Subject Eligibility Criteria: Adults with history of chronic migraine and who completed the 12-week double-blind treatment phase of the parent study. For a full list of eligibility criteria, please refer to Section 4.1.

Amgen Investigational Product Dosage and Administration: Investigational product (IP) (ie, AMG 334 70 mg or 140 mg) will be dosed QM by SC injection. **For subjects participating in the CHU substudy, IP is AMG 334 140 mg in either a PFS or prefilled AI/Pen.**

Procedures: Prior to enrolling in this study, subjects will need to undergo week-12 procedures for the parent study. In addition, subjects will need to meet eligibility criteria requirements, which includes review by the investigator of the parent study week-12 labs and electrocardiogram (ECG) central reader report. Subject numbers will be the same as those in the parent study.

After signing informed consent, subjects will have monthly in-clinic study visits throughout the 13-month treatment phase. During these visits, IP will be administered and study-related procedures will be completed.

All subjects will receive open-label AMG 334 QM SC for 13 months followed by a 12-week safety follow up visit (16 weeks after the last dose of IP).

Subjects will use an electronic diary (eDiary) every day between the Day 1 and month 3 visit, between the month 5 and 6 visit, between the month 9 and 10 visit, and between the month 12 and 13 visit to report information about their migraine and non-migraine headaches and acute medication use.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 1).

Statistical Considerations:

For the purpose of primary analysis for secondary and exploratory endpoints in the 20130255 OLE study, baseline is defined as baseline of the AMG 334 20120295 parent study (from the first day subject used eDiary in baseline at week -4 study visit through the day prior to study day 1). However, change from parent study Month 3 data will also be evaluated.

Descriptive statistics will be provided for all endpoints, including efficacy endpoints.

The exposure-adjusted 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, and adverse events leading to withdrawal from investigational product will be provided.

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

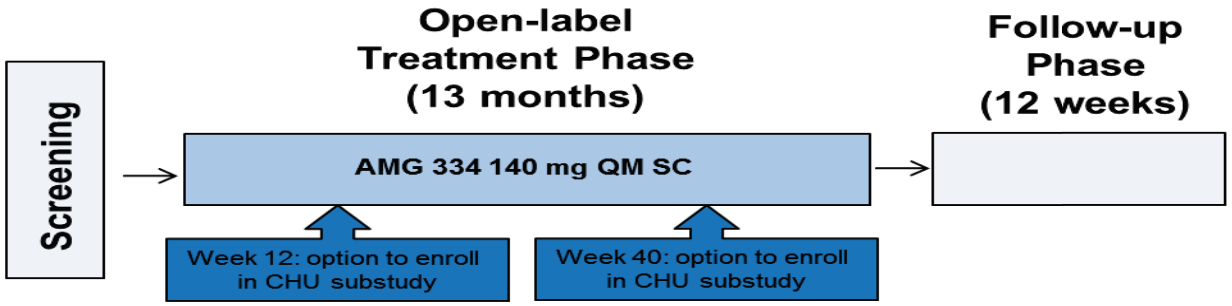
Sponsor: Amgen Inc.

Data Element Standards Version/Date:	Version 4.0 – 01 November 2013

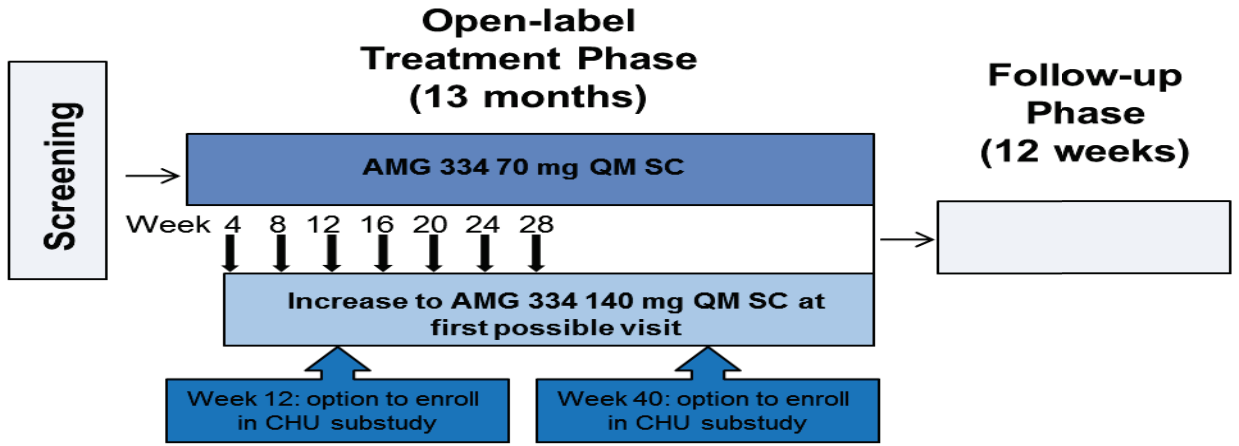
Study Design and Treatment Schema

Study Design and Treatment Schema

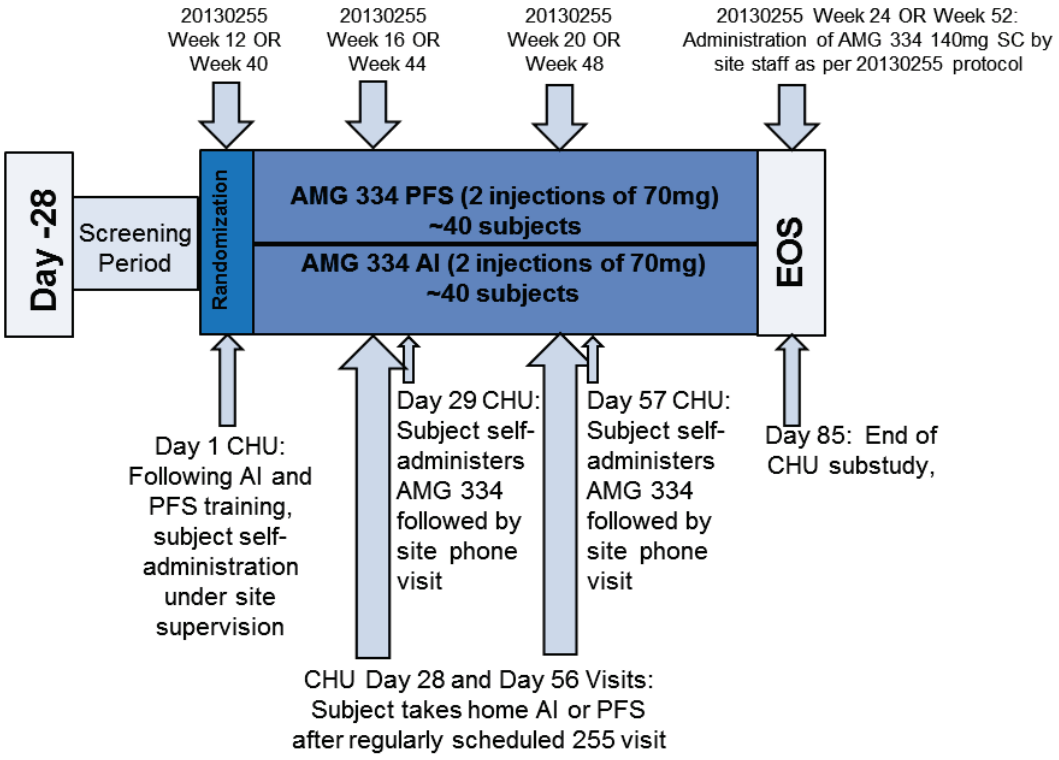
All subjects who have not yet enrolled in the study:



All subjects who are already enrolled in the 20130255 Study:



Optional Clinical Home Use Substudy Design and Treatment Schema (only available in US, Germany and Sweden)



Study Glossary

Abbreviation or Term	Definition/Explanation
ADL	Activities of daily living
ADE	Adverse Device Effects
AE	Adverse event
AI/pen	Autoinjector/pen
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
Baseline	For the purpose of primary analysis for secondary and exploratory endpoints in the 20130255 OLE study, baseline is defined as baseline of the AMG 334 20120295 parent study (from the first day subject used eDiary in baseline at week -4 study visit through the day prior to study day 1). Change from week 8 through 12 data of the parent study (referred to as parent study Month 3 data) will also be evaluated.
BIL	Bilirubin
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CGRP	Calcitonin gene-related peptide
CHU	Clinical Home Use
C_{max}	Peak concentration
COAs	Clinical Outcomes Assessments
Combination-analgesic	combination formulations of simple analgesics with opiates or butalbital
CPK	Creatine phosphokinase
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
Day 1 / Study Day 1	The first day that protocol-specified investigational product is administered to the subject
DBF	Dermal blood flow
DILI	Drug-induced liver injury
EC_{90}	90% effective concentration
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	**Electronic case report form**

Abbreviation or Term	Definition/Explanation
eDiary(ies)	Electronic diary(ies)
End of study for individual subject	The last day at which protocol-specified procedures are conducted for an individual subject.
End of Trial	The time when the last subject is assessed for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit after the last dose of investigational product, or is discontinued from the study).
Enrollment	Timepoint at which a subject meets all screening eligibility criteria and enrolls into the baseline phase of the study.
ET	Early termination
ETO System	Electronic Trial Operations System; an electronic system that is used to facilitate the operations of a clinical trial through the collection of study-related data. The most common applications of an ETO system within a clinical trial are subject randomization and investigational product management. The term is synonymous with the industry term Interactive Voice Response (IVR) / Interactive Web Response (IWR) System.
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
HDL	High-density lipoprotein
Headache	A migraine or non-migraine headache
Headache Day	Any calendar day in which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache) lasting ≥ 4 continuous hours, or a headache of any duration for which acute medication (simple analgesics, combination analgesics, triptans, ergot-derivatives, opiates) was administered for treatment of headache pain.
Headache Day with moderate or severe intensity	Any calendar day in which the subject experiences a headache, with headache pain lasting ≥ 4 continuous hours, and a peak severity of moderate to severe, or of any severity or duration if the subject takes a triptan or ergot-derivative for headache pain
ICF	Informed consent form
ICH GCP	International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice
ICMJE	**International Committee of Medical Journal Editors**
IEC	Independent Ethics Committee
IFU	Instructions for Use
INR	International normalized ratio
IP	Investigational product (ie, AMG 334 **or if participating in CHU substudy, AMG 334 in either a PFS or prefilled AI/Pen**)
IPIM	Investigational Product Instructional Manual

Abbreviation or Term	Definition/Explanation
IRB	Institutional Review Board
IVR/IWR System	Interactive Voice Response (IVR) / Interactive Web Response (IWR) System; telecommunication / internet technology that is linked to a central computer in real time as an interface to collect and process information.
K_d	The equilibrium dissociation constant
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
M	Month
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MIDAS	Migraine Disability Assessment
Migraine Attack	An episode of any qualified migraine headache or episode for which the subject took a triptan or ergot-derivative to treat headache or aura. The following rules will be used for distinguishing an attack of long duration from two attacks, or for distinguishing between attacks and relapses: a) A migraine attack which is interrupted by sleep or temporarily remits, and then recurs within 48 hours after onset of the attack will be considered as one attack, and not two. b) An attack primarily treated successfully with medication but with relapse within 48 hours will be considered as one attack.

