Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Amgen Protocol Number (AMG 334) 20120309

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Date:	20 August 2015
Amendment 1:	**26 April 2017**
Amendment 2:	**05 June 2017**

NCT Number: 2630459
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled "A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention," dated **05 June 2017**, 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 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: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Study Phase: 2

Indication: Prevention of migraine

Primary Objective: To evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine days, in subjects with episodic migraine

Secondary Objectives:

Efficacy:

- To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects with at least 50% reduction from baseline in mean monthly migraine days
- To evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly acute migraine-specific medication treatment days

Safety: To evaluate the safety and tolerability of AMG 334

Clinical Home Use Substudy (During the Open-label Treatment Phase [OLTP]) Objectives:

- **Primary Objective: To assess users' ability to administer a full dose (140 mg) of AMG 334 in home-use, using either 2 pre-filled 70 mg/mL autoinjectors/pens (AIs/pens) or 1 pre-filled 140 mg/mL AI/pen**
- **Secondary Objective: To assess the safety and tolerability of AMG 334 administered using either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen**

Hypothesis: In subjects with episodic migraine, AMG 334 reduces the mean monthly migraine days from baseline, compared to placebo. **In the clinical home use (CHU) substudy, it is hypothesized that users will be able to administer a full dose of AMG 334 comparably using 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. No formal hypotheses will be tested in the CHU substudy.**

Primary Endpoint: Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each of the last three months (months 4, 5, and 6) of the double-blind treatment phase.

Secondary Endpoints:

Efficacy:

- Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in mean monthly acute migraine-specific medication treatment days over the last three months (months 4, 5, and 6) of the double-blind treatment phase

Safety:

- Adverse events
- Clinical laboratory values and vital signs
- Anti-AMG 334 antibodies

Clinical Home Use Substudy (During the OLTP) Endpoints:

Primary Endpoint: Subject-reported outcome of attempted full-dose administration at day 29 and day 57.

Secondary Endpoint: Subject incidence of adverse events, serious adverse events, and adverse device effects

Study Design: Phase 2, multicenter, randomized, stratified, double-blind, placebo-controlled, parallel-group study of subjects with episodic migraine. Approximately 459 subjects will be

randomized 2:1:2:2 to placebo, AMG 334 28 mg, AMG 334 70 mg, or AMG 334 140 mg, respectively. The randomization will be stratified by prior/current treatment with migraine prophylactic medication (current migraine prophylactic medication treatment vs prior migraine prophylactic medication treatment only vs no prior or current migraine prophylactic medication treatment).

Approximately 50 subjects will be enrolled in the AMG 334 20120309 CHU substudy to assess the subject's ability to self-administer 140 mg of AMG 334 for in-home use. Subjects will be randomized 1:1 to use either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. Participation in the substudy is optional, and no additional samples will be collected for the substudy.

Sample Size: Approximately 459 randomized

Summary of Subject Eligibility Criteria: Adults 20 to 65 years of age with history of migraine with or without aura for ≥ 12 months and who experience ≥ 4 to < 15 migraine days per month with < 15 headache days per month.

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.2.

Amgen Investigational Product Dosage and Administration: Investigational product (IP) (ie, AMG 334 and placebo) will be dosed monthly (QM) by subcutaneous (SC) injection. Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20). **During the OLTP, AMG 334 70 mg or 140 mg QM SC will be administered, depending on the subject's visit completion status after institutional review board (IRB) approval of Protocol Amendment 2.**

Investigational product will be packaged in 3 mL clear glass vials for the double-blind treatment phase and 1 mL pre-filled syringes for the **OLTP**. For the vials and pre-filled syringes, AMG 334 will be presented as 70 mg/mL AMG 334. Placebo vials will be packaged to match AMG 334 but will not contain AMG 334.

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

See Section 6.2.1 for further details.

Procedures: After signing informed consent, subjects will enter the screening phase. The screening phase is composed of an initial screening phase (up to 3 weeks) followed by a 4-week baseline phase. At the day 1 visit, eligible subjects will be enrolled (ie, randomized) into the 24-week double-blind treatment phase and will begin to receive double-blind investigational product QM SC. During the double-blind treatment phase, 3 SC injections are to be given for each investigational product administration (ie, at day 1 and weeks 4, 8, 12, 16, and 20) to maintain the dose-level blinding. At the week 24 visit, subjects will be entered into the **76**-week **OLTP** and will begin to receive open-label AMG 334.

After IRB approval of Protocol Amendment 2, the 24-week double-blind treatment phase is followed by a 76-week OLTP with the dose determined by the subject's week 48 status:

(1) Subjects who have already completed the week 48 visit will continue to receive open-label AMG 334 70 mg QM SC (OL70) for a total of 76 weeks.

(2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label AMG 334 140 mg QM SC for 76 weeks.

(3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open label phase duration of 76 weeks. The dose increase should be done at the first available opportunity, defined as the first

visit after IRB approval of Protocol Amendment 2. Refer to Table 3 for assessments to be collected at the visit of the dose increase and 12 weeks after the dose increase. At the time of the dose increase, the End of Open-label 70 mg electronic case report form (eCRF) page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.

As a result of Protocol Amendment 2, there will be 3 possible dose sequences in the open-label phase, depending on completion of week 48 visit as noted above: (1) subjects receiving only AMG 334 70 mg QM SC in the open-label phase (OL70), (2) subjects receiving only AMG 334 140 mg QM SC in the open-label phase (OL140), and (3) subjects receiving both AMG 334 70 mg (for up to 24 weeks) and 140 mg QM SC (OL70-140).

Subjects assigned to receive AMG 334 140 mg QM SC during the open-label phase will not have the option to decrease open-label AMG 334 from 140 mg QM to 70 mg QM. A safety follow-up visit occurs 16 weeks after the last dose of investigational product. Subjects will use an electronic diary (eDiary) every day throughout the baseline phase **and** double-blind treatment phase and for the first 6 months and **between the week 72 and week 76 study visits and between the week 96 and week 100/early termination (ET) study visits** of the **OLTP** to report information about their migraine and non-migraine headaches and acute headache medication use. Subjects will have in-clinic study visits monthly after the week 4 visit.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2**-Table 3, and Table 4 for CHU substudy**).

Statistical Considerations: The primary analysis will occur after all subjects have completed their week 24 visit (or discontinued from the study). The final analysis for the study will occur after all subjects have completed safety follow-up through week **112** or discontinued from the study. Using the treatment effect compared to placebo of -1.12 and -1.30 for the AMG 334 70 mg and 140 mg dose groups, respectively and a common standard deviation of 2.8 based on a Japan topiramate trial (www.clinicaltrial.gov), the planned sample size of 131 subjects in the placebo, 70 mg and 140 mg dose groups will provide 90% and 96% power for a two-sided test with significance level of 0.05 to show the superiority of AMG 334 70 mg and 140 mg compared to placebo, respectively. The proposed number of subjects in the 28 mg (n=66) dose group with the placebo (n=131), the 70 mg (n=131) and the 140 mg (n=131) dose groups is sufficient to demonstrate a dose-response using the Multiple Comparison Procedure–Modelling (MCP-Mod) analysis with the minimum power of 95% and provide the estimates of response in a Japanese population, using an assumed treatment effect of -0.55 for the AMG 334 28 mg dose group.

The continuous efficacy endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation of missing data. The primary endpoint will be tested for each AMG 334 treatment group compared to the placebo group using appropriate contrasts in a closed testing procedure. The mean change from baseline for each treatment group, and the treatment difference, 95% confidence intervals, and p-value will be reported. For all efficacy endpoints, nominal p-values will be provided for the comparisons between each AMG 334 treatment group vs the placebo group without multiplicity adjustment.

Dichotomous efficacy endpoints will be analyzed using a stratified Cochran-Mantel-Haenszel (CMH) test after the missing data are imputed as non-response. The odds ratio for each AMG 334 treatment group vs placebo group and associated 95% confidence intervals will be reported. As safety analyses, subject incidence of treatment-emergent adverse events will be tabulated by system organ class and preferred term by treatment group for the double-blind treatment phase. For the **OLTP**, **exposure-**adjusted subject incidence rate of treatment-emergent adverse events will be tabulated overall. Measurements of safety laboratory and vital sign data will be summarized over time and laboratory shift tables will be provided.

The proportion of subjects who administer a full dose of AMG 334 in home-use will be summarized by treatment group at CHU day 29 and day 57. Subject incidence of adverse

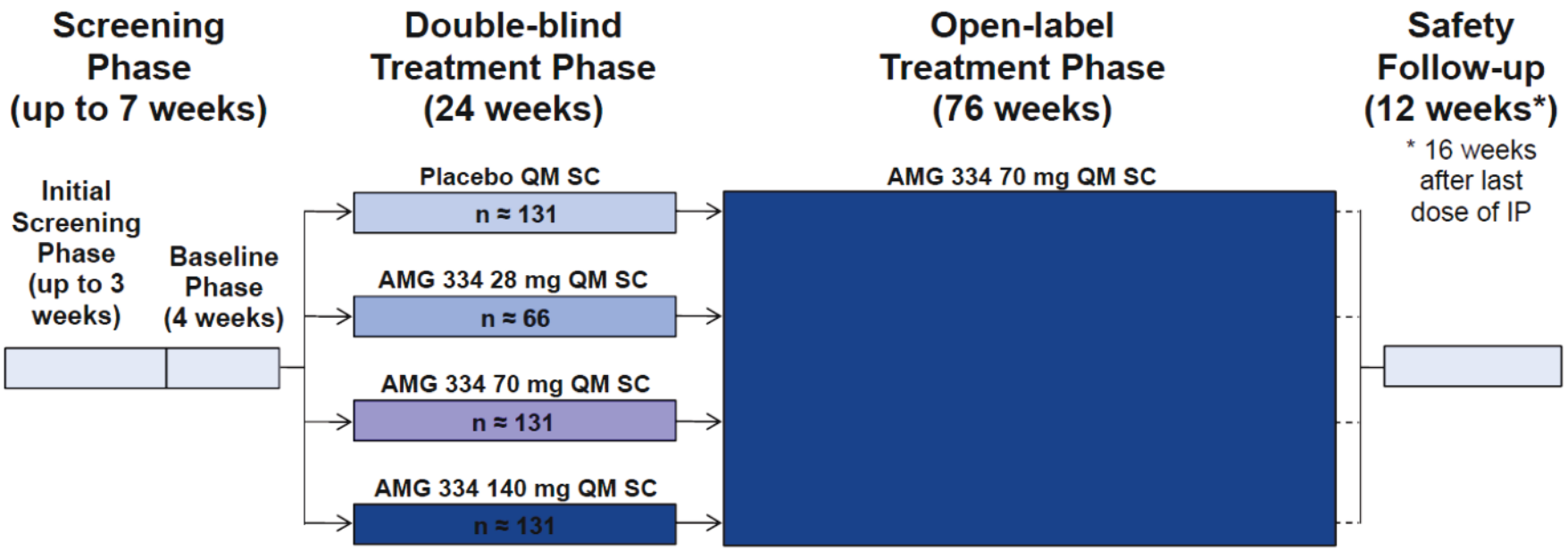
events, serious adverse events, and adverse device effects will be summarized by system organ class and preferred term for subjects enrolled in the CHU substudies.