Abbreviation or Term	Definition/Explanation
Migraine Day	Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined either as a migraine without aura or a migraine with aura as outlined below: 1. A migraine without aura, lasting for ≥ 4 continuous hours, and meeting criteria a and/or b: a) ≥ 2 of the following pain features: • Unilateral • Throbbing • Moderate to severe • Exacerbated with exercise/physical activity b) ≥ 1 of the associated symptoms: • Nausea and/or vomiting • Photophobia and phonophobia OR 2. A migraine with aura and meeting criteria a and b: a) Meeting ≥ 1 of the following fully reversible aura symptoms: • Visual • Sensory • Speech and/or language • Retinal • Brainstem b) Aura is accompanied, or followed within 60 minutes, by headache lasting for ≥ 4 continuous hours. If the subject took a triptan or ergot-derivative on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
Monthly Headache Days	Number of headache days in any 28-consecutive day interval relative to study day 1.
Monthly Migraine Days	Number of migraine days in any 28-consecutive day interval relative to study day 1.
MPFID	Migraine Physical Function Impact Diary
MSQ	Migraine-specific Quality of Life Questionnaire
MWt	molecular weight
NOAEL	No observed adverse effect level
OLE	Open-label extension

Abbreviation or Term	Definition/Explanation
Parent study	AMG 334 20120295 A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention
Parent study Month 3 data	Week 8 through 12 data of the parent study
PD	Pharmacodynamic
PE	Physical examination
PET	Positron emission tomography
PFS	Prefilled syringe
PG	Pharmacogenetic
PK	Pharmacokinetic
Primary Completion	The time when the last subject is assessed for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit after the last dose of investigational product, or is discontinued from the study).
PRO	Patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System Pain Interference Scale short form
QM	Every month / Monthly
RBC	Red blood cell
RDW	Red blood cell distribution width
RG	Reference Guide
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SEC	**Self-evident corrections**
SGOT	serum glutamic-oxaloacetic transaminase; see AST
SGPT	serum glutamic-pyruvic transaminase; see ALT
Simple analgesic	Includes non-narcotic analgesics such as acetaminophen or NSAIDs
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 and randomization identification.
TBL	Total bilirubin
t_{max}	time to peak concentration

Abbreviation or Term	Definition/Explanation
True abstinence	To refrain from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur.
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
Wk	Week
WOCBP	Woman/women of childbearing potential; any female who has experienced menarche and does not meet the criteria for “Women not of childbearing potential”
Women not of childbearing potential	Any female who: • Is post-menopausal by history defined as o Age ≥ 55 years with cessation of menses for 12 or more months, OR o Age < 55 years but no spontaneous menses for at least 2 years, OR o Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved. OR • Underwent bilateral oophorectomy OR • Underwent hysterectomy OR • Underwent bilateral salpingectomy.

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1. OBJECTIVES

1.1 Primary

To characterize the safety and tolerability of long-term administration of AMG 334

- Primary Objective of Clinical Home Use (CHU) Substudy: To assess users' ability to administer a full dose of AMG 334 in home-use, using either two prefilled syringes (PFS) or two prefilled autoinjector/pens (AI/pen)

1.2 Secondary

To characterize the efficacy of long-term administration of AMG 334 as assessed by:

- Change from baseline in monthly migraine days
- Proportion of subjects with at least 50% reduction from baseline in monthly migraine days
- Change from baseline in monthly acute migraine-specific medication treatment days
- Change from baseline in monthly cumulative hours of headache

For the purpose of primary analysis for secondary and exploratory endpoints in the 20130255 open-label extension (OLE) study, baseline is defined as baseline of the AMG 334 20120295 parent study (from the first day subject used eDiary in baseline at week -4 study visit through the day prior to study day 1). However, change from week 8 through 12 data of the parent study (hereafter referred to as parent study Month 3 data) will also be evaluated.

- Secondary Objective of CHU Substudy: To assess the safety and tolerability of AMG 334 administered using two 1-mL PFS or two 1-mL AI/pens

1.3 Exploratory

- To evaluate the effect of AMG 334 as measured by reduction from baseline in monthly migraine attacks, in subjects with chronic migraine
- To evaluate the effect of AMG 334 as measured by the reduction from baseline in monthly headache (migraine and non-migraine headache) days, headache days with moderate or severe intensity, monthly average severity of migraine pain
- To evaluate the effect of AMG 334 as measured by the change from baseline on monthly average severity of migraine related symptoms (nausea, vomiting, phonophobia, photophobia) for qualified migraine headaches
- To evaluate the effect of AMG 334 on migraine-specific quality of life (as measured by the Migraine-Specific Quality of Life Questionnaire [MSQ], version 2.1), migraine-related disability (as measured by the Migraine Disability Assessment [MIDAS]), pain interference with daily activities and migraine-specific impact (as measured by the Patient-Reported Outcomes Measurement Information System [PROMIS] Pain Interference Scale short form and single pain and migraine symptom interference questions)
- To evaluate effect of AMG 334 on change in physical impairment over time as measured by the Migraine Physical Function Impact Diary (MPFID)

- To evaluate the effect of AMG 334 on change in impact on everyday activities over time as measured by the MPFID
- To evaluate AMG 334 pharmacokinetic (PK) in subjects with migraine
- To investigate potential biomarker development by analysis of blood samples

2. BACKGROUND AND RATIONALE

2.1 Disease

Migraine

Migraine is a disabling disorder characterized by primary recurrent headaches with or without aura lasting 4 to 72 hours with at least two 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). The pathophysiology of aura may differ from that of migraine pain (Eikermann-Haerter and Ayata, 2010). Migraine is a highly prevalent disease worldwide. The prevalence of migraine is approximately 11.7% in the USA, 14.6% in Canada, and 14.7% in Europe (Lipton et al, 2007; Stovner and Andree, 2010). The disease is more common in women than in men and presents most often during the period of an individual's peak economic productivity between the ages of 30 and 50 years of age (Lipton et al, 2007; Stovner et al, 2007; Stovner and Andree, 2010). Depending on the headache frequency, migraine is divided into two broad forms: episodic migraine and chronic migraine [ICHD-3]. Episodic migraine is characterized by migraine with fewer than 15 headache days per month, while chronic migraine is characterized by 15 or more headache days per month (where at least 8 of those days are migraine days). Episodic and chronic migraine share many common features in terms of the clinical presentation, which include the headache pain features and associated symptoms. However, there are also differences between patients with episodic and those with chronic migraine including epidemiologic profiles, risk factors and co-morbidities. In general, patients with chronic migraine experience more severe and disabling migraine attacks, and have more co-morbidities (eg, depression and anxiety, chronic pain and cardiovascular disorders) than patients with episodic migraine. Individuals with chronic migraine are typically older, have lower levels of overall education, lower household incomes and are less likely to be working full time than individuals diagnosed with episodic migraines (Diener et al, 2012; Katsarava et al, 2012).

Migraine headaches are commonly treated acutely. The most frequently used acute migraine medications include analgesics and a class of drugs called triptans (Houston and Vanhoutte, 1986; Humphrey et al, 1990). It has been demonstrated the triptans are effective in both episodic and chronic migraine, although those with chronic migraine tend to have less robust response to triptans than those with episodic migraine (Lipton and Chu, 2009). Based on published treatment guidelines, up to 40% of the migraine patient population (including all patients with chronic migraine) would benefit from preventive therapy (Lipton et al, 2001). The available migraine preventive therapies are associated with modest efficacy and significant tolerability and safety issues. Migraine prophylaxis is an area of large unmet medical need. While recommendations exist for the preventive treatment of migraine headache in the U.S. and Europe, most of the medications were evaluated in episodic migraine (Silberstein et al, 2012; Evers et al, 2009). Topiramate is the only migraine prophylactic agent with demonstrated efficacy in both episodic and chronic migraine patients through randomized placebo-controlled trials (Diener et al, 2007; Silberstein et al, 2007). However, topiramate is poorly tolerated due to common adverse events such as paresthesias, anorexia, psychomotor slowing, somnolence, language difficulties, and difficulties with memory and concentration (Adelman et al, 2008; Brandes et al, 2004). Additionally, onabotulinumtoxinA was recently approved by United States Food and Drug Administration (FDA), several EU countries, and Canada for prophylaxis of chronic migraine, based on 2 randomized, placebo-controlled, double-blind studies (Aurora et al, 2010; Diener et al, 2010).

Calcitonin Gene-related Peptide (CGRP)

Migraine was historically considered to be due to vasodilatation of cranial blood vessels. More recent understanding of the pathophysiology of migraine indicates that the vasodilatation of the cranial blood vessels is secondary to activation of the trigeminal nociceptive pathway (Goadsby et al, 2002). CGRP is a 37 amino acid peptide expressed in both the central and peripheral nervous systems including the trigeminal ganglion and nucleus, and is believed to be a key mediator of migraine based on several lines of evidence. CGRP was elevated in jugular venous blood in migraine attacks (Goadsby et al, 1990) and was also elevated interictally in migraine patients (Ashina et al, 2000), and trials with antagonists to the CGRP receptor demonstrated efficacy in acute migraine with aura and migraine without aura (Connor et al 2009; Ho et al, 2008; Ho et al, 2010; Olesen et al, 2004). It is expected that mechanistically antagonism of the

CGRP pathway could be a potentially effective treatment for prophylaxis of episodic as well as chronic migraine.

2.2 AMG 334 Background

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

The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Durham, 2004; Poyner, 1992; Wang et al, 1995; Zimmermann et al, 1996). The site of action for AMG 334 will be predominantly restricted to the periphery due to AMG 334's physical size and structure (antibody). While it is not definitively known whether the CGRP receptors that are relevant for migraine lie within or outside of the blood brain barrier, the following scientific evidence argues strongly for a predominant role for peripheral CGRP in the generation of migraine:

1) CGRP-induced migraine headaches via intravenous (IV) infusion are most likely initiated through peripheral CGRP receptor signaling systems.
    a. Migraine can be initiated by IV infusion of peripherally restricted CGRP peptides in migraine patients (Lassen et al, 2002).
    b. CGRP is a 37-amino acid peptide (molecular weight [MWt] >3700 daltons). It most likely has limited brain penetration across the blood brain barrier (MWt cut off for brain penetration is ~ 500 daltons).
    c. CGRP peptide has a short plasma half -life [mean plasma $T_{½}$~11 min in man (Kraenzlin et al, 1985)].
2) The physical and chemical properties of the CGRP-receptor antagonists olcegepant and telcagepant suggest that their site of action is likely to be in the periphery.
    a. Olcegepant is a peptidic IV CGRP-receptor antagonist that has a molecular weight (MWt 870 daltons) that is greater than the upper limit for blood brain barrier penetration with low oral bioavailability (Rudolf et al, 2005).
    b. A positron emission tomography (PET) study showed minimal brain penetration of telcagepant and low central receptor occupancy (4-10%) at the clinically efficacious dose of 140 mg (Connor et al, 2009; Ho et al, 2010; Hostetler et al, 2013). This degree of receptor occupancy would be unlikely to produce a functional effect.

Furthermore, in a large clinical study, a higher dose of 300 mg was not more efficacious than the 150 mg dose, suggesting that the treatment effect was saturated at a lower dose of 150 mg, which has little to no evidence of brain receptor occupancy (Connor et al, 2009).

3) Antagonist mechanisms typically require much higher receptor occupancy (>60%) to produce a pharmacodynamic (PD) effect resulting in efficacy (Grimwood and Hartig, 2009).

Given the likely peripheral activity of AMG 334 and its mechanism of action, it is unlikely that it will impact the treatment of aura, which is considered a central phenomenon (Eikermann-Haerter et al, 2012).

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

The safety and PK of AMG 334 have been evaluated in three phase 1 studies that administered a single SC dose up to 210 mg, multiple doses up to 140 mg in healthy male subjects, and multiple dose studies of 21 mg and 140 mg in male and female migraine subjects.

Preliminary PK data are available from all subjects in the single dose first-in-human study. AMG 334 exposure increased more than dose proportionally at doses from 1 to 70 mg SC and increased approximately dose proportionally from 70 to 210 mg SC in healthy subjects. The median time of maximum observed concentration (t_{max}) ranged from 4 to 11 days within the dose range of 1 to 210 mg SC. There was no apparent difference in PK results between the healthy subject cohorts and the migraineur cohort.

In preliminary PK results from healthy subjects in the multiple-dose study, the observed mean area under the curve $(AUC)_{0\text{-}28d}$ accumulation ratio at all 3 dose levels (21, 70, and 140 mg) after 3 monthly SC administrations was < 2, which is consistent with the dosing frequency and half-life of monoclonal antibodies.

Refer to the AMG 334 Investigator's Brochure for additional information.

2.3 Rationale

Migraine prophylaxis in chronic migraine is an area of large unmet medical need, with existing therapies not fully efficacious or poorly tolerated. While a variety of medications are used off-label for prophylaxis of chronic migraine, only onabotulinumtoxinA is approved for this indication. CGRP receptor antagonism represents a novel approach to migraine therapies. Results from the AMG 334 phase 2 study (Study 20120178) in subjects with episodic migraine demonstrated that the 70 mg dose resulted in statistically significant and clinically meaningful reductions in monthly migraine days at week 12 compared with placebo (70 mg: -3.40 vs Placebo: -2.28; Difference: -1.12; p = 0.02). Neither the 7 mg nor the 21 mg dose was associated with statistically significant reductions in monthly migraine days. The 70 mg dose produced statistically significant improvements in multiple secondary and exploratory outcome measures, including the 50% responder rate, monthly headache days, and monthly migraine-specific medication treatment days, while neither the 7 mg nor the 21 mg dose resulted in improvements in these measures. Exposure-response analyses over a large range of PK exposures indicate that 70 mg is the lowest dose that results in efficacious concentrations (Lenz et al, 2015; Sun et al, 2015). This study is designed to assess whether a CGRP receptor antagonist is safe and well tolerated in subjects with chronic migraine.

Rationale for AMG 334 Open-label Treatment Dose

A dose of AMG 334 70 mg was originally chosen for this phase 2 study based on the demonstration that this dose and higher doses have been generally well tolerated in phase 1 studies and that this dose is predicted to result in near complete inhibition of the peripheral CGRP receptor for a month. To ensure optimal efficacy is achieved with AMG 334, a higher dose, 140 mg, is currently being evaluated in the double-blind placebo-controlled parent study in chronic migraine (Study 20120295) as well as in a phase 3 study in Episodic Migraine (Study 20120296) and efficacy data are being collected. Based on the AMG 334 phase 2 data in Episodic Migraine, the open-label dose of AMG 334 is being increased in this study to 140 mg to provide additional 6-month and one-year safety data.

The no observed adverse effect level from preclinical toxicology studies was determined to be the high dose, 150 mg/kg SC twice weekly, corresponding to a maximum concentration (C_{max}) of 2620 µg/mL, and $AUC_{0\text{-}7d}$ of 15300 µg•day/mL. This is 275-fold and 296-fold higher than the observed mean C_{max} and $AUC_{0\text{-}28d,}$ in humans after the third

dose of the repeated monthly SC administration of 70 mg and 111-fold and 129-fold higher than the observed mean C_{max} and $AUC_{0\text{-}28\ day}$ after the third monthly subcutaneous administration in humans of 140 mg, after correcting the different dosing frequency in cynomolgus monkeys and humans.

Based on the clinical data generated to date, it is expected that multiple doses of AMG 334 up to 140 mg will be well tolerated in subjects with migraine. AMG 334 has been administered at single doses up to 210 mg SC and 140 mg IV and at doses up to 140 mg SC administered monthly for 3 months in migraine subjects, and in healthy subjects at doses of 280 mg SC administered on day 1 followed by 210 mg SC administered on days 29 and 57. Refer to the AMG 334 Investigator's Brochure for details.

The ability of AMG 334 to inhibit CGRP receptors in humans was evaluated by inhibition of the DBF increase induced by topical application of capsaicin. This capsaicin-induced DBF model has been used to demonstrate proof of pharmacological activity for CGRP antagonists (eg, telcagepant, olcegepant) (Sinclair et al, 2010). Based on the results of the study with AMG 334, a dose of 70 mg is predicted to result in near complete inhibition of the peripheral CGRP receptor for a month. The plasma concentration achieved at 70 mg is approximately 10 fold higher than the 90% effective concentration (EC_{90}) from the DBF model and is sustained for greater than 28 days (Figure 1). The correlation between the DBF model and clinical efficacy in migraine prophylaxis has not been established with AMG 334 although clinical efficacy has been demonstrated in acute migraine treatment for telcagepant (a small molecule CGRP antagonist) at doses with concentrations approximately 2 - 4 fold higher than EC_{90} from the DBF model studies (Connor et al, 2009; Ho et al, 2008; Sinclair et al, 2010).

Figure 1. Predicted Capsaicin-induced Dermal Blood Flow (DBF) Inhibition (Left) and AMG 334 Exposure (Right) for the Phase 2 Doses

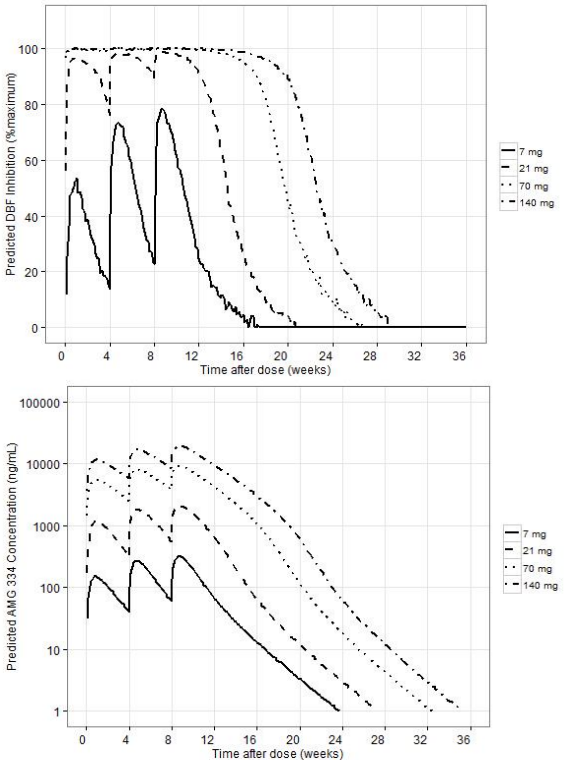

Figure legends: Lines in figures are median predicted DBF inhibition as percent of maximum inhibition (Left) and time courses by dose for AMG 334 concentration (Right). Estimated mean maximum inhibition in DBF response from phase 1 study is approximately 93%.

2.4 Clinical Hypotheses

The clinical hypothesis is that long-term exposure of AMG 334 will be safe and well tolerated in subjects with chronic migraine. In the CHU substudy, it is hypothesized that users will be able to administer a full dose of AMG 334 comparably using either the PFS or **prefilled** AI/pen. No formal hypotheses will be tested.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter, open-label study designed to assess the long-term safety and efficacy of AMG 334. Subjects who complete the 12-week double-blind treatment phase of the AMG 334 20120295 parent study and meet all AMG 334 20130255 eligibility criteria will be enrolled into the study. Enrollment should occur within 14 days after the parent study's week 12 visit. Subjects who enroll in the AMG 334 20130255 study will end the AMG 334 20120295 study and will not participate in the parent study safety follow-up visit.

All subjects who have not yet enrolled in the study will receive open-label AMG 334 140 mg every month (QM) SC for 13 months. Subjects who are already enrolled in the 20130255 study will increase the open-label dose from 70 mg QM to 140 mg QM at the first available opportunity at either week 4, 8, 12, 16, 20, 24, or 28 visits. Subjects who have already completed the week 28 visit will continue to receive 70 mg QM.

All subjects will receive open-label AMG 334 QM SC for 13 months followed by a 12-week safety follow up visit (16 weeks after the last dose of investigational product [IP]).

Investigational product (ie, AMG 334 70 mg or 140 mg) will be dosed QM, SC.

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

It is anticipated that approximately 60 sites across North America and Europe will participate in the study. The same sites that participate in the parent study will be utilized for the study. All sites in the US, Sweden, and Germany may participate in the CHU substudy.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Up to 651 subjects may participate in the study. Up to 80 subjects may participate in the CHU substudy.

The sample size justification is described in Section 10.2.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The planned length of participation in the study for an individual subject is up to 16 months, which includes the 13-month open-label treatment phase and 3 month (12 weeks) safety follow-up after treatment phase.

3.5.2 End of Study

Primary Completion and End of Trial: The time when the last subject is assessed for evaluation in the study (ie, when the last subject completes the study, which includes the

safety follow-up visit after the last dose of investigational product, or is discontinued from the study).

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

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

102 Completed the 12-week study visit and did not end IP early during the double-blind treatment period of the AMG 334 20120295 parent study, and is appropriate for continued treatment

4.1.2 Exclusion Criteria

201 Development of any unstable or clinically significant medical condition, laboratory or ECG abnormality following randomization into the parent study, that in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

Note: Any ECG abnormality noted by the central reader must be evaluated by the investigator to determine if the ECG finding is representative of an unstable or clinically significant medical condition.