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

Sponsor: Amgen Inc.

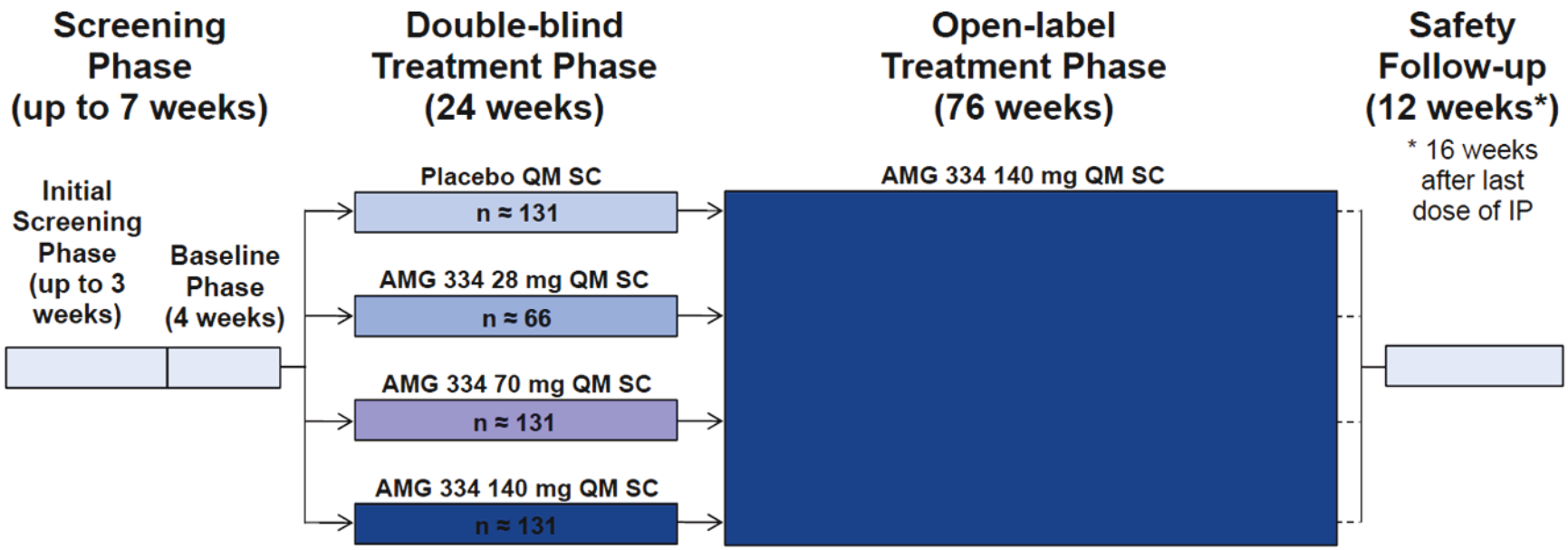
Data Element Standards Version/Date:	Version 4, 31 October 2013

Study Design and Treatment Schema for Subjects That Completed Week 48 Under Protocol Amendment 2 (OL70 subjects)



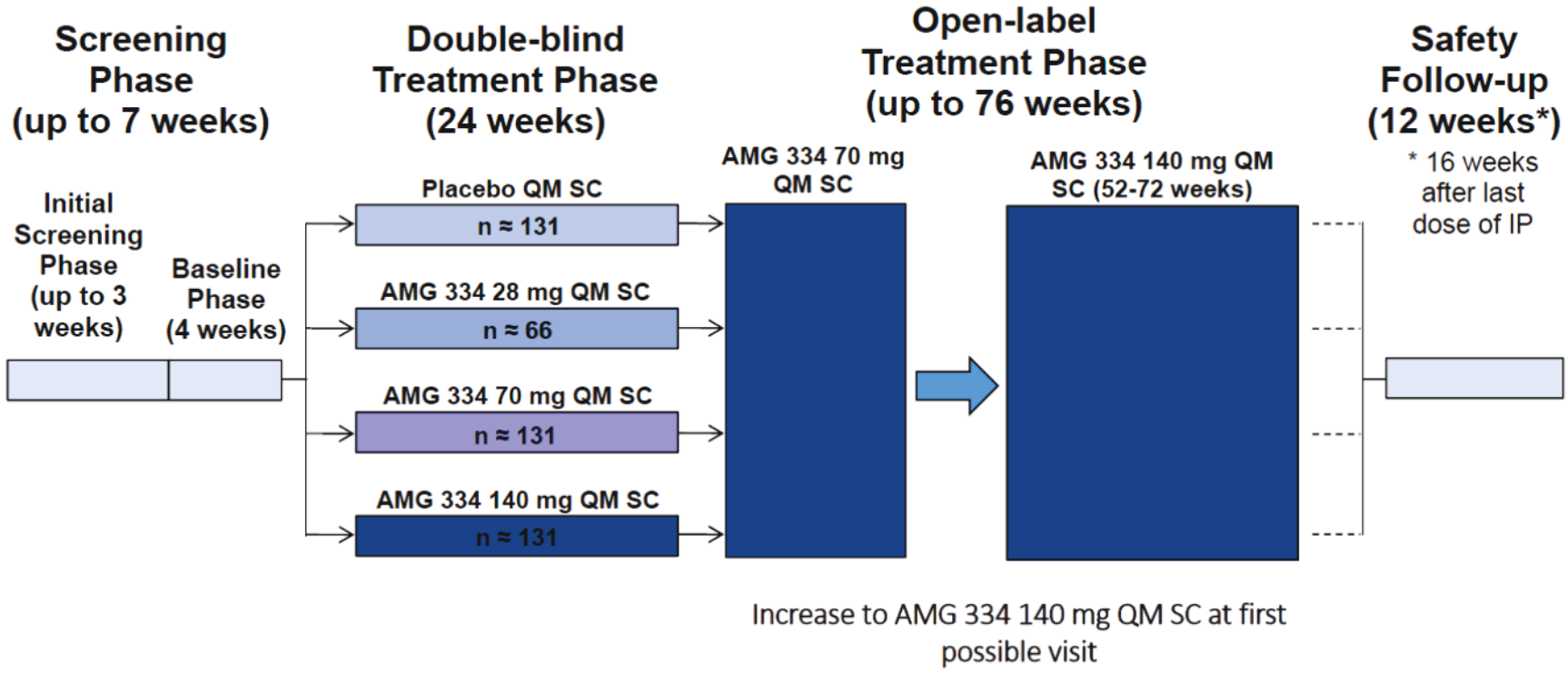
IP = investigational product; QM = monthly; SC = subcutaneous

Study Design and Treatment Schema for Subjects Still in the Double-blind Treatment Phase Protocol Amendment 2 (OL140 Subjects)



IP = investigational product; QM = monthly; SC = subcutaneous

Study Design and Treatment Schema for Subjects in the Open-label Phase AND Not Yet Completed W48 Under Protocol Amendment 2 (OL70-140 Subjects)



IP = investigational product; QM = monthly; SC = subcutaneous

Study Glossary

Abbreviation or Term	Definition/Explanation
ADE	Adverse device effect
AI/Pen	**Autoinjector/pen**
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	**Analysis of covariance**
AST	Aspartate aminotransferase
BDI-II	Beck Depression Inventory-II
BIL	Bilirubin
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CGRP	Calcitonin gene-related peptide
CHU	**Clinical home use**
C_{max}	Peak concentration
CMH	**Cochran-Mantel-Haenszel**
COAs	Clinical Outcome Assessments
cont	Continued
CPK	Creatine phosphokinase
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
Day 1 / Study Day 1	The first day that protocol-specified investigational product is administered to the subject
DBF	Dermal blood flow
DBTP	Double-blind treatment phase
DILI	Drug-induced liver injury
dL	Deciliter
DMC	Data Monitoring Committee
EC_{50}	50% effective concentration
EC_{90}	90% effective concentration
ECG	Electrocardiogram
eCRF	**Electronic case report form**

Abbreviation or Term	Definition/Explanation
EDC	Electronic data capture
eDiary(ies)	Electronic diary(ies)
End of study for individual subject	The last day that protocol-specified procedures are conducted for an individual subject
End of **Study**	The **end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (ie, the last subject **last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.**
Enrollment	Randomization of a subject into the double-blind treatment phase of the study via the Interactive Voice Response / Interactive Web Response System
EOS	End of study
E-R Analysis	Exposure-response analysis; mechanism-based modeling and simulation and statistical analyses based on individual pharmacokinetic exposure (eg, population pharmacokinetic modeling) and response, which may include biomarkers, pharmacodynamic effects, efficacy and safety endpoints.
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
FSH	Follicle-stimulating hormone
F/U	Follow-up
g	Gram
GLP	Good Laboratory Practice
Hb	Hemoglobin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
Headache	A migraine or non-migraine headache