202 Any subject who experienced an SAE in the parent study (AMG 334 20120295) for whom the investigator determined that there was a reasonable possibility that the event may have been caused by investigational medicinal product

203 In the opinion of the investigator, subject demonstrated poorly controlled hypertension following randomization into the parent study

204 Systolic blood pressure (BP) 160 mm Hg and/or diastolic BP 100 mm Hg or greater at screening/Day 1

If the systolic BP is > 160 mm Hg or diastolic BP is > 100 mm Hg when initially assessed, BP may be repeated 30 minutes after the initial measurement. BP measurements may only be repeated once after the initial measurement

205 Subject is currently or plans to participate in another clinical study during participation in this study

206 Subject who used excluded concomitant medications between week 8 and week 12 of the parent study

207 Pregnant (as confirmed by the week 12 urine pregnancy test of parent study) or breastfeeding, or is a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product

208 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with AMG 334 through 16 weeks after the last dose of investigational product. Acceptable methods of effective birth control include not having intercourse (true abstinence, when this is in line with the preferred and usual lifestyle of the subject), hormonal birth control methods (pills, shots/injections, implants or patches), intrauterine devices, surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two barrier methods (each partner must use one barrier method) with spermicide - males must use a condom with spermicide; females must choose either a Diaphragm with spermicide, OR Cervical cap with spermicide, OR Contraceptive sponge with spermicide

Female subjects not of childbearing potential are defined as any female who:

- Is post-menopausal by history, defined as
  - Age ≥ 55 years with cessation of menses for 12 or more months, OR
  - Age < 55 years but no spontaneous menses for at least 2 years, OR
  - Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved.

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

209 Likely to not be able or available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (eg, independent completion of electronic diary [eDiary] items) to the best of the subject's and investigator's knowledge

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the IRB/IEC and Amgen-approved ICF before commencement of study-specific procedures.

The screening phase starts when the subject signs and dates the ICF and ends when the subject is enrolled or screen failed (does not meet all screening eligibility criteria, refer to Section 4). The screening phase must not begin prior to the completion of all week 12 procedures in the AMG 334 20120295 parent study and must be completed within 14 days following the week 12 procedures in the parent study. Amgen may grant approval in cases for which additional time is required to confirm eligibility.

Subjects are considered eligible for participation once they have completed week 12 procedures in the parent study and meet all OLE study eligibility criteria. Subjects will be considered enrolled once they have received at least one dose of IP. The investigator is to document the date of enrollment in the subject's medical record and on the enrollment CRF.

Investigators may re-test laboratory values within the allowed screening window (within 14 days after the week 12 visit of the parent study). Reasons for a re-test may include:

- Laboratory value(s) out of range for unclear reasons
- The subject has a medical condition that can be resolved prior to the re-test attempt.

Subject numbers for this study will be an 11 digit number; the first 3 digits will be 255 and the remaining 8 digits will match the last 8 digits of the 11 digit number assigned by IVR System in the parent study. 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.

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

6. TREATMENT PROCEDURES

6.1 Classification of Product and Medical Devices

The Amgen investigational product used in this study is AMG 334.

For subjects participating in the CHU substudy, Amgen investigational product used is AMG 334 either in a PFS or prefilled AI/pen.

6.2 Investigational Product

The double-blind treatment assignments from the parent study will remain blinded after subjects are enrolled into the OLE study until the primary analysis of the 20120295 study is conducted.

6.2.1 Amgen Investigational Product - AMG 334

Amgen investigational product will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Amgen investigational product is also referred to as "study drug."

For subjects in Study 20130255, AMG 334 will be supplied in 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted] % (w/v) polysorbate [redacted], at pH [redacted].

Subjects randomized as part of the CHU substudy will be supplied with a sterile, single use, preservative free solution for SC injection in either two PFS or two **prefilled** AI/pens each containing 1 mL AMG 334 at a concentration of 70 mg/mL formulated with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted] % (w/v) polysorbate [redacted], pH [redacted]

Detailed information regarding the storage and preparation of investigational product will be provided separately in the Investigational Product Instruction Manual (IPIM).

6.2.1.1 Dosage, Administration, and Schedule

Amgen investigational product (ie, AMG 334 70 or 140 mg) will be dosed QM, SC.

The quantity, start date, start times, injection site, stop date, and box number of investigational product are to be recorded on each subject's case report form (CRF) when the site administers the IP. If a subject is enrolled in the CHU substudy, the box number provided to the subject and information obtained at telephone visits should be recorded by the site on each subject's CRF, as described in Section 7.2.1.16.

Overdose with this product has not been reported.

Investigational product will be administered by authorized investigational site study staff as the last procedure after all other study visit procedures have been completed. The one (for 70 mg dose) or two injections (for 140 mg dose) will be administered into the anterior abdominal wall, upper thigh, or upper arm. The injection site location should be the same if two syringes are used. During the CHU substudy, the site will provide IP to the subject to self-administer (two injections using either PFS or AI/pens) on the following day. The injection site location should be the same for both injections. For further details regarding self-administration procedures, the Instructions for Use (IFU) should be consulted.

Subjects should be observed for approximately 30 minutes after IP administration on day 1.

Please refer to specific instructions provided in the IPIM for additional information.

6.2.1.2 Rules for Withholding or Restarting Investigational Product

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

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 for details regarding adverse event reporting.

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

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransaminase [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 (**US FDA**, 2009).

6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product due to Potential Hepatotoxicity

Amgen investigational product will be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

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

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or 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, 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 an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen investigational product should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined above and have no underlying liver disease, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Amgen investigational product should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. 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 (Section 6.3.3).

6.3.3 Criteria for Rechallenge of Amgen Investigational Product After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then Amgen investigational product will be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

6.4 Concomitant Therapy

Throughout the study and while the subject is receiving investigational product, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except **as noted** in Section 6.5. For a subject who prematurely discontinues investigational product, concomitant therapy may be adjusted as needed.

Concomitant therapies are to be collected from enrollment through the end of study. The therapy name, indication, dose, unit, frequency, route, start date, and stop date are to be recorded on each subject's CRF or eDiary.

During the parent study, the subject and investigator are to agree on the medications for the acute treatment of migraine pain and the appropriate dose(s) that the subject may take on an as-needed basis throughout the parent and open-label extension study. Medications for acute treatment of migraine pain include: simple analgesics, combination analgesics, triptans, ergot derivatives, opiates. To avoid confounding the study results, new acute medications for treatment of headache pain should not be introduced and addition of daily medications that fall into the categories of simple analgesics, combination analgesics, triptans, and ergot-derivatives should be avoided, even if the medication is used for indications other than headache.

6.5 Excluded Treatments During Study Period

1. The following medications are excluded **between screening and 4 weeks after last dose of IP**:
    - Divalproex sodium, sodium valproate, topiramate, carbamazepine or gabapentin,
    - All beta blockers (for example: metoprolol, propranolol, timolol, atenolol, nadolol, nebivolol, pindolol, bisoprolol),
    - All tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline),
    - Flunarizine or verapamil,
    - Venlafaxine, desvenlafaxine, duloxetine or milnacipran,
    - Botulinum toxin (injected in the head and/or neck region),
    - Lisinopril,
    - Candesartan,
    - Butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day),
    - Clonidine or guanfacine,
    - Cyproheptadine,
    - Methysergide,
    - Pizotifen

2. The following medications are excluded only if used daily throughout the month for migraine prophylaxis **between screening and 4 weeks after last dose of IP**:
    - Fluoxetine, fluvoxamine,
    - Acetazolamide,
    - Picotamide,
    - Cyclandelate,
    - Ergot-derivatives, steroids, triptans,
    - Nicardipine, nifedipine, nimodipine

    If the above medications are used daily, but not for migraine prophylaxis, the doses should remain stable **between screening and 4 weeks after last dose of IP**.

3. Investigational drugs, devices or procedures (eg, acupuncture, occipital stimulator, transcranial magnetic stimulation) **between screening and 4 weeks after last dose of IP**.

6.6 Medical Devices

The AMG 334 70 mg/mL SureClick™ AI/pen is a single-use, disposable, handheld mechanical injection device that administers a fixed dose of AMG 334 70 mg/mL into subcutaneous tissue. The AMG 334 **prefilled** AI/pen uses the same components as the

commercially available Enbrel SureClick® autoinjector but assembled with a HyFlow syringe.

The AMG 334 PFS is a single-use, disposable, manual injection device that administers a single dose of AMG 334 into subcutaneous tissue. Amgen has developed the AMG 334 PFS presentation using the commercially available sterile 1-mL long glass syringe components procured from Becton Dickinson Pharmaceutical Systems (BD).

In addition, tuberculin 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.

Subjects participating in the CHU substudy will return the AI/pens or PFS back to the clinic for reconciliation and disposal by the site staff using a plastic box provided by Amgen to the clinical sites. Medical devices that are not considered test articles may be used in the conduct of the study as part of standard of care (except for AI/pen or PFS). These devices, such as alcohol prep pads, are commercially available and 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.

Detailed information regarding the medical devices will be provided separately in the IPIM.

6.7 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 any product(s) or device(s) after it is released to the clinic by Amgen or by distributors, and partners with whom Amgen manufactures the material. This includes any products**,** devices**, or combination products** provisioned and/or repackaged/modified by Amgen. **Product(s) or device(s) includes IP.** Any product complaint(s) associated with an investigational product or device supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Refer to the Schedule of Assessments (Table 1) for an outline of the procedures required at each study visit. Each study visit during the open-label treatment phase and the safety follow-up phase has a window of ± 4 consecutive calendar days. The day 1 visit should occur once a subject has completed all 12-week procedures of the parent

study and within 14 days of the 12-week visit of the parent study. The subject may not enroll in this study on the same day as the week 12 visit of the parent study as the investigator must review the week 12 laboratory data and the central read of the week 12 ECG prior to enrolling the subject in order to assess clinical significance of this data as per exclusion criteria.

All study procedures for a given study visit are to be completed on the same day.

Investigators are responsible for ensuring that all study procedures are performed as specified in the protocol.

Study visits should be conducted without additional non-protocol therapies and subjects should be reminded about the investigational nature of the study drug.

Refer to the applicable supplemental (eg, laboratory) manuals for detailed collection and handling procedures.