Abbreviation or Term	Definition/Explanation
Headache Day	Any calendar day in which the subject experiences a qualified headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as: • a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or • a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or • a headache of any duration for which acute headache treatment is administered.
HepBcAb	Hepatitis B Core Antibody
HepBsAg	Hepatitis B Surface Antigen
HIT-6	Headache Impact Test
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH GCP	International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice
ICHD	The International Classification of Headache Disorders
ID	Identification
IFU	**Instructions for use**
IgG2	Immunoglobulin G2
IHS	International Headache Society
INR	International normalized ratio
IP	Investigational product (ie, AMG 334 and placebo)
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IU	International unit
IVR/IWR System	Interactive Voice Response (IVR) / Interactive Web Response (IWR) System; telecommunication / web-based technology that is linked to a central computer in real time as an interface to collect and process information
K_d	Equilibrium dissociation constant
kg	Kilogram
Last IP Dose Date	The last date investigational product is administered
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
M	Month
MAR	**Missing at random**

Abbreviation or Term	Definition/Explanation
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-Mod	Multiple Comparison Procedure–Modelling
MCV	Mean corpuscular volume
mg	Milligram
MI	**Multiple imputation**
Migraine Attack	An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses: a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two. b) An attack treated successfully with medication but with relapse within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.
Migraine Day	Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b): a) ≥ 2 of the following pain features: • Unilateral • Throbbing • Moderate to severe • Exacerbated with exercise/physical activity b) ≥ 1 of the following associated symptoms: • Nausea and/or vomiting • Photophobia and phonophobia If the subject took a migraine-specific medication (ie, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
Migraine-specific medications	Triptans and ergotamine-derivatives
mL	Milliliter
MNAR	**Missing not at random**
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
ng	Nanogram
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
OLTP	Open-label treatment phase

Abbreviation or Term	Definition/Explanation
PC	Product complaint
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PE	Physical examination
PET	Positron emission tomography
PFS	Pre-filled syringe
pg	Picogram
PGt	Pharmacogenetics
PK	Pharmacokinetic
pM	Picomolar
Primary Completion	**The primary completion date is defined as t**he time when the last subject is assessed or receives an intervention for the final collection of data for the primary **endpoint(s), for the purpose of conducting the primary** analysis**, whether the study concluded as planned in the protocol or was terminated early.** **The primary completion date is the date** when the last subject **has** complete**d** the **assessments for** week 24 or is discontinued from the study**.**
PRN	As needed (pro re nata)
PRO	Patient-reported outcome
PT	Prothrombin time
QM	Monthly
rand.	Randomized / randomization
RBC	Red blood cell
RDW	Red blood cell distribution width
SAE	Serious adverse event
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase; see AST
SGPT	Serum glutamic-pyruvic transaminase; see ALT
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.
Study Day 1 / Day 1	The first day that protocol-specified investigational product is administered to the subject
TBL	Total bilirubin

Abbreviation or Term	Definition/Explanation
t_{max}	Time to peak concentration
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
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 **a** follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved. OR • Underwent bilateral oophorectomy OR • Underwent hysterectomy OR • Underwent bilateral salpingectomy.

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1. OBJECTIVES

1.1 Primary

To evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine days, in subjects with episodic migraine

1.2 Secondary

Efficacy:

- To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects with at least 50% reduction from baseline in mean monthly migraine days
- To evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly acute migraine-specific medication treatment days

Safety: To evaluate the safety and tolerability of AMG 334

1.3 Exploratory

- To evaluate the effect of AMG 334 compared to placebo on change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6)
- To evaluate the month of onset of action of AMG 334 compared to placebo as assessed by monthly migraine days
- To evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine attacks
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in mean monthly headache (migraine and non-migraine headache) days
- To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects with at least 75% reduction from baseline in mean monthly migraine days
- To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects with 100% reduction from baseline in mean monthly migraine days
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in monthly acute headache medication treatment days
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in monthly hours of migraine headache
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in monthly average severity of migraine pain
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in mean monthly migraine days with severe pain
- To evaluate the effect of AMG 334 compared to placebo on change from baseline in mean monthly hours of severe migraine pain
- To evaluate the effect of AMG 334 compared to placebo on migraine pain interference with daily activities as measured by the migraine symptom interference items

- To evaluate the effect of AMG 334 compared to placebo on the change from baseline in the overall impact on everyday activities score as measured by the Migraine Physical Function stand-alone item
- To evaluate AMG 334 pharmacokinetics (PK) in subjects with migraine and characterize the exposure-response (E-R) relationships for efficacy and safety endpoints
- To investigate the dose-response relationship of AMG 334 for efficacy
- CCI [redacted]
- CCI [redacted]
- To evaluate the long-term safety, tolerability and maintenance of effect of AMG 334 after **100** weeks of treatment

1.4 Clinical Home Use Substudy

1.4.1 Primary

The primary objective of the clinical home use (CHU) substudy (during the open-label treatment phase [OLTP]) is to assess users' ability to administer a full dose (140 mg) of AMG 334 in home-use, using either 2 pre-filled 70 mg/mL autoinjectors/pens (AIs/pens) or 1 pre-filled 140 mg/mL AI/pen.

1.4.2 Secondary

Secondary objective of the CHU substudy (OLTP): To assess the safety and tolerability of AMG 334 administered using either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen.

2. BACKGROUND AND RATIONALE

2.1 Disease

Migraine

Migraine is a disabling disorder characterized by primary recurrent headaches lasting 4 to 72 hours (if not treated) 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). Migraine has two major subtypes: Migraine with aura (visual, sensory, and/or speech symptoms that occur just prior to or at the onset of migraine headache) and migraine without aura (The International Classification of Headache Disorders, 3rd edition [ICHD-3]). Migraine is a highly prevalent disease worldwide. Overall prevalence in Japan has been estimated to be 8.4% of the population (Sakai and Igarashi, 1997). Seventy-four percent of migraine patients feel daily life disturbance. However, in Japan, only a small number of

prophylactics are currently indicated for migraine, and the available options are insufficient. Moreover, prophylactic strategies for migraine are frequently based on literature published in North America and Europe (Shimizu, 2009). An international cross-sectional survey of adults with migraine revealed low rates of prophylaxis use due to discontinuation either because of lack of efficacy and/or adverse events (Blumenfeld et al, 2013).

Globally, the classes of drugs that are used for acute and prophylactic treatment of migraine are similar across countries, although specific agents vary depending upon availability and approval. Currently approved migraine prophylaxis agents in Japan include lomerizine hydrochloride (calcium channel antagonist approved in 1999), dihydroergotamine mesilate, sodium valproate (antiepileptic) and propranolol (beta blocker). The indication of migraine prophylaxis recently was approved for sodium valproate and propranolol agents (2011 and 2013, respectively) based on available global evidence without Japanese clinical trials, according to the requests through "the Review Committee on Unapproved Drugs and Indications" that concluded the usefulness of the drugs for prophylaxis of migraine is widely recognized medically and pharmaceutically. Other agents that are not approved in Japan but that have Grade A evidence (based on consistent results from multiple randomized controlled trials) for migraine prophylaxis according to the Japanese Headache Society include amitriptyline, timolol, flunarizine, and methysergide (Japanese Headache Society, 2013).

Calcitonin Gene-related Peptide (CGRP)

CGRP belongs to the calcitonin family of peptides and is widely expressed in the peripheral and central nervous systems including the trigeminal system, which is implicated in the pathophysiology of migraines. CGRP is a nociceptive modulator and potent vasodilator that has been associated with migraine pathophysiology based on several lines of evidence: 1) it is expressed in the trigeminal system (Tajti et al, 1999), 2) CGRP levels are elevated in migraineurs during an attack (Bellamy et al, 2006; Gallai et al, 1995; Goadsby et al, 1988; Goadsby et al, 1990), 3) triptans (approved acute / abortive migraine medications) restore CGRP levels to normal after treatment in a time frame that corresponds to significant pain relief and alleviation of accompanying symptoms (Juhasz et al, 2005; Sarchielli et al, 2006), 4) infusion of CGRP into migraine sufferers triggers the onset of a migraine headache (Lassen et al, 2002; Petersen et al, 2005), 5) small molecule CGRP receptor antagonists have demonstrated clinical efficacy in acute migraine reversal (Connor et al, 2009; Hewitt et al, 2011; Ho et al, 2008a;

Ho et al, 2008b; Olesen et al, 2004), and 6) small molecule CGRP receptor antagonists and antibody CGRP ligand antagonists have demonstrated clinical efficacy in migraine prevention (Dodick et al, 2014a; Dodick et al, 2014b; Ho et al, 2014).

The consistent efficacy data provide strong clinical validation of CGRP as a promising target for treatment of migraine.

2.2 Amgen Investigational Product AMG 334 Background

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

The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Durham, 2004; Poyner, 1992; Wang et al, 1995; Zimmermann et al, 1996). Many of these components associated with migraine pathophysiology are outside the blood-brain barrier, and thus a peripherally restricted CGRP receptor antagonist could be efficacious. More recently, a positron emission tomography (PET) study with telcagepant, a small molecule CGRP receptor antagonist, showed little central nervous system receptor occupancy at a clinically efficacious dose (Vermeersch et al, 2012). Therefore, it is hypothesized that AMG 334, a CGRP receptor antibody, will selectively antagonize the CGRP receptors for prolonged periods, preventing and/or reversing the activation of the trigeminal-vascular system, resulting in the prevention of migraine headaches.

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

AMG 334 has demonstrated an acceptable safety profile following single dose administration up to 280 mg SC in healthy subjects (up to 140 mg in Japanese healthy

subjects) and ascending multiple dose administration up to 210 mg SC in healthy subjects and migraineurs. Additionally, AMG 334 has shown efficacy at the 70 mg monthly (QM) SC dose compared to placebo in the reduction of monthly migraine days in a 12-week randomized, double-blind, placebo-controlled global Phase 2 episodic migraine study (Study 20120178). AMG 334 demonstrated a favorable benefit:risk profile in that study.

As of **January** 201**7**, approximately **3623** subjects (**2786.43 subject years) have received at least 1 dose of AMG 334. This includes 613** healthy **volunteers and 2917 migraine** subjects. AMG 334 has **to date,** demonstrated a favorable safety and tolerability profile similar to placebo in these studies. Refer to the AMG 334 Investigator's Brochure for details.

PK data from the single dose first-in-human study showed that following a single SC dose, AMG 334 exposure (C_{max} and $AUC_{0\text{-}28day}$) increased more than dose proportionally from 1 mg to 70 mg and increased approximately dose proportionally from 70 mg to 210 mg. The median t_{max} ranged from 4 days to 11 days within the dose range of 1 to 210 mg. Preliminary PK data from the multiple dose study showed an accumulation ratio of 1.5-1.7 following monthly SC injection of AMG 334.

Refer to the AMG 334 Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulations.

2.3 Rationale

Migraine prophylaxis is an area of a large unmet medical need, with existing therapies having modest efficacy and poor tolera**bility**. CGRP receptor antagonism is a novel approach to migraine prophylactic therapy.

AMG 334 is a human monoclonal antibody, with a PK profile consistent with slow rise in serum concentration and relatively long half-life. The PK profile of AMG 334 is suitable for migraine prophylaxis.

The current study was designed according to the principles outlined in European Medicines Agency (EMA) Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine (CHMP/EWP/788/01 Rev. 1) and the International Headache Society (IHS) Guidelines for Controlled Trials of Drugs in Migraine (Tfelt-Hansen et al, 2012) and based on scientific advice obtained from the Japan Pharmaceuticals and Medical Devices Agency (PMDA). Many study elements are aligned with a pivotal, Phase 3 registrational trial (20120296) intended to assess the efficacy and safety of

AMG 334 for prevention of migraine in subjects with episodic migraine, to allow for the comparison of the results from this study and the global Phase 3 trial (20120296) and extrapolation of other global study results to Japan.

Rationale for Endpoints

For migraine prophylaxis studies, the EMA guideline recommends assessing change in the number of monthly migraine attacks as the primary efficacy endpoint. Difficulties with defining the duration of a migraine attack have led to proposals for migraine days as an alternative and perhaps simpler efficacy endpoint. The IHS guideline for controlled trials of drugs in migraine (Tfelt-Hansen et al, 2012) recommends without preference, either migraine attacks or migraine days for the primary endpoint. In addition, migraine day is a more sensitive efficacy endpoint to detect treatment effect of prophylactic treatment based on recent onabotulinumtoxinA experience in Phase 3 trials (Aurora et al, 2011; Dodick et al, 2010). In the current study, the primary endpoint is change from baseline in mean monthly migraine days. Migraine attack will be evaluated as an exploratory endpoint.

Refer to Section 10.1.1.4 for the definition of migraine day. This definition of migraine day is consistent with the diagnostic criteria of migraine and probable migraine according to ICHD-3 and is consistent with those of the 20120178 Phase 2 episodic migraine trial. The mean monthly migraine days will be calculated using monthly migraine day data from the last 3 months (months 4, 5, and 6) of the double-blind treatment phase. A migraine day will be determined based on headache and medication information entered by subjects daily into a handheld electronic device (electronic diary; eDiary).

The secondary efficacy endpoints are the 50% responder rate and mean monthly migraine-specific medication treatment days. These secondary endpoints were selected because they are highly clinically relevant and provide complementary information to the primary endpoint in the evaluation of AMG 334 as a migraine prophylactic agent.

Rationale for AMG 334 Doses

Three dose levels of AMG 334 (ie, 28 mg, 70 mg, and 140 mg) were chosen for this Phase 2 study with the intent to bridge the data from the global Phase 3 episodic migraine study (20120296). These doses were selected in order to 1) demonstrate statistically significant improvement from placebo on the primary outcome measure, and 2) to establish the dose-response relationship of AMG 334 in Japanese subjects. **In the open-label phase, the dose of AMG 334 is being increased to 140 mg in a subset**

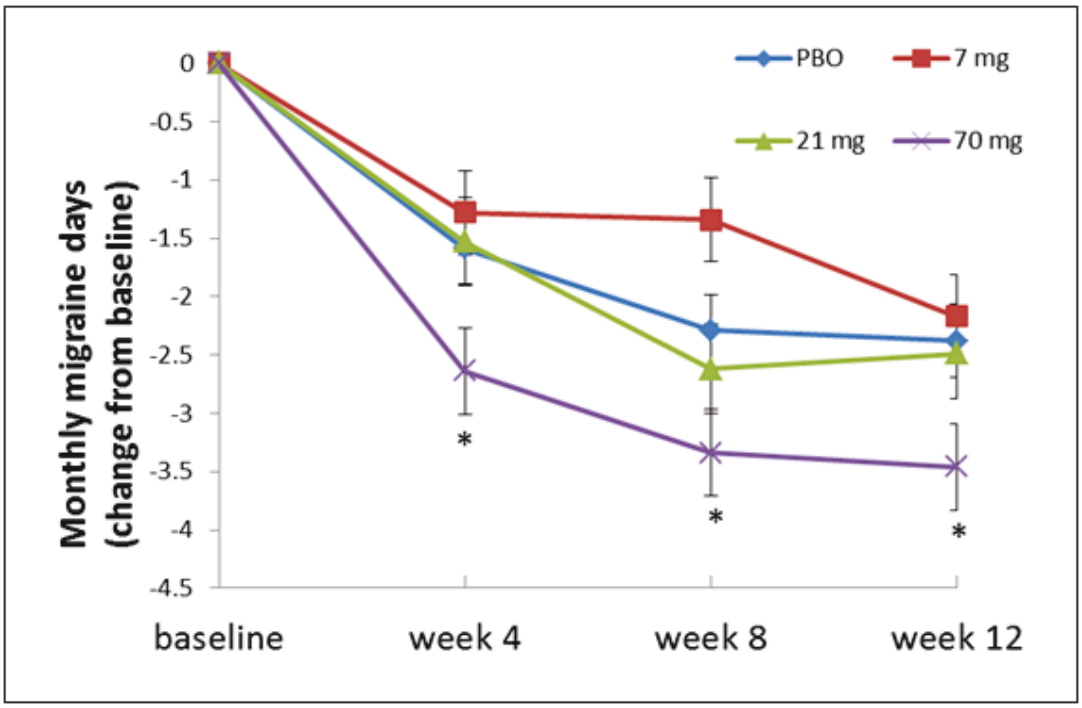
of subjects to provide continuous 1-year safety data for subjects receiving either AMG 334 70 mg or 140 mg.

The efficacy and safety of AMG 334 (7 mg, 21 mg, and 70 mg QM SC) were evaluated for the prevention of episodic migraine in a 12-week global Phase 2 study (20120178). The study randomized 483 subjects (AMG 334 7 mg [n=108], AMG 334 21 mg [n=108], AMG 334 70 mg [n=107] and placebo [n=160], QM SC) with a history of migraine for ≥ 12 months and a monthly migraine frequency of ≥ 4 and ≤ 14 migraine days.

For the primary endpoint of change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase, only the 70 mg dose was significantly different from placebo (-3.40 days vs. -2.28 days, p=0.021). The 7 mg and 21 mg doses only demonstrated changes of -2.18 days and -2.39 days, respectively, which were not significantly different from placebo (Figure 1). The results of the primary endpoint were consistent with those of the secondary endpoints. 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, and suggested that greater reductions in migraine day could be achieved with higher exposures. Therefore, to more fully establish the dose-response relationship, a higher dose, 140 mg, also is included in the present study.

A lower dose also was selected in order to maximize the probability of having at least 2 doses in the current study that demonstrate some efficacy, and that there is differential efficacy achieved with at least 2 doses. The 28-mg QM dose was chosen as it is expected to result in numerical improvements in the monthly migraine days, but not to achieve full efficacy. Using a pharmacokinetic-pharmacodynamic (PK-PD) model developed for the AMG 334 exposure and migraine day data from the study 20120178, the treatment effect in Japanese patients was predicted for the 28-mg QM dose. According to the model predictions, the expected mean (SE) placebo-corrected change from baseline in monthly migraine days with the 28-mg dose will be -0.55 (0.68) days in Japanese patients. The intermediate dose of 70 mg QM, which was shown to be efficacious in study 20120178, is predicted to result in a mean (SE) placebo-corrected change from baseline in monthly migraine days of -1.51(0.36) days in Japanese patients.

Figure 1. Change From Baseline on Mean Monthly Migraine Days by Treatment Groups in the Double-Blind Treatment Phase of Study 20120178



The safety data generated to date with AMG 334 support evaluating the 3 doses in this Phase 2 study. In the **double blind treatment phase of the** global Phase 2 episodic migraine study (Study 20120178), treatment-emergent adverse events were reported by 165 (51.7%) subjects across all AMG 334 arms, and 82 (53.6%) subjects in the placebo arm. All doses of AMG 334 were associated with only mild to moderate adverse events with no dose-dependent increase in adverse events. Study drug discontinuations due to adverse events were seen in 7 (2.2%) of subjects treated with AMG 334 and 2 (1.3%) of subjects treated with placebo. The most commonly reported **adverse event**s occurring in ≥ 3% of all AMG 334 treated subjects were nasopharyngitis and fatigue. Only 2 serious adverse events were reported, with none considered by the investigator to be related to investigational product. One subject from the AMG 334 7 mg dose group reported a ruptured ovarian cyst, and one subject from the AMG 334 70 mg dose group reported migraine and vertigo. The safety and tolerability data generated to date support**ed** further evaluation of the 70-mg dose in the Phase 3 studies. The study 20120178 **OLTP** is ongoing **and the protocol has been amended to increase the open-label dose from 70 mg to 140 mg**. Ongoing data review has not revealed any new safety signal. Refer to the AMG 334 Investigator's Brochure for additional information.