Table 1. Schedule of Assessments

General Assessments and Administrative Procedures

	Screening	Day 1[a]	Wk 4 / M1	Wk 8 / M2	Wk 12 / M3	Wk 16 / M4	Wk 20 / M5	Wk 24 / M6	Wk 28 / M7	Wk 32 / M8	Wk 36 / M9	Wk 40 / M10	Wk 44 / M11	Wk 48 / M12	Wk 52 / M13 / ET	Wk 64/M16 (16 Wks/4M After Last Dose of IP)
Informed Consent	X															
Physical Examination															X	
Weight															X	X
Vital Signs	X[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG			X		X			X[c]			X[d]				X	
Concomitant Medications Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Administration		X	X	X	X	X	X	X	X	X	X	X	X	X		
SAE/AE Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Enrollment		X														
Calls to IVR/IWR System[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Brings eDiary to Site	X	X	X	X	X			X				X			X	

Footnote defined on last page of the table

Table 1. Schedule of Assessments

Laboratory Procedures and Clinical Outcome Assessments

	Screening	Day 1[a]	Wk 4 / M1	Wk 8 / M2	Wk 12 / M3	Wk 16 / M4	Wk 20 / M5	Wk 24 / M6	Wk 28 / M7	Wk 32 / M8	Wk 36 / M9	Wk 40 / M10	Wk 44 / M11	Wk 48 / M12	Wk 52 / M**13** / ET	Wk 64/M16 (16 Wks/4M After Last Dose of IP)
UDS	Testing as needed throughout study based on investigator's clinical suspicion															
Pregnancy Test-Urine			X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test-Serum																X
Chemistry, Hematology			X		X			X[c]			X[d]				X	X
Urinalysis																X
Biomarker Development																X
PK Sampling								X							X	X
Anti-AMG 334 Antibodies								X							X	X
COAs		Daily[f]					Daily[f]				Daily[f]			Daily[f]		
Migraine Symptom Interference Items		Daily[f]					Daily[f]				Daily[f]			Daily[f]		
PROMIS		Weekly[f]					Weekly[f]				Weekly[f]			Weekly[f]		
MSQ			X	X	X	X	X	X	X	X	X	X	X	X	X	
MIDAS					X			X			X				X	
Novel PRO Substudy: The Migraine Physical Function Impact Diary (MPFID)		Daily[f]					Daily[f]				Daily[f]			Daily[f]		
C-SSRS			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnote defined on last page of the table

Table 1. Schedule of Assessments

Clinical Home Use Substudy Assessments

	Screening[g]	Day 1[h]	Day 28 visit[i]	Day 29 Telephone visit	Day 56 visit[j]	Day 57 Telephone visit	Day 85 visit[k]/ ET[l]
Informed Consent	X						
Randomization to PFS or AI/pen IP self-administration arm		X					
PFS or AI/pen Instruction[m]	X	X					
Physical Examination		X					
Self-administration IP on-site		X					
Self-administration IP at non-clinic setting				X		X	
Study coordinator IP dispense			X		X		
Study coordinator IP reconcile		X			X		X
Inquiry re: administration of IP				X		X	
Review for ADEs		X	X	X	X	X	X
Review for AEs/SAEs				X		X	
Product Complaints Recording (if applicable)		X	X	X	X	X	X

Footnote defined on last page of the table

[a] Day 1 visit should occur once a subject has completed all 12-week procedures of the parent study and within 14 days of the 12-week visit of the parent study.
[b] BP should be measured as part of the screening criteria to determine eligibility (no later than at day 1 as long as BP is taken before subject is enrolled via IVR). Note: BP taken at week 12 of the parent study (AMG 334 20120295) should not be used as screening BP.
[c] Only for subjects who increased IP to 140 mg at week 12, 16, or 20
[d] Only for subjects who increased IP to 140 mg at week 24 or 28
[e] Additional steps during IVR/IWR call to accommodate IP dose increase from 70 mg to 140 mg (between week 4 and week 28).
[f] Collection will start at the end of the applicable scheduled visit and finish at the beginning of the applicable scheduled visit.
[g] Screening must occur 4 weeks prior to the planned start of the CHU substudy (week 8 or week 36 of the 20130255 study). IVR System will be adjusted to accommodate CHU screening and randomization information as required.
[h] Day 1 of the CHU is equivalent to either week 12 or week 40 of the 20130255 study.
[i] Day 28 of the CHU is equivalent to either week 16 or week 44 of the 20130255 study.
[j] Day 56 of the CHU is equivalent to either week 20 or week 48 of the 20130255 study.
[k] Day 85 of the CHU is equivalent to either week 24 or week 52 of the 20130255 study; subject will receive AMG 334 140mg SC administered by site staff using vial formulation and will continue scheduled procedures and assessments as per 20130255 study.
[l] ET: If a subject early terminates the CHU substudy, he/she may receive administration of AMG 334 140 mg SC at site as per 20130255 protocol and will continue 20130255 scheduled procedures and assessments as per 20130255 protocol.
[m] Study coordinator will review PFS or AI/pen training materials (Reference Guide and Instructions for Use) with subject.

7.2 General Study Procedures

7.2.1 Study Specific Assessments

7.2.1.1 Informed Consent

All subjects or legally authorized representatives must personally sign and date the Amgen/IRB/IEC approved ICF before any study-specific procedures are performed.

7.2.1.2 Calls to Interactive Voice Response (IVR) / Interactive Web Response (IWR) System

Sites are to call the Interactive Voice Response (IVR) / Interactive Web Response (IWR) System for the following: to enroll an eligible subject, to obtain the investigational product assignment, to register the end of investigational product, and to register study early termination (ET) or completion. Subject data will be collected in the IVR/IWR system.

7.2.1.3 Physical Examination

A complete physical examination (PE) per standard of care (including neurological exam) will be performed on all subjects.

7.2.1.4 Weight Measurements

Weight is to be measured without shoes and is to be recorded on the Physical Measurements CRF.

7.2.1.5 Vital Signs

The following measurements are to be performed: Systolic/diastolic blood pressure, heart rate, and body temperature.

Blood pressure will be measured in the following manner:

- Subjects should be lying in a supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level (such as with a pillow approximately 13 centimeters tall).
- Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement.
- An appropriately-sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least two measurements (separated by at least 5 minutes) should be made and the average recorded. If there is a high value, it is acceptable to wait approximately 30 minutes before the next two blood pressure measurements are taken for the purpose of averaging and recording in the CRF.
- Neither the subject nor the observer (measurer) should talk during measurement.

The position selected for a subject should be the same that is used throughout the study and documented on the Vital Signs CRF.

If the screening systolic BP is > 160 mm Hg or diastolic BP is > 100 mm Hg when initially assessed, BP may be repeated 30 minutes after the initial measurement. BP measurements may only be repeated once after the initial measurement.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the Vital Signs CRF.

All measurements are to be recorded on the Vital Signs CRF.

7.2.1.6 Urine Drug Screening

During the study, urine drug tests may 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.

7.2.1.7 Pregnancy Testing for Women of Childbearing Potential

Female subjects of childbearing potential will have urine pregnancy tests throughout the treatment phase and a serum pregnancy test at the safety follow-up visit. All urine pregnancy testing will be performed by the local laboratory.

7.2.1.8 Electrocardiogram (ECG)

The subject must be in a supine position in a rested and calm state for at least 5 minutes before the 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.

Sites will use ECG equipment supplied by Amgen. 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 and sign the original ECG tracing and retain the signed tracing with the subject's source documents. The central reader will review all ECGs. At the request of Amgen, 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.

Please refer to the central ECG reader manual for details.

7.2.1.9 Pharmacokinetic (PK) Sampling

Blood samples will be collected and assayed for AMG 334 serum concentration. 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.

Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples.

7.2.1.10 Clinical Outcomes Assessments (COAs) and Electronic Diaries (eDiaries)

Clinical Outcomes Assessments (COAs) will be collected by subjects using a handheld electronic diary (eDiary). The eDiary will collect the following COAs:

- Incidence of headache (ie, migraine with or without aura or non-migraine headache)
- Time of onset of headache
- Time of resolution of headache
- Pain severity per headache
- Pain features (eg, one-sided, throbbing, pain severity, worsens with exercise/physical activity)
- Symptoms (eg, nausea, vomiting, photophobia, phonophobia) and related severity
- Presence of aura
- Use of acute medication

Subjects will use an eDiary every day between the Day 1 and month 3 visit, between the month 5 and 6 visit, between the month 9 and 10 visit, and between the month 12 and 13 visit to report information about their migraine and non-migraine headaches and acute medication use. Subjects will be instructed to bring their eDiary to every study visit during the visits they interact with the eDiary.

The subject's eDiary will also be used for the completion of the following patient-reported outcomes (PROs) measures: Migraine symptom interference items (daily between the Day 1 and month 3 visit, between the month 5 and 6 visit, between the month 9 and 10 visit, and between the month 12 and 13 visit), Patient Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale short form (weekly between the Day 1 and month 3 visit, between the month 5 and 6 visit, between the month 9 and 10 visit, and between the month 12 and 13 visit), Migraine-specific Quality

of Life Questionnaire (MSQ) (monthly), and Migraine Disability Assessment Questionnaire (MIDAS) (every 3 months).

Refer to the eDiary manual for details.

7.2.1.11 Migraine Symptom Interference Items

Individual items will assess the extent to which migraine symptoms interfered with the subject's daily activities within the past 24 hours.

Subjects will complete the migraine symptom interference items using the eDiary.

7.2.1.12 Patient Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale Short Form

The Patient Reported Outcomes Measurement Information System (PROMIS) is a system of reliable, precise measures of patient-reported health status. PROMIS instruments measure concepts such as pain, fatigue, physical function, depression, anxiety, and social function. PROMIS tools can be adapted for use across a wide variety of diseases and conditions.

The PROMIS Pain Interference Scale short form is a 6-item instrument measuring level of pain interference on enjoyment of life, ability to concentrate, day-to-day activities, enjoyment of recreational activities, doing activities away from home, and socializing with others. The recall period is the past 7 days. A single total score of interference is generated.

Subjects will complete the PROMIS Pain Interference Scale short form using the eDiary.

7.2.1.13 Migraine-specific Quality of Life Questionnaire (MSQ)

CCI

7.2.1.14 Migraine Disability Assessment Questionnaire (MIDAS)

CCI

Subjects will complete the MIDAS using the eDiary.

7.2.1.15 Novel PRO Instrument Substudy (Optional)

Subjects may elect to participate in a separate novel PRO substudy to evaluate the impact of migraine. Subjects may elect to participate in both the Novel PRO Instrument substudy and the CHU substudy. The MPFID, a self-administered 13-item instrument that measures physical functioning, will be used to measure physical impairment and the impact of migraine on subjects' everyday activities. Participation in the substudy is optional. Subjects who elect to participate in this PRO substudy will be required to provide separate informed consent and must be willing to complete the MPFID daily during the study timepoints noted below. Approximately 200 subjects will participate in this substudy.

The Migraine Physical Function Impact Diary (MPFID)

CCI

CCI

Subjects participating in the novel PRO substudy will complete the MPFID every day using the eDiary between the Day 1 and month 3 visit, between the month 5 and 6 visit, between the month 9 and 10 visit, and between the month 12 and 13 visit. Subjects may begin to participate in the substudy at any time on or before the month 12 visit.

7.2.1.16 Clinical Home Use Substudy (Optional; Limited to Subjects in US, Germany and Sweden)

Up to 80 subjects may elect to participate in a separate CHU substudy to assess subjects' ability to self-administer 140 mg of AMG 334 for in-home use using either two PFS or two prefilled AI/pens. It is hypothesized that users will be able to self-administer a full dose of AMG 334 comparably using either the PFS or AI/pen. No formal hypotheses will be tested. Safety and tolerability of AMG 334 self-administered using two 1-mL PFS or two 1-mL AI/pens will also be assessed. Participation in the substudy is optional and no additional samples are collected for the substudy. Subjects who elect to participate in this CHU substudy will be required to provide separate informed consent and must meet the following inclusion and none of the exclusion criteria:

Inclusion Criteria: Subjects entering the substudy at week 12 of the 20130255 study must have received open-label 140 mg AMG 334 since day 1 of the 20130255 study. Subjects entering the substudy at week 40 must have received open-label 140 mg AMG 334 since week 28 of the 20130255 study or earlier.