AMG 334 140 mg has been evaluated for the prevention of episodic migraine in a global Phase 3 study (20120296) with a 24-week double-blind treatment phase. The study randomized 955 subjects (AMG 334 70 mg [n = 317], AMG 334 140 mg [n = 319], and placebo [n = 319], QM SC) with a history of migraine with or without aura for ≥ 12 months and a monthly migraine frequency of ≥ 4 to < 15 migraine days. For the primary endpoint of change in monthly migraine days from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase, the 70 mg and 140 mg doses were significantly different from placebo (-3.23 days and -3.67 days vs. -1.83 days, $p < 0.001$). Both doses produced statistically significant improvements in the secondary outcome measures of 50% responder rate and monthly migraine-specific medication treatment days. The results of the other secondary endpoints were consistent with those of the primary endpoint. Across the primary and all secondary endpoints, AMG 334 140 mg showed numerically greater efficacy than 70 mg. At the end of the double-blind treatment phase, subjects in each treatment group are re-randomized 1:1 in a blinded fashion to AMG 334 70 mg or AMG 334 140 mg for the 28-week active treatment phase, which is ongoing.

During the placebo-controlled double-blind treatment phase of the 20120296 study, treatment-emergent adverse events were reported in 57.3%, 55.5%, and 63.0% of subjects in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively, and most were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 (mild to moderate in severity). Study drug discontinuations due to adverse events were reported in 7 subjects (2.2%), 6 subjects (1.9%), and 7 subjects (2.2%) in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively. The most frequent adverse events occurring in ≥ 2% of all AMG 334 treated subjects were nasopharyngitis, upper respiratory tract infection, sinusitis, constipation, arthralgia, fatigue, and nausea. Serious adverse events were reported in 2.5%, 1.9%, and 2.2% of subjects in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively. No serious adverse event occurred in more than 1 subject, except cholelithiasis which was reported by 2 subjects in the AMG 334 70 mg group (one of whom had clear risk factors). Study 20120296 and Study 20120309 are being monitored by the same independent Data Monitoring Committee (DMC).

In the global 12-week study 20120295, 667 subjects with chronic migraine (≥ 15 headache days per month, with ≥ 8 migraine days) were randomized to AMG 334 70 mg (n = 191), AMG 334 140 mg (n = 190), or placebo (n = 286), QM SC. For the primary endpoint of change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase, the 70 mg and 140 mg doses were significantly different from placebo (-6.64 days and -6.63 days vs. -4.18 days, p < 0.001). Treatment-emergent adverse events were reported in 39.0%, 43.7%, and 46.8% of subjects in the placebo, AMG 334 70 mg, and AMG 334 140 mg groups, respectively. No apparent dose-response pattern was observed across the most common treatment-emergent adverse events. The most commonly reported adverse events occurring in ≥ 2% of all AMG 334 treated subjects were injection site pain, upper respiratory tract infection, nausea, nasopharyngitis, constipation, muscle spasms, and migraine. Serious adverse events were reported in 2.5%, 3.2%, and 1.1% of subjects in the placebo, AMG 334 70 mg, and AMG 334 140 mg groups, respectively. No individual serious adverse event was reported in more than 1 subject in the placebo, AMG 334 70 mg, or AMG 334 140 mg groups. Subjects from 20120295 were eligible to enroll in an ongoing 52-week open-label extension study (20130255), in which the original dose was 70 mg QM SC, but subsequently the dose was increased to 140 mg QM SC. Of the 609 subjects enrolled, 259 subjects received at least one dose of AMG 334 140 mg. Based on the interim analysis data cut-off of 01 September 2016 with a mean (SD) duration of exposure to AMG 334 140 mg of 176.4 (70.9) days, the reported adverse events were consistent with the known safety profile of AMG 334.

The global Phase 2 study (20120178) in episodic migraine has an ongoing open-label phase of up to 256 weeks. The original dose was 70 mg but a protocol amendment dated 07 April 2016 increased the dose to 140 mg for all subjects. Thus 140 mg has been investigated in the double-blind portions of studies 20120296 and 20120295, as well in open-label or active treatment extension phases (studies 20120296, 20130255, 20120178), and no new safety signal has been detected.

2.4 Clinical Hypothesis

In subjects with episodic migraine, AMG 334 reduces the mean monthly migraine days from baseline, compared to placebo. **In the CHU substudy, it is hypothesized that**

users will be able to administer a full dose of AMG 334 comparably using 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. No formal hypotheses will be tested in the CHU substudy.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2, multicenter, randomized, stratified, double-blind, placebo-controlled, parallel-group study of subjects with episodic migraine. The study is composed of an initial screening phase (up to 3 weeks), a 4-week baseline phase, a 24-week double-blind treatment phase, a **76**-week **OLTP**, and a 12-week safety follow-up phase (16 weeks after the last dose of investigational product).

Approximately 459 eligible subjects will be randomized 2:1:2:2 to:

- Placebo (n ≈ 131)
- AMG 334 28 mg (n ≈ 66)
- AMG 334 70 mg (n ≈ 131)
- AMG 334 140 mg (n ≈ 131)

The randomization will be stratified by prior/current treatment with migraine prophylactic medication (current migraine prophylactic medication treatment vs prior migraine prophylactic medication treatment only vs no prior or current migraine prophylactic medication treatment).

Investigational product (ie, placebo or AMG 334) 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 Clinical Home Use Study Design (Optional)

Approximately 50 subjects will be enrolled in this AMG 334 20120309 CHU substudy to assess subjects' ability to self-administer 140 mg of AMG 334 for in-home use. Subjects will be randomized 1:1 to use either 2 pre-filled 70 mg/mL AIs/pens (for a total dose of 140 mg) or 1 pre-filled 140 mg/mL AI/pen. It is hypothesized that users will be able to self-administer a full dose of AMG 334 comparably using either dosage. No formal hypotheses will be tested.

Safety and tolerability of AMG 334 self-administered using two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen 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 eligibility criteria.

CHU substudy screening (day -28) should occur during or after a subject has received at least 1 dose of open-label AMG 334 140 mg. Subjects should also review the AI/pen instructions for use (IFU) at day -28 of the CHU substudy to determine if they wish to enroll in the substudy at day 1. Subjects must have received at least 1 dose of AMG 334 140 mg by day 1 of the CHU substudy.

Day 1 of the CHU substudy should correspond with any 20120309 study visit up through week 88. At day 1, subjects who meet all eligibility criteria will be randomized via Interactive Voice Response (IVR) System to self-administer AMG 334 using either two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen (approximately 25 subjects in each arm).

At CHU substudy day 1, areas that may be injected (upper arm, abdomen, or upper thigh) should be examined for any skin abnormalities; adverse events, serious adverse events, and adverse device effects will be collected during the CHU substudy, and will be assessed on CHU screening, day 1, day 28 (at site), and day 56 (at site) and on CHU substudy days 29 and 57 (assessed by telephone visit). Adverse event, serious adverse event, adverse device effect, concomitant medication therapies, 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 main study. On the CHU substudy day 1 visit, the site should review the IFU with the subject before administration of investigational product (IP). On day 1 of the substudy, subjects will self-administer IP (two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen) under clinical site supervision.

Subjects will be provided a box containing either two 70 mg/mL AI/pens or one dose of 140 mg AI/pen at the CHU substudy day 28 and day 56 visits and will self-administer IP individually without supervision at home on substudy 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 the AI/pen was injected) and will document the subject's response in the electronic case report

form (eCRF). 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 adverse device effects.

Day 85 (clinic visit) is the end of the CHU substudy and sites will inquire about adverse events, serious adverse events, and adverse device effects. At day 85 of the CHU substudy, site staff will administer AMG 334 140 mg SC and will continue the scheduled procedures and assessments as per the 20120309 protocol. If a subject terminates the CHU substudy early, the subject may receive administration of AMG 334 140 mg SC at the site as per the 20120309 protocol and will continue 20120309 scheduled procedures and assessments as per the 20120309 protocol.

3.3 Number of Sites

Approximately 50 sites across Japan will participate in this study. Additional sites may be added.

Sites that do not enroll subjects within 2 months of site initiation may be closed.

3.4 Number of Subjects

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

Approximately 459 subjects will be enrolled (ie, randomized) into the study, with approximately 131 subjects assigned to placebo, approximately 66 subjects assigned to AMG 334 28 mg, approximately 131 subjects assigned to AMG 334 70 mg, and approximately 131 subjects assigned to AMG 334 140 mg.

To allow for 459 eligible subjects to be randomized, it is anticipated that approximately 800 will need to enter the initial screening phase, and approximately 600 will need to enter the baseline phase.

Approximately 50 subjects may participate in the CHU substudy.
The sample size justification is described in Section 10.2.

Approximately 91 subjects will participate in the PK substudy.

3.5 Replacement of Subjects

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

3.6 Estimated Study Duration

3.6.1 Study Duration for Subjects

The planned length of participation in the study for an individual subject is up to **119** weeks, which includes the following:

- initial screening phase of up to 3 weeks
- 4-week baseline phase
- 24-week double-blind treatment phase
- **76-**week **OLTP**
- 12-week safety follow-up phase (16 weeks after the last dose of investigational product)

3.6.2 End of Study

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

The primary completion date is the date when the last subject **has** complete**d** the **assessments for** week 24 or is discontinued from the study.

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

End of **Study**: The **end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (ie, last subject **last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.**

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). This log may be completed and updated via an IVR/Interactive Web Response (IWR) system.