Exclusion Criteria: Unreliability as a study participant based on the investigator's (or designee's) knowledge of the subject [eg, unwillingness to adhere to the protocol, unwilling to self-inject using either an AI/pen or a PFS after review of the IFU and Reference Guide (RG)].

Subjects must provide informed consent and review the **prefilled** AI/pen or PFS IFU and RG either at week 8 or at week 36 to determine if they wish to enroll in the substudy at weeks 12 or 40, respectively. After confirming that the optional CHU substudy ICF has been signed, subjects who meet all inclusion/exclusion criteria may be randomized via IVR System to self-administer AMG 334 using either the PFS or AI/pen (approximately 40 subjects in each arm). Physical examination of the subject with a focus on any skin abnormalities in areas that may be injected will be obtained at enrollment for this substudy; adverse device effects (ADEs) will be assessed on CHU day 1, day 28 and day 56 (at site) and on CHU days 29 and 57 (assessed by telephone visit). Adverse

event**, serious adverse event,** and concomitant medication assessment, vital signs measurement, ECGs, urinalysis, and blood draw for serum chemistry and hematology analytes and anti-AMG 334 antibody assay will be performed as described in the 20130255 study. Subjects will be randomized to self-administer either 2x70mg AMG 334 via PFS or 2x70mg AMG 334 via **prefilled** AI/pen. On the CHU day 1 visit (week 12 or week 40 of AMG 334 20130255 study) the site should review the IFU and RG for AI/pen or PFS with the subject prior to administration of IP (depending upon device subject has been randomized to use). On day 1 of the substudy, subjects will self-administer IP, AMG 334 140 mg SC with either two x 70 mg **prefilled** AI/pen or two x 70 mg PFS, under clinical site supervision. Subjects will be provided a box containing either 2x70 mg PFS or 2x70 mg **prefilled** AI/pen at the CHU day 28 (week 16 or week 44 of AMG 334 20130255 study) and day 56 (week 20 or week 48 of AMG 334 20130255 study) visits and will self-administer IP individually without supervision at home on days 29 and 57 of the CHU substudy. On CHU day 29 and day 57, site staff will call the subject at a previously scheduled time and will ask the subject which injection site was used, if the subject administered a full, partial, or no dose of AMG 334 (after explaining that a full dose means that the entire volume of both PFS or AI/pens were injected) and will document the subject's response in the CRF. If the subject was not able to administer a full dose of AMG 334, the site staff will inquire further to determine if the subject experienced a device failure or use error that prevented the full-dose administration. Safety will be monitored as adverse events, serious adverse events, and ADEs. Day 85 is the end of the CHU substudy and sites will inquire about ADEs. Day 85 of the CHU substudy is equivalent to either week 24 or week 52 of the 20130255 study; site will administer AMG 334 140 mg SC and will continue 20130255 scheduled procedures and assessments as per the 20130255 protocol. If a subject early terminates the CHU substudy, he/she may receive administration of AMG 334 140 mg SC at site as per the 20130255 protocol and will continue 20130255 scheduled procedures and assessments as per the 20130255 protocol. Subjects who elect to early terminate the CHU substudy will not be replaced.

7.2.1.17 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinical rating of suicide behavior and ideation, which consists of a maximum of 20 items and which defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. C-SSRS will be administered to study subjects at each study visit to assess possible suicide 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.

7.2.1.18 Concomitant Medications Recording

Data on all concomitant therapies being taken by the subject should be collected throughout the study. Acute medications taken during aura or to treat headache will be collected in the eDiary during the periods of daily diary collection, and data will include the medication name, date of administration, time of administration, dose, and route of administration. Acute medications ongoing at the time of enrollment will be collected in the CRF. Any new or change to dose regimen for an ongoing acute medication will also be collected in the CRF.

Other concomitant therapies will be collected from the time of enrollment and throughout the end of study or ET in the CRF, and data will include the generic drug name/treatment, indication, and dates of administration.

Refer to Section 6.4 regarding concomitant therapy and Section 6.5 for the list of treatments excluded during the study.

7.2.1.19 Adverse Event Reporting

Adverse event information should be collected throughout the study and recorded at each study visit. Refer to Section 9 for details.

7.2.1.20 Laboratory Assessments

Sites must utilize the central laboratory for subject eligibility and assessments during the study, unless stated otherwise. Laboratory samples will be processed and sent to the central laboratory which is responsible for either completing the assessment or shipping the samples to Amgen for assay, depending on the assessment. The central laboratory will be utilized for parameters such as complete blood count (CBC) with differential, serum chemistry, urine drug screening and urinalysis. Samples for PK testing, biomarker development, and anti-AMG 334 antibody testing will be sent to the central laboratory and the central laboratory will forward the samples to Amgen (or designee) for analysis. Sites will use their local laboratory for urine pregnancy testing (for WOCBP).

Please refer to the central laboratory manual for instructions on the collection, processing, and shipping of samples.

Any sample collected according to the Schedule of Assessments (Table 1) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to

ensure subject safety. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This may also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

Analyte Listing (all run by central laboratory, unless otherwise noted as "Amgen/designee" or "local" laboratory. Please refer to the central laboratory manual for the complete listing of analytes run by the central laboratory):

Chemistry	**Urinalysis**	**Hematology**	**Other Labs**
Sodium	Specific gravity	RBC	Pregnancy testing-urine (local)
Potassium	pH	Hemoglobin	Pregnancy testing-serum
Chloride	Blood	Hematocrit	Urine drug screening
Bicarbonate	Protein	MCV	PK (Amgen/designee)
Total protein	Glucose	MCH	Anti-AMG 334 antibodies (Amgen/designee)
Albumin	Bilirubin	MCHC	Biomarker development (Amgen/designee)
Calcium	WBC	RDW	
Magnesium	RBC	Reticulocytes	
Phosphorus	Epithelial cells	Platelets WBC	
Glucose	Bacteria	WBC Differential	
BUN or Urea	Casts	• Bands/stabs	
Creatinine eGFR MDRD Uric acid	Crystals	• Eosinophils • Basophils	
Total bilirubin CPK		• Lymphocytes • Neutrophils	
Direct bilirubin		• Monocytes	
Alk phos		Myeloblasts	
AST (SGOT)		• Promyelocytes	
ALT (SGPT)		• Myelocytes	
Cholesterol		• Metamyelocytes	
HDL LDL		• Atypical lymphocytes	
Triglycerides TSH		Nucleated RBC	

7.2.2 Screening

After confirming the ICF has been signed, the following procedures are to be completed:

- Vital signs
- Subject brings eDiary to site
- Screening call to IVR/IWR System

7.2.3 Day 1

Review laboratory and central reader ECG report from week 12 visit of AMG 334 20120295 study

Vital signs (if not measured at Screening visit)

After confirming subject eligibility, the following procedures are to be completed:

- Enrollment of the subject using the IVR/IWR System
- Concomitant medications recording
- Serious and non-serious adverse event recording
- Subject brings eDiary to site
- Novel PRO Substudy: The MPFID (optional)
- Administration of AMG 334 140 mg SC. Administration of AMG 334 should be the last procedure performed at each study visit.

7.2.4 Open-label Treatment Phase

The following procedures are to be completed during the open-label treatment phase at time points designated in the Schedule of Assessments (Table 1).

- Physical examination (including neurological examination) as per standard of care
- Weight
- Vital signs
- ECG
- Laboratory assessments using the central laboratory: urine drug screen (based upon the investigator's clinical suspicion), chemistry and hematology panels
- Urine pregnancy test
- PK sampling
- AMG 334 antibody collection
- COAs, migraine symptom interference items and PROMIS
- C-SSRS
- MSQ and MIDAS. The subject will complete these PROs while in the clinic, using the eDiary. For each study visit, these PROs should be completed prior to invasive procedures (eg, blood draws).

- Novel PRO Substudy: The MPFID (optional)
- Concomitant medications recording
- Serious and non-serious adverse event recording
- Subject brings eDiary to site
- Administration of AMG 334 70 mg or 140 mg SC QM. Administration of AMG 334 should be the last procedure performed at each study visit.
- Increase IP to 140 mg for subjects enrolled on 70 mg at first available opportunity at either week 4, 8, 12, 16, 20, 24 or 28 (during regular IP Assignment IVRS/IWRS call)
- CHU Substudy in US, Germany, and Sweden (optional)
  - After confirming the ICF has been signed, the following procedures are to be completed:
  - Screening (20130255 week 8 or 36): Review of IFU and RG for both PFS and **prefilled** AI/pen with subject
  - After confirming subject eligibility, the following procedures are to be completed:
    - Day 1 (20130255 week 12 or 40):
      - Randomization of the subject to PFS or **prefilled** AI/pen self-administration using the IVR/IWR System
      - Site to instruct subject on how to self-administer AMG 334 with either PFS or **prefilled** AI/pen by reviewing entire IFU and RG
      - Physical examination of subject with particular attention to any skin abnormalities in areas that might be used for IP self-administration
      - Subject self-administration using either PFS or **prefilled** AI/pen under site supervision
      - Review for ADEs**, adverse events, and serious adverse events**
      - Study Coordinator to reconcile IP (PFS or **prefilled** AI/pen)
      - Product Complaint Recording (if applicable)
    - Day 28 (20130255 week 16 or 44):
      - Study coordinator dispenses PFS or **prefilled** AI/pen to subject for self-administration on day 29
      - Telephone call time scheduled for day 29 (Note, telephone visit must occur after subject has self-administered IP)
      - Product Complaint Recording (if applicable)
    - Day 29:
      - Subject self-administers AMG 334 using either PFS or **prefilled** AI/pen in non-clinic setting
      - Telephone visit with study coordinator to inquire of subject if he/she administered a full, partial, or no dose of AMG 334
      - If the subject was not able to administer a full dose of AMG 334, the site staff will inquire further to determine if the subject experienced a device failure or use error that prevented the full-dose administration

- Review adverse events/ADEs/serious adverse events
- Product Complaint Recording (if applicable)

- Day 56 (20130255 week 20 or 48):
  - Study coordinator dispenses PFS or **prefilled** AI/pen to subject for self-administration on day 57
  - Telephone call time scheduled for day 57 (Note, telephone visit must occur after subject has self-administered IP)
  - Product Complaint Recording (if applicable)
- Day 57:
  - Subject self-administers AMG 334 using either PFS or **prefilled** AI/pen in non-clinic setting
  - Telephone visit with study coordinator to inquire of subject if he/she administered a full, partial, or no dose of AMG 334
  - If the subject was not able to administer a full dose of AMG 334, the site staff will inquire further to determine if the subject experienced a device failure or use error that prevented the full-dose administration
  - Review adverse events/ADEs/serious adverse events
  - Product Complaint Recording (if applicable)
- Day 85 (20130255 week 24 or 52): End of CHU substudy
  - Study coordinator inquires about any ADEs, product complaint recording (if applicable)
  - Subject continues all 20130255 study assessments and IP is administered at site as per 20130255 protocol using vial formulation

7.2.5 Safety Follow-up

The following procedures are to be completed for the safety follow-up as designated in the Schedule of Assessments (Table 1):

- Register subject's end of study using the IVR/IWR System
- Weight
- Vital signs
- Laboratory assessments using the central laboratory: urine drug screen (based upon the investigator's clinical suspicion), urinalysis, pregnancy testing (serum), chemistry and hematology panels
- PK sampling
- Biomarker development collection
- AMG 334 antibody serum sampling
- C-SSRS

- Concomitant medications recording
- Serious and non-serious adverse event recording. (Note: Serious and non-serious adverse events are to be collected through 16 weeks after the last dose of investigational product).