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

4.1 Inclusion Criteria

Criteria to be Assessed Prior to Entering the Subject into the Initial Screening Phase and/or Baseline Phase:

101 Adults ≥ 20 to ≤ 65 years of age upon entry into screening

102 Provided informed consent prior to initiation of any study-specific activities/procedures

103 History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or patient self-report

104 Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening (refer to Section 10.1.1.4 for definition of migraine day)

105 Headache (ie, migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening (refer to Section 10.1.1.4 for definition of headache day)

Criteria to be Assessed During the Baseline Phase and Confirmed Prior to Randomizing the Subject into the Double-blind Treatment Phase:

106 Migraine frequency: ≥ 4 and < 15 migraine days during the baseline phase based on the eDiary calculations

107 Headache frequency: < 15 headache days during the baseline phase based on the eDiary calculations

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

CHU Substudy:

109 **Subjects must have provided informed consent for the substudy. Subjects enrolling in the CHU substudy must have received open-label 140 mg AMG 334 for at least 1 dose.**

4.2 Exclusion Criteria

201 Older than 50 years of age at migraine onset

202 History of cluster headache or hemiplegic migraine headache

203 Unable to differentiate migraine from other headaches

204 No therapeutic response with > 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

- Category 1: Divalproex sodium, sodium valproate
- Category 2: Topiramate
- Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)

- Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 6: Flunarizine, verapamil, lomerizine
- Category 7: Lisinopril, candesartan

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

The following scenarios do not constitute lack of therapeutic response:

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

205 Used a prohibited medication, device or procedure within 2 months prior to the start of the baseline phase or during the baseline phase (Refer to Section 6.7 for the list of these excluded treatments).

206 Received botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline phase or during the baseline phase

207 Taken the following for any indication in any month during the 2 months prior to the start of the baseline phase:

- Ergotamines or triptans on ≥ 10 days per month, or
- Simple analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or
- Opioid- or butalbital-containing analgesics on ≥ 4 days per month

208 Anticipated to require any excluded medication, device or procedure during the study (Refer to Section 6.7 for the lists of these medications, devices and procedures)

209 Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain)

210 History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a Beck Depression Inventory (BDI)-II total score > 19 at screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline phase.

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

212 Malignancy within the 5 years prior to screening, except non melanoma skin cancers, cervical or breast ductal carcinoma in situ

213 Human immunodeficiency virus (HIV) infection by history

214 Hepatic disease by history, or total bilirubin (TBL) ≥ 2.0 x upper limit of normal (ULN) or alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥ 3.0 x ULN, as assessed by the central laboratory at initial screening, or evidence of acute or chronic hepatitis B or hepatitis C virus. Hepatitis status will be evaluated by testing for hepatitis B surface antigen (HepBsAg), total hepatitis B core antibody (HepBcAb) and hepatitis C antibody by the central laboratory at initial screening. Polymerase chain reaction (PCR) should be performed to confirm active disease only if total HepBcAb is positive and HepBsAg is negative or if C antibody is positive.

215 Myocardial infarction, stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening

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

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

218 The subject is at risk of self-harm or harm to others as evidenced by past suicidal behavior or endorsing items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) assessed at screening

219 Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates)

220 Pregnant or breastfeeding, or is a female expecting to conceive during the study, including through 16 weeks after the last dose of investigational product

221 Female subject of childbearing potential who is unwilling to use an acceptable method of effective contraception during treatment with **IP** through 16 weeks after the last dose of investigational product. Acceptable methods of effective birth control include

- Not having intercourse
- Hormonal birth control methods (not for subjects with migraine with aura, and also cannot be recommended for subjects aged ≥35 years old who have migraine without aura except when there is no other appropriate birth control method)
- Drug releasing intrauterine devices
- Surgical contraceptive methods (vasectomy or bilateral tubal ligation), or
- Combination use of two barrier method with spermicide (each partner must use one barrier method, for example, a condom with spermicide [male] and a cervical cap [female])

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 **a** follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved.

○ OR

○ Underwent bilateral oophorectomy OR

○ Underwent hysterectomy OR

○ Underwent bilateral salpingectomy

222 Currently receiving treatment in another investigational device or drug study, or less than 90 days prior to screening since ending treatment on another investigational device or drug study(-ies)

223 Known sensitivity to any component of the investigational product (Refer to the Investigational Product Instruction Manual [IPIM] for details)

224 Previously randomized into an AMG 334 study

225 Member of investigational site staff or relative of the investigator

226 Unlikely to be able to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, independent completion of eDiary items) to the best of the subject's and investigator's knowledge

CHU Substudy

227 **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 an AI/pen after review of the IFU). Subjects receiving AMG 334 70 mg in the open-label phase are not eligible.**

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 (IRB) 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 and Amgen approved ICF before commencement of study-specific activities/procedures.

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

The screening phase starts when the subject signs and dates the ICF and ends when the subject is randomized or screen failed. The screening phase is composed of an initial screening phase, followed by a 4-week baseline phase. Certain initial screening

phase procedures may be repeated during the original initial screening phase. (Note: Repeating procedures during the original initial screening phase is a part of screening and is not considered "re-screening.") These procedures include laboratory assessments due to value(s) out of range due to sampling error or that could be within range with repeat sampling. The initial screening phase must not exceed 3 weeks, except after consultation with and approval by Amgen. Amgen may grant such approval in cases for which additional time is required to confirm eligibility.

Each subject who enters the screening phase for the study receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the Interactive Voice Response (IVR)/ Interactive Web Response (IWR) System. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is re-screened.

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

Re-screening

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

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

or

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

Investigators are requested to consult with Amgen prior to re-screening subjects for other reasons.

A subject must provide informed consent prior to the initiation of any re-screening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. The subject is entered into re-screening in the IVR/IWR System, and

all screening procedures must be repeated except as noted in the inclusion/exclusion criteria. A subject may be screened up to 2 times (ie, no more than 1 re-screen).

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

5.1 Randomization/Treatment Assignment

Randomization must occur on day 1 and after the completion of procedures associated with the end of the baseline phase.

Eligible subjects will be randomized in a 2:1:2:2 ratio to 1 of 4 treatment groups: placebo, AMG 334 28 mg, AMG 334 70 mg, or AMG 334 140 mg, with approximately 131 subjects assigned to placebo, approximately 66 subjects assigned to AMG 334 28 mg, approximately 131 subjects assigned to AMG 334 70 mg, and approximately 131 subjects assigned to AMG 334 140 mg. The randomization will be stratified by prior/current treatment with migraine prophylactic medication (current migraine prophylactic medication treatment vs prior migraine prophylactic medication treatment only vs no prior or current migraine prophylactic medication treatment). There may be a limit on the percentage of subjects on current migraine prophylactic medication treatment.

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

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

For the CHU substudy, after confirming that the optional CHU substudy ICF has been signed, subjects who meet all inclusion/exclusion criteria may be randomized at CHU day 1 via IVR System to self-administer AMG 334 using either two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen (approximately 25 subjects in each arm).

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen clinical study manager or

designee before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Please refer to the IPIM for details.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s), Medical Devices and/or Combination Product(s)

The Amgen Investigational Product used in this study is AMG 334 and/or placebo **in a** pre-filled syringe.

For subjects participating in the CHU substudy, Amgen investigational product used is AMG 334 in a pre-filled AI/pen.

6.2 Investigational Product

6.2.1 Amgen Investigational Product

AMG 334 and placebo will be considered as Amgen IP. 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."

Investigational product will be packaged in 3 mL clear glass vials for the double-blind treatment phase and 1 mL pre-filled syringes for the **OLTP**. For the vials, AMG 334 will be presented as 70 mg/mL AMG 334 formulated with CCI acetate (sodium counter ion), CCI sucrose, CCI polysorbate CCI, at pH CCI. Placebo will be formulated with CCI acetate, CCI sucrose, CCI polysorbate CCI, pH CCI and packaged to match AMG 334 but will not contain AMG 334. For the pre-filled syringes, AMG 334 will be presented as 70 mg/mL AMG 334 formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate CCI, at pH CCI. **If and when available, the AMG 334 140 mg dose in the open-label phase may be made available for use as a 140 mg/mL pre-filled syringe formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate CCI, at pH CCI.**

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, **destruction** and administration of **AMG 334 and placebo**.

Subjects randomized as part of the CHU substudy will be supplied with a sterile, single-use, preservative-free solution(s) for SC injection as either: (1) an AI/pen containing 1 mL AMG 334 at a concentration of 140 mg/mL formulated with CCI

sodium acetate, CCI sucrose, CCI polysorbate C CI, pH CC I or (2) two AIs/pens, each containing 1 mL AMG 334 at a concentration of 70 mg/mL formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate C CI, pH CC I.

6.2.1.1 Dosage, Administration, and Schedule

Amgen investigational product (ie, AMG 334 28 mg, AMG 334 70 mg, AMG 334 140 mg, or placebo) will be dosed monthly (QM) by subcutaneous (SC) injections. Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20)**. During the OLTP,** AMG 334 70 mg **or AMG 334 140 mg QM SC** will be administered**, depending on the subject's visit completion status after IRB approval of Protocol Amendment 2**.

During the double-blind treatment phase, 3 SC injections are to be given for each investigational product administration (ie, at day 1 and weeks 4, 8, 12, 16, and 20) to maintain the dose-level blinding. The 3 SC injections should be separated by no more than approximately 1 minute. During the **OLTP**, 1 SC injection is to be given for **AMG 334 70 mg and 2 SC injections for AMG 334 140 mg**. **If and when 140 mg/mL pre-filled syringes become available during the open-label phase, the 140 mg dose may be administered by a single 140 mg/mL SC injection.**

After IRB approval of Protocol Amendment 2, after the 24-week double-blind treatment phase, there is a 76-week OLTP with the dose determined by the subject's week 48 status:

(1) Subjects who have already completed the week 48 visit will continue to receive open-label AMG 334 70 mg QM SC (OL70) for a total of 76 weeks.

(2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label 140 mg QM SC for 76 weeks.

(3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open-label phase duration of 76 weeks. The dose increase to 140 mg should be done at the first available opportunity, defined as the first visit after IRB approval of Protocol Amendment 2. At the time of the dose increase, the End of Open-label 70 mg eCRF page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.

As a result of Protocol Amendment 2, there will be 3 possible dose sequences in the open-label phase, depending on completion of week 48 visit as noted above: (1) subjects receiving only AMG 334 70 mg QM SC in the open-label phase (OL70), (2) subjects receiving only AMG 334 140 mg QM SC in the open-label phase (OL140), and (3) subjects receiving both AMG 334 70 mg (for up to 24 weeks) and 140 mg QM SC (OL70-140). Subjects assigned to receive AMG 334 140 mg QM SC during the open-label phase will not have the option to decrease open-label AMG 334 from 140 mg QM to 70 mg QM.

The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Please see the IPIM for investigational product details.

Following the first 3 doses of investigational product in the double-blind treatment phase (ie, day 1, week 4, week 8), subjects are to remain in the clinic for approximately 1 hour for observation.

During the CHU substudy, the subject will self-administer IP (1 or 2 injections using AI/pen) under site supervision on day 1. On day 28 and day 56 during the CHU substudy, the site will provide IP to the subject to self-administer (1 or 2 injections using AI/pen) on the next day. The anatomical sites for self-administration are the upper thigh or abdomen. The upper arm should only be used if administered by a care-giver. During the CHU substudy the injection site location should be the same for all injections but do not use the same spot on the injection site you used for a previous injection. For further details regarding self-administration procedures, the IFU should be consulted.

Overdose with this product has not been reported.

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

The quantity, start date, and box number of investigational product are to be recorded on each subject's CRF.

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 7.2.25.

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

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

The dosage of investigational product is fixed for all subjects and cannot be adjusted.

Missed or delayed doses should be noted on the investigational product administration CRF, but no attempt should be made to administer any missed doses at the subject's next visit.

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.

Subjects who permanently discontinue investigational product during the double-blind treatment phase are to continue to return for all other study procedures until the end of the double-blind treatment phase and study procedures for the safety follow-up visit 16 weeks after the last dose of investigational product.

Subjects who permanently discontinue investigational product during the **OLTP** are to complete the study procedures for the week **100**/ET visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

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

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

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 for those listed in Section 6.7. For a subject who prematurely discontinues investigational product, concomitant therapy may be adjusted as needed.

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

The subject may take 1 medication with possible migraine prophylactic effects. These medications (listed in Section 6.7) should not change for the duration of the study and the doses should be stable for 2 months prior to the start of the baseline phase and throughout the study.

During the initial screening phase, the subject and investigator are to agree on the acute headache medications shown below **(Table 1)** and the appropriate dose(s) that the subject may take on an as-needed basis (PRN) throughout the study. To avoid confounding the study results, efforts should be made throughout the study to not introduce new acute migraine-specific medications (ie, triptans or ergotamines).

Table 1. List of Acute Headache Medications

Non-proprietary name	Trade name
Triptans	
Sumatriptan	Imigran (tablet, injection, kit, nasal liquid)
Zolmitriptan	Zomig (tablet, RM tablet)
Eletriptan hydrobromide	Relpax (tablet)
Rizatriptan benzoate	Maxalt (tablet, RPD tablet)
Naratriptan hydrochloride	Amerge (tablet)
NSAIDS	
Acetaminophen	Calonal etc
Aspirin	Aspirin etc
Ibupurofen	Brufen etc
Diclofenac sodium	Voltaren etc
Naproxen	Naixan (tablet)
Etodolac	Hypen/ Osteluc (tablet)
Celecoxib	Celecox (tablet)
Mefenamic acid	Pontal (powder, fine granule, tablet capsule, syrup)
Zaltoprofen	Soleton/ Peon (tablet)
Pranoprofen	Niflan (tablet, syrup)/ Pransus (syrup)
Loxoprofen	Loxonin (fine granule, tablet)
Lornoxicam	Lorcam (tablet)

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Table 1. List of Acute Headache Medications

Non-proprietary name	Trade name
Ergotamines	
Ergotamine tartrate, anhydrous caffeine, isopropylantipyrine	Cleamine combination tablet A, S
Dihydroergotamine mesilate	Dihydergot (tablet)
Steroids	
Dexamethasone sodium phosphate	Orgadrone/ Decadron (injection)
Hydrocortisone	Cortril (tablet)
Others	
Tramadol hydrochloride	Tramal (capsule, injection)
Tramadol hydrochloride, acetaminophen	Tramcet (combination tablet)

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6.5 Medical Devices

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.

Medical devices which are not considered test articles may be used in the conduct of the study as part of standard of care (except for devices excluded in Section 6.7). 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.

In the CHU substudy, the AMG 334 SureClick AI/pen is a single-use, disposable, handheld mechanical injection device that administers a fixed-dose of AMG 334 into SC tissue. The AMG 334 AI/pen uses the same components as the commercially available Repatha SureClick autoinjector.

Subjects participating in the CHU substudy will return the AIs/pens 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). The investigator will be responsible for obtaining supplies of these devices.

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

6.6 Product Complaints

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

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

6.7 Excluded Therapies Prior to the Start of the Baseline Phase and Throughout the Study

1. More than 1 of the following medications with possible migraine prophylactic effects are excluded within 2 months prior the start of the baseline phase and throughout the study. If 1 of the following medications is used, doses must be stable within 2 months prior to the start of the baseline phase and throughout the study:
    - Divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin
    - Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
    - Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
    - Venlafaxine, desvenlafaxine, duloxetine, milnacipran
    - Flunarizine, verapamil, lomerizine
    - Lisinopril, candesartan
    - Clonidine, guanfacine
    - Cyproheptadine
    - Methysergide
    - Pizotifen
    - Butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
2. Botulinum toxin (in the head and/or neck region) is excluded within 4 months prior to the start of the baseline phase and throughout the study.
3. Ergotamine-derivatives, steroids, and triptans used for migraine prophylaxis are excluded within 2 months prior to the start of the baseline phase and throughout the study.

4. Devices and procedures used for migraine prophylaxis are excluded within 2 months prior to the start of the baseline phase and throughout the study.
5. Investigational medications **and** devices, and procedures are excluded throughout the study. Subjects also must not have used investigational medications, devices or procedures for at least 90 days prior to screening (refer to Exclusion Criterion 222).

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 2 **-Table 4**) for an outline of the procedures required at each study visit.

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

Allowable windows for visits are the following:

- Each study visit during the 24-week double-blind treatment phase and safety follow-up has a window of ± 3 consecutive calendar days.
- The day 1 visit (randomization day) has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date.
- Each study visit during the **76**-week **OLTP** has a window of ± 4 consecutive calendar days.
- All study visit target dates are to be calculated from the day 1 visit date.
- All study procedures for a given study visit are to be completed on the same day.
- Each PK substudy sampling has a window of ± 3 consecutive calendar days.

Refer to the Schedule of Assessments (Table 4) for an outline of the procedures required at each study visit in the CHU substudy.

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.

7.1 Schedule of Assessments

Table 2. Schedule of Assessments - Study Visits Through Double-blind Treatment Phase

Procedures	Screening Phase (up to 7 wks)			Double-blind Treatment Phase (24 wks) [1]						
	Initial Screening (up to 3 wks) [2]	Baseline Phase (4 wks) [1] Wk -4	Baseline Phase (4 wks) [1] D 1 (pre-rand.)	D 1 (post-rand.)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 / ET [3]
Study Visit	X	X	X	X	X	X	X	X	X	X
Phone Call to Subject	Approximately 7 and 14 days after first dose of IP and approximately 7 days after each subsequent dose of IP									
Informed Consent	X									
Calls to IVR/IWR System [2]	X		X		X	X	X	X	X	X
Entry into the Baseline Phase [4]		X								
Randomization into the Double-blind Treatment Phase [5]			X							
Demography	X									
Medical and Medication History	X							**X**		
Physical Exam	X									X
Physical Measurements [7]	X		X				X			X
Vital Signs [8]	X	X	X		X	X	X	X	X	X
Hepatitis Sample Collection	X									
UDS	X	Testing as needed throughout study based on investigator's clinical suspicion								
Pregnancy Testing- Serum [9]	X									
Pregnancy Testing- Urine [9]		X	X		X	X	X	X	X	X

Footnotes defined on last page of **Table 4**.

Table 2. Schedule of Assessments - Study Visits Through Double-blind Treatment Phase

Procedures	Screening Phase (up to 7 wks)			Double-blind Treatment Phase (24 wks) [1]						
	Initial Screening (up to 3 wks) [2]	Baseline Phase (4 wks) [1] Wk -4	Baseline Phase (4 wks) [1] D 1 (pre-rand.)	D 1 (post-rand.)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 / ET [3]
Chemistry, Hematology	X			X	X		X			X
Urinalysis	X									X
ECG	X			X	X	X	X			X
PK Sampling [10]				X [11]	X [11]	X[11]	X [11]			X [11]
PK Substudy Sampling [10,12] (~91 subjects)						Day 8 and Day 64				
Biomarker Development; Blood				X						X
Pharmacogenetic Studies [13] (Optional)				X						
Anti-AMG 334 Antibodies; Serum				X	X		X			X

Footnotes defined on last page of **Table 4**.

Table 2. Schedule of Assessments - Study Visits Through Double-blind Treatment Phase

Procedures	Screening Phase (up to 7 wks)			Double-blind Treatment Phase (24 wks) [1]						
	Initial Screening (up to 3 wks) [2]	Baseline Phase (4 wks) [1] Wk -4	Baseline Phase (4 wks) [1] D 1 (pre-rand.)	D 1 (post-rand.)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 / ET [3]
COAs [14]						X (Daily)				
Site Assigns eDiary to Subject		X								
Subject Brings eDiary to Site for Use during Study Visit			X		X	X	X	X	X	X
Migraine Symptom Interference Items [14]						X (Daily)				
Migraine Physical Function Impact Stand-alone Item [14]						X (Daily)				
HIT-6 [14]		X		X	X	X	X	X	X	X
C-SSRS	X	X	X		X	X	X	X	X	X
BDI-II	X		X							
Employment Status [17]			**X**				**X**			**X**
Prior / Concomitant Medications Recording	X	X	X		X	X	X	X	X	X
IP Administration [15]				X	X	X	X	X	X	
Adverse Event/**Serious Adverse Event Collection**/Recording/**Reporting** [16]		X (SAEs only)		X	X	X	X	X	X	X
Product Complaints Recording				X	X	X	X	X	X	

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Footnotes defined on last page of **Table 4**.