7.3 Antibody Testing Procedures

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

Sites will be notified of any positive neutralizing antibody results to the investigational product at the end of the study for each subject. If results are not provided, no neutralizing antibodies to the investigational product have been detected.

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

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-AMG 334 antibody response may also be asked to return for additional follow-up testing.

7.4 Biomarker Development

Blood samples are to be collected for biomarker development, and samples collected for other testing could be utilized for 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 identifying disease subtypes, guiding therapy, and/or predicting disease severity.

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

7.5 Sample Storage and Destruction

Any sample collected according to the Schedule of Assessments (Table 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 migraine, the dose response and/or prediction of response to AMG 334, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining 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.

Refer to Section 11.3 regarding subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

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 options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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

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

8.3 Reasons for Removal From Treatment and Study

8.3.1 Reasons for Removal From Treatment

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

- Subject request
- Safety concern (eg, due to an adverse event, failure to follow contraception, breast feeding, requirement for treatment not allowed in the protocol, and/or protocol requirements)
- Death
- Lost to follow-up
- Decision by sponsor (other than subject request, safety concern, lost to follow-up)
- Lack of efficacy

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

An adverse device effect (ADE) is any adverse event related to the use of a 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.

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

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

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

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could

include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of study are reported using the applicable CRF (eg, Adverse Event Summary), including events that are reported to the Event Adjudication Committee for adjudication.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of relatedness to investigational product **and/or any study-mandated activity or procedure**, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The 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.

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a new event on the Adverse Event Summary CRF.

The investigator must assess whether the adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the investigational product?"

During the CHU, the investigator must assess whether the adverse event is possibly related to the IP and/or device. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the IP. The investigator must assess whether the adverse event is possibly related to the PFS or **prefilled** AI/pen used to administer IP. The relationship is indicated by a

"yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the device?

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

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the ICF through end of study are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF**,** including events that are reported to the Event Adjudication Committee for adjudication.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

In addition to the attributes listed in Section 9.1.2, the investigator must also complete the Serious Adverse Events section of the Adverse Event Summary CRF.

See Appendix B for a sample of the Serious Adverse Event Worksheet.

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

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

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

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

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

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

9.3 Adverse Event Adjudication

In order to carefully evaluate cardiovascular and cerebrovascular events during the trial, all adverse events that are deemed to be of potential cardiovascular or cerebrovascular etiology will be submitted to an independent committee for adjudication. Detailed definitions of these events to be adjudicated, including mapping of pre-defined preferred terms potentially indicative of cardiovascular or cerebrovascular etiology, will be provided in the Event Adjudication Committee Charter. Adjudication of these adverse

events will be based on clinical, laboratory, and/or imaging data ordered at the treating physician's discretion to assess and treat the event.

The Event Adjudication Committee will be comprised of a group of experienced clinicians with expertise in cardiology and neurology. The Event Adjudication Committee will be responsible for the review and adjudication of the selected adverse events in a blinded manner. The responsibilities and procedures of the Event Adjudication Committee will be described in the Event Adjudication Committee Charter.

9.4 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject while the subject is taking investigational product through 16 weeks after the last dose of investigational product, report the pregnancy to Amgen as specified below.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen's Global Patient Safety will follow**-up with** the **investigator regarding additional information that may be requested.**

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

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, neonatal death, or there is a fetal or neonatal congenital anomaly), the investigator will report the event as a serious adverse event.

If a lactation case occurs while the female subject is taking investigational product through 16 weeks after the last dose of investigational product, report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). **Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.**

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

The primary endpoint for the study is subject incidence of adverse events.

CHU Substudy

- Subject-reported outcome of attempted full-dose administration at each of day 29 and day 57

10.1.1.2 Secondary Endpoints

- Change from baseline in monthly migraine days at assessment timepoints
- Achievement of at least a 50% reduction from baseline in monthly migraine days at assessment timepoints
- Change from baseline in monthly acute migraine-specific medication treatment days at assessment timepoints
- Change from baseline in cumulative monthly headache hours at assessment timepoints

CHU Substudy

- Subject incidence of adverse events, serious adverse events, and adverse device effects

10.1.1.3 Exploratory Endpoints

- Change from baseline in monthly migraine attacks at assessment timepoints
- Change from baseline in monthly headache (migraine and non-migraine headache) days at assessment timepoints
- Change from baseline in monthly moderate and severe headache (migraine and non-migraine headache) days at assessment timepoints
- Reduction from baseline in monthly average severity of migraine pain at assessment timepoints
- Change from baseline in monthly average severity of migraine related symptoms (nausea, vomiting, phonophobia, photophobia) for qualified migraine headaches at assessment timepoints
- Change from baseline in migraine-specific quality of life, as measured by the MSQ, version 2.1 at assessment timepoints
- Change from baseline in migraine-related disability, as measured by the MIDAS at assessment timepoints
- Change from baseline in pain interference with daily activities and migraine-specific impact, as measured by the PROMIS Pain Interference Scale short form and single pain and migraine symptom interference questions at assessment timepoints
- Change in physical impairment over time as measured by the MPFID

- Change in impact on everyday activities over time as measured by the MPFID
- AMG 334 exposure

10.1.1.4 Clinical Outcome Assessments - Definition of Terms Included in Endpoints

Clinical outcome assessments will be determined via diary data.

- Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined either as a migraine without aura or a migraine with aura as outlined below:

  1. A migraine without aura, lasting for ≥ 4 continuous hours, and meeting criteria a and/or b:

     a) ≥ 2 of the following pain features:
        - Unilateral
        - Throbbing
        - Moderate to severe
        - Exacerbated with exercise/physical activity

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

OR

  2. A migraine with aura and meeting criteria a and b:

     a) Meeting ≥ 1 of the following fully reversible aura symptoms:
        - Visual
        - Sensory
        - Speech and/or language
        - Retinal
        - Brainstem

     b) Aura is accompanied, or followed within 60 minutes, by headache lasting for ≥ 4 continuous hours

  If the subject took a triptan or ergot-derivative on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

- Headache Day: Any calendar day in which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache lasting ≥ 4 continuous hours, or a headache of any duration for which acute medication was administered (Refer to Section 6.4) for treatment of headache pain.

- Headache Day with moderate or severe intensity: Any calendar day in which the subject experiences a headache, with headache pain lasting ≥ 4 continuous hours, and a peak severity of moderate to severe, or of any severity or duration if the subject takes a triptan or ergot-derivative for headache pain
- Monthly Migraine Days: Number of migraine days in any 28-consecutive day interval relative to study day 1. See above for the definition of a migraine day.
- Monthly Headache Days: Number of headache days in any 28-consecutive day interval relative to study day 1. See above for the definition of a headache day.
- Migraine Attack: An episode of any qualified migraine headache or episode for which the subject took a triptan or ergot-derivative to treat headache or aura. The following rules will be used for distinguishing an attack of long duration from two attacks, or for distinguishing between attacks and relapses:

  a) A migraine attack which is interrupted by sleep or temporarily remits, and then recurs within 48 hours after onset of the attack will be considered as one attack, and not two.

  b) An attack primarily treated successfully with medication but with relapse within 48 hours will be considered as one attack.

10.1.2 Analysis Sets

The full analysis set (FAS) includes all subjects who were enrolled in the study and received at least one dose of investigational product. All subjects participating in the PRO substudy and have at least one monthly score for the MPFID will be included in the PRO analysis set. All subjects enrolled in the CHU substudy will be included in the CHU analysis set.

10.1.3 Covariates and Subgroups

Since no formal statistical testing is planned for either safety or efficacy endpoint, no covariate analysis will be performed.

Subgroups:

- Region (North America vs. other)
- Medication overuse (Yes vs. no)

10.2 Sample Size Considerations

All subjects who completed the 12-week double-blind treatment phase of the parent study, meet the inclusion and exclusion criteria for the 20130255 OLE study, and consent to receive IP will be eligible to be enrolled. Up to 651 subjects may participate in the study.

In the CHU Substudy: Assuming 5% of subjects per treatment group discontinue IP and 90% of the remaining subjects respond that they administered a full dose, then the anticipated distribution of responses per treatment group at a planned visit would be

5% categorized as not attempting due to discontinuing IP, 85.5% responding that they administered a full dose, and 9.5% responding that they did not administer a full dose. The associated 95% confidence interval halfwidths with 40 subjects per group are 6.8%, 10.9%, and 9.1%, respectively. The anticipated 95% confidence interval halfwidth for the difference between treatment groups in the proportion of subjects administering a full dose is 15.4%. The discontinuation rate is expected to be less than 5% and the rate of administering a full dose is expected to be greater than 90%, and therefore these calculations are anticipated to be lower bounds. Calculations were performed using nQuery Advisor 7.0.

10.3 Planned Analyses

10.3.1 Interim Analyses

On an annual basis or until an administrative decision is made to close the study, descriptive statistics of safety and efficacy will be produced for use in the annual report and/or to support publications, if warranted.

An analysis of the data collected as part of the CHU substudy will be performed once the substudy has been completed. In addition, an additional interim analysis may be performed as deemed necessary. However, there are no stopping rules applied based on any interim analysis.

10.3.2 Final Analysis

The final analysis for the study will be performed at the end of study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

All subjects who have received at least one dose of AMG 334 in the study will be included in the data analysis according to their allocated treatment groups in the parent study, as well as an overall analysis (of all subjects in the OLE study).

For the purpose of primary analysis for secondary and exploratory endpoints in the 20130255 OLE study, baseline is defined as baseline of the AMG 334 20120295 parent study (from the first day subject used eDiary in baseline at week -4 study visit through the day prior to study day 1). However, change from the parent study Month 3 data will also be evaluated.

Descriptive statistics will be presented for all endpoints. Summary statistics for continuous variables will include number of subjects, mean, median, standard deviation,

standard error, lower and upper quartiles, minimum, and maximum. For categorical variables, frequency and percentage will be given.

No formal statistical tests will be performed. Missing values for safety endpoints will not be imputed.

Subject disposition, demographics, and baseline characteristics will be summarized. The full analysis set will be utilized to tabulate subject disposition of all enrolled subjects, the demographic data, baseline disease characteristics, efficacy, and safety endpoints.

10.4.2 Efficacy Endpoint

Descriptive summaries on efficacy endpoints will be provided by treatment group of the AMG 334 20120295 parent study (ie, AMG 334 70 mg, AMG 334 140 mg), treatment group of the AMG 334 20130255 study (AMG 334 70 mg if the max dose for a subject is 70 mg, AMG 334 140 mg if the max dose for a subject is 140 mg), and study visit using the efficacy analysis set.

10.4.3 Safety Endpoints

For safety endpoints, all enrolled subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed based on the maximum actual treatment dose received using safety analysis set.

The Medical Dictionary for Regulatory Activities (MedDRA) version 16 or later will be used to code all adverse events.

The exposure-adjusted subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term.

Overall summary table of all treatment-emergent adverse events, serious, fatal, leading to withdrawal from investigational products, and treatment-related adverse events will be provided. Tables of fatal adverse events, serious adverse events, and adverse events leading to withdrawal from investigational product will also be provided by system organ class and preferred term.

Treatment-emergent adverse events and serious adverse events will be tabulated by preferred term in descending order of frequency.

Subject incidence of adverse events, serious adverse events, and ADEs will be summarized by system organ class and preferred term for subjects enrolled in the CHU substudy.

Shift tables based on CTCAE grade relative to baseline will be tabulated by treatment group for selected laboratory analytes.

The analyses of vital signs (systolic blood pressure, diastolic blood pressure, heart rate, temperature, weight) will include summary statistics of change from baseline measure over time by treatment group.

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.

The incidence and percentage of subjects who develop anti-AMG 334 antibodies (binding and if positive, neutralizing) at any time will be tabulated by treatment group.

The analysis of subject-reported outcome of attempted full-dose administration at each of day 29 and day 57 as collected in the CHU substudy will include calculating the proportion of each of the subject reported outcomes of attempted full-dose administration at each of weeks 4 and 8. For all subjects who have not discontinued IP, a subject report of full dose administration will be considered a “yes” response, and a subject report of partial or no dose administered will be considered a “no” response. The proportion of each possible pattern of responses across the two visits will also be estimated. Ninety-five percent confidence intervals will be provided for each group and the difference in proportions between the groups.

10.4.4 Others

Descriptive summaries of the primary and secondary endpoints may be provided by subgroups stated in Section 10.1.3.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the 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 date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (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.

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

Amgen **may** amend the protocol **at any time. After Amgen amends the protocol, Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment.**

The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the **Clinical Trial Agreement**. The investigator is to notify the IRB/IEC in writing of the study's completion or ET and send a copy of the notification to Amgen.

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

12.2 Study Documentation and Archive

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

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

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, the MSQ and MIDAS CRFs can be used as source documents.

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, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Medical devices (ie, syringes) documentation, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

All paper CRFs are to be typed or filled out with a black ballpoint pen and must be legible.

- Corrections to paper forms are to be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Amgen Delegation of Authority Form. No erasures, correction fluid, or tape are to be used.

- Corrections to electronic forms are automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are sent to the site for completion and returned to Amgen.
- The investigator signs (or inscribes and seals, if applicable) and dates the indicated places on the CRF. These signatures indicate that the investigator inspected or reviewed the data on the CRF the data queries, and the site notifications, and agrees with the content.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform **S**elf-**E**vident **C**orrections **(SEC)** to obvious data errors in the clinical trial database. **SECs will be** documented in the **eCRF instructions available in the EDC system**. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and ET) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the

Schedule of Assessments (Table 1), the investigator can search publicly available records [where permitted]) to ascertain survival status. This ensures that the data sets produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the **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 should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; (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 should meet conditions 1, 2, 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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.

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version 4 (CTCAE v4) is available at the following location:

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

Grade	Clinical Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

A semi-colon indicates 'or' within the description of the grade.
Activities of Daily Living (ADL):
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 Section 6.3 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.

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

Sections 6.3.1 and 6.3.2 or who experience AST or ALT elevations >3 x ULN are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct bilirubin), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for PK analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)

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

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

Appendix B. Sample Serious Adverse Event Report Form

AMGEN 20130255 | Clinical Trial Serious Adverse Event Report – Phase 1–4 | ❑New ❑Follow-up

Notify Amgen Within 24 Hours of knowledge of the event

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ❑F ❑M	Race

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day_____Month____Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *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	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by AMG 334? **If yes see section 10** No✓	Yes✓	**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device? No✓	Yes✓	If Yes, what device?	**Outcome of Event** **01** Resolved **02** Resolving **03** Not resolved **04** Fatal	Check only if event is related to study procedure *eg, biopsy*

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized? ❑No ❑Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date 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
AMG 334 ✓Open Label						

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant 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✓

AMGEN 20130255

Clinical Trial Serious Adverse Event Report – Phase 1–4

Notify Amgen Within 24 Hours of knowledge of the event

☐New ☐Follow-up

Site Number	Subject ID Number

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:

Test										
Date (Day Month Year)	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

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

Signature of Investigator or Designee	Title	Date

Appendix C. Pregnancy 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: 20130255

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

Appendix D. Lactation Notification Worksheet

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: 20130255

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

Amendment 3

Protocol Title: An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334

Amgen Protocol Number AMG 334 20130255

EudraCT number 2013-005311-27

Amendment Date: 31 March 2016

Rationale:

This protocol is being amended to:

- clarify language regarding length of time surrounding excluded treatments
- align with current protocol template language (Sections 9 and 12)
- update pregnancy and lactation notification worksheets
- clarifications made to product complaints section
- review of adverse events and serious adverse events added to Open-label treatment phase
- serious adverse events collection added for Clinical Home Use Substudy
- correct typographical, grammatical, and formatting errors throughout the protocol

Description of Changes:

Section: Global

Change: Updated version date from 14 October 2015 to **31 March 2016** throughout the protocol.

Section: Global

Change: Added "**prefilled**" before all instances of "AI/Pen" to maintain consistency throughout the document.

Section: Global

Change: Typographical, grammatical, and formatting errors were corrected throughout the protocol.

Section: Title Page

Add:

Amendment 3 **31 March 2016**

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration

Add:

Investigational product (IP) (ie, AMG 334 70 mg or 140 mg) will be dosed QM by SC injection. **For subjects participating in the CHU substudy, IP is AMG 334 140 mg in either a PFS or prefilled AI/Pen.**

Section: Study Glossary

Add:

eCRF	**Electronic case report form**
ICMJE	**International Committee of Medical Journal Editors**
IP	Investigational product (ie, AMG 334 **or if participating in CHU substudy, AMG 334 in either a PFS or prefilled AI/Pen)**
SEC	**Self-evident corrections**

Section: 6.3 Hepatotoxicity Stopping and Rechallenge Rules

Add:

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransaminase [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 **(US FDA**, 2009).

Section: 6.4 Concomitant Therapy, Paragraph 1

Replace:

Throughout the study and while the subject is receiving investigational product, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

With:

Throughout the study and while the subject is receiving investigational product, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except **as noted** in Section 6.5.

Section: 6.5 Excluded Treatments During Study Period, Bullet 1

Replace:

1. The following medications are excluded throughout the study:

With:

1. The following medications are excluded **between screening and 4 weeks after last dose of IP**:

Section: 6.5 Excluded Treatments During Study Period, Bullet 2

Add:

2. The following medications are excluded only if used daily throughout the month for migraine prophylaxis **between screening and 4 weeks after last dose of IP**:

Section: 6.5 Excluded Treatments During Study Period, Bullet 2, Paragraph 2

Add:

If the above medications are used daily, but not for migraine prophylaxis, the doses should remain stable **between screening and 4 weeks after last dose of IP**.

Section: 6.5 Excluded Treatments During Study Period, Bullet 3

Replace:

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

With:

3. Investigational drugs, devices or procedures (eg, acupuncture, occipital stimulator, transcranial magnetic stimulation) **between screening and 4 weeks after last dose of IP**.

Section: 6.7 Product Complaints

Add:

This includes any products**,** devices**, or combination products** provisioned and/or repackaged/modified by Amgen. **Product(s) or device(s) includes IP.**

Section: 7.2.1.16 Clinical Home Use Substudy (Optional; Limited to Subjects in US, Germany and Sweden), Paragraph 4

Add:

Adverse event**, serious adverse event,** and concomitant medication assessment, vital signs measurement, ECGs, urinalysis, and blood draw for serum chemistry and hematology analytes and anti-AMG 334 antibody assay will be performed as described in the 20130255 study.

Section: 7.2.4 Open-label Treatment Phase, Day 1 (20130255 week 12 or 40), Bullet 5

Add:

- Review for ADEs, adverse events, and serious adverse events

Section: 9.1.1 Definition of Adverse Events, Paragraphs 2 and 3

Add:

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

An adverse device effect (ADE) is any adverse event related to the use of a 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.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria, Paragraph 2, Bullet 4

Add:

- Assessment of relatedness to investigational product **and/or any study-mandated activity or procedure**, and

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria, Paragraph 7

Add:

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

Section: 9.4 Pregnancy and Lactation Reporting, Paragraph 2

Replace:

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen's Global Patient Safety will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With:

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen's Global Patient Safety will follow**-up with** the **investigator regarding additional information that may be requested.**

Section: 9.4 Pregnancy and Lactation Reporting, Paragraphs 3 and 4

Add:

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

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, neonatal death, or there is a fetal or neonatal congenital anomaly), the investigator will report the event as a serious adverse event.

Section: 9.4 Pregnancy and Lactation Reporting, Paragraph 6

Add:

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). **Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.**

Section: 12.1 Protocol Amendments and Study Termination, Paragraph 1

Replace:

If Amgen amends the protocol, agreement from the investigator must be obtained.

With:

Amgen **may** amend the protocol **at any time. After Amgen amends the protocol, Investigator is to return the signed Investigator's Signature page confirming agreement to continue participation in the study according to the amendment.**

Section: 12.1 Protocol Amendments and Study Termination, Paragraph 2

Replace:

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract.

With:

Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the **Clinical Trial Agreement**.

Section: 12.3 Study Monitoring and Data Collection, Paragraph 7

Replace:

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan.

With:

Amgen (or designee) will perform **S**elf-**E**vident **C**orrections **(SEC)** to obvious data errors in the clinical trial database. **SECs will be** documented in the **eCRF instructions available in the EDC system**.

Section: 12.6 Publication Policy, Paragraph 1

Replace:

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, 2013), which states:

With:

Authorship of any publications resulting from this study will be determined on the basis of the **International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals,** which states:

Section: 13. References

Add:

United States Food Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf. Accessed 05 April 2016.

Section: Appendix C. Pregnancy Notification Worksheet

Replace:

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: AMG 334 20130255

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Effective Date: March 27, 2011 Page 1 of 1

With:

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: 20130255

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

Section: Appendix D. Lactation Notification Worksheet

Replace:

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: AMG 334 20130255

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

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

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With:

AMGEN® Lactation Notification Worksheet

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

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Effective Date: 03 April 2012, version 2. Page 1 of 1