Table 3. Schedule of Assessments - Study Visits Through Open-label Treatment Phase and Safety Follow-up

Procedures	Open-label Treatment Phase (OLTP) (**76** wks) [1]																					Safety F/U [1]
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100 /ET[3]**	**Dose increase to 140 mg visit[18]**	**12 wk post increase[18]**	16 Wks After Last Dose of IP
Study Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Calls to IVR/IWR System [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Entry into the OLTP [6]	X																						
PE														X						**X**	**X**	**X**	**X**
Body Weight Measurement [7]		X			X			X			X			X						**X**	**X**		X
Vital Signs [8]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
UDS	Testing as needed throughout study based on investigator's clinical suspicion																						
Pregnancy Testing-Serum [9]																							X
Pregnancy Testing-Urine [9]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry, Hematology		X		X				X						X						**X**	**X**	**X**	X
ECG		X		X			X				X			X			**X**			**X**	**X**	**X**	
PK Sampling [10]		X		X				X						X						**X**	**X**	**X**	X
Anti-AMG 334 Antibodies; Serum		X		X				X						X						**X**	**X**	**X**	X

Footnotes defined on last page of Table 4.

Table 3. Schedule of Assessments - Study Visits Through Open-label Treatment Phase and Safety Follow-up

Procedures	Open-label Treatment Phase (OLTP) (**76** wks) [1]																					Safety F/U [1]
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100 /ET[3]**	**Dose increase to 140 mg visit[18]**	**12 wk post increase[18]**	16 Wks After Last Dose of IP
COAs [14]	X (Daily)												X (Daily)						**X (Daily)**				
Subject Brings eDiary to Site for Use during Study Visit		X	X	X	X	X	X	X						X						**X**			
Migraine Symptom Interference Items [14]	X (Daily)												X (Daily)						**X (Daily)**				
Migraine Physical Function Impact Stand-alone Item [14]	X (Daily)												X (Daily)						**X (Daily)**				
HIT-6 [14]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Employment Status [17]								**X**							**X**					**X**			
Concomitant Medications Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
IP Administration [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	
Adverse Event/**Adverse Device Effect/Serious Adverse Event Collection** /Recording/**Reporting** [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Product Complaints Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	

Footnotes defined on last page of Table 4.

Table 4. Clinical Home Use Substudy Assessments

	Screening[19]	Day 1[20]	Day 28 visit	Day 29 Telephone visit	Day 56 visit	Day 57 Telephone visit	Day 85 visit[21]/ ET[22]
Informed Consent	X						
Randomization to AMG 334 70 mg/ml AI/pen x2 or AMG 334 140 mg/ml AI/pen IP self-administration arm		X					
AI/pen Instruction[23]	X	X					
Examination of areas for injection		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 Adverse Device Effects	X	X	X	X	X	X	X
Review for adverse events/serious adverse events	X	X	X	X	X	X	X
Product Complaints Recording (if applicable)		X	X	X	X	X	X

Footnote defined on next page

ADE = adverse device effect; AI = autoinjector; BDI-II = Beck Depression Inventory-II; CGRP = Calcitonin gene-related peptide; **CHU = clinical home use;** COAs = Clinical Outcomes Assessments; cont = continued; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; DBTP = Double-blind Treatment Phase; ECG = electrocardiogram; eDiary = electronic diary; EOS = end of study; EOT = end of treatment; ET = early termination; F/U = follow-up; HIT-6 = Headache Impact Test; IP = investigational product; IVR = interactive voice response; IWR = interactive web response; M = month (end of month x); OLTP = open-label treatment phase; PE = physical exam; per. = period; **PFS = pre-filled syringe;** PK = pharmacokinetics; **PROs = Patient-reported Outcomes;** QM = monthly; rand. = randomized / randomization; SAE = serious adverse event; SC = subcutaneous; UDS = urine drug screen; Wk = week (end of week x); Wkly = weekly**; WOCBP = women of childbearing potential**

[1] Each study visit during the double-blind treatment phase and safety follow-up has a window of ± 3 consecutive calendar days. The day 1 visit (randomization day) has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. Each study visit during the open-label treatment phase has a window of ± 4 consecutive calendar days. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

[2] Sites to access the Interactive Voice Response (IVR) / Interactive Web Response (IWR) System for the following: to enter the subject into the initial screening phase, to randomize an eligible subject, to obtain the investigational product assignment, to enter the subject into the open-label treatment phase, to register the end of investigational product, and to register study early termination or completion. Subject data will be collected in the IVR/IWR System including, but not limited to reason for screen fail (if applicable).
Sites to access the IVR/IWR System to obtain the investigational product assignment at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72. The IVR/IWR System will automatically assign investigational product when a subject is randomized at day 1 and when a subject is entered into the open-label treatment phase at week 24. Investigational product is dosed QM, SC.

[3] A subject who discontinues the study during the double-blind treatment phase will complete the week 24/early termination (ET) visit. A subject who discontinues open-label investigational product or the study during the open-label treatment phase will complete the week **100**/early termination (ET) visit. Subjects also will complete the safety follow-up visit 16 weeks after the last dose of investigational product.

[4] Entry into the baseline phase must occur only after completion of initial screening phase procedures

[5] Enrollment (ie, randomization) into the double-blind treatment phase using the IVR/IWR System must occur only after completion of all baseline phase procedures and prior to the first dose of double-blind investigational product (randomization and administration of the first dose of investigational product should occur on day 1)

[6] Entry into the open-label treatment phase using the IVR/IWR System must occur only after completion of all double-blind treatment phase procedures and prior to the first dose of open-label AMG 334

[7] Height and weight, measured without shoes. Height to be collected at the initial screening phase visit only.

[8] Systolic/diastolic blood pressure, heart rate and body temperature. Blood pressure to be obtained after the subject has been in a semi-recumbent position (partial semi- Fowler's position) or supine position in a rested and calm state for at least 5 minutes. At least 2 measurements (separated by at least 5 min) should be made and the average recorded. The position selected for a subject should be used for all blood pressure measurements throughout the study.

[9] Pregnancy testing for women of childbearing potential (WOCBP) **Note: Additional on treatment pregnancy testing may be performed at the investigator's discretion or per local laws and regulation.**

[10] Samples for PK assessment will be serum**.**

[11] PK samples collected at a study visit during which investigational product will be administered should be collected before dosing with investigational product (trough)

[12] Only subjects participating in the optional PK substudy (must have provided informed consent for the PK substudy) will have blood samples collected on day 8 and day 64. The PK substudy sampling window is ± 3 consecutive calendar days.

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

[14] Clinical Outcomes Assessments (COAs) and Patient-reported Outcomes (PROs) to be collected by subjects using eDiaries. The HIT-6 is to be completed during applicable study visits before invasive procedures (eg, blood draws) and investigational product administration.

[15] Site study staff to administer investigational product to subjects on day 1 (only after randomization and completion of all day 1 procedures) and at weeks 4, 8, 12, 16, 20, 24 (only after entering the open-label treatment phase and completion of all week 24 procedures), 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72**, 76, 80, 84, 88, 92, and 96.** Investigational product administration should occur after any trough PK sampling. Sites are to record the time of investigational product administration. Following the first 3 doses of investigational product in the double-blind treatment phase (ie, day 1, week 4, week 8), subjects are to remain in the clinic for approximately 1 hour for observation.

[16] S**erious adverse events** are to be collected after signing of the informed consent through end of study (16 weeks after the last dose of investigational product). Non-serious **adverse events and adverse device effects (for OLTP only)** are to be collected after the first dose of investigational product through end of study (16 weeks after the last dose of investigational product).

[17] **Current employment status will be collected at D1 (pre-rand.), week 12, week 24, and during the open label phase; the status should be collected retrospectively if needed.**

[18] **Visit for Dose Increase to 140 mg and 12Wk Post Increase to 140 mg apply only to subjects in the open-label phase who have not completed W48 after IRB approval of Protocol Amendment 2.**

[19] **Screening must occur 4 weeks prior to the planned start of the CHU substudy (day 1). IVR System will be adjusted to accommodate CHU substudy screening and randomization information as required.**

[20] **Day 1 of the CHU substudy may occur at any visit as long as subject has received at least 1 open-label dose of AMG 334 140 mg in the 20120309 main study.**

[21] **At day 85 of the CHU substudy, subject will receive AMG 334 140 mg SC administered by site staff using PFS formulation and will continue scheduled procedures and assessments as per 20120309 main study.**

[22] **ET: If a subject early terminates the CHU substudy, he/she may receive administration of AMG 334 140 mg SC at the site as per 20120309 main study and will continue 20120309 scheduled procedures and assessments as per 20120309 main study.**

[23] **Study coordinator will review AI/pen training materials (Instructions for Use) with subject at screening and will review AI/pen training materials at day 1 of the CHU substudy.**

7.2 General Study Procedures

7.2.1 Informed Consent

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

7.2.2 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 enter the subject into the initial screening phase, to randomize an eligible subject, to obtain the investigational product assignment, to enter the subject into the **OLTP**, to register the end of investigational product, and to register study **ET** or completion. Subject data will be collected in the IVR/IWR System including, but not limited to reason for screen fail (if applicable).

7.2.3 Medical and Medication History

A review of medical and medication history will be performed at initial screening to confirm subject eligibility **and at week 16**.

Targeted medical history is to be recorded in the Neurologic Medical History CRF and Cardiovascular Medical History CRF, and other medical history is to be recorded in the General Medical History CRF.

Source notes for subjects referred to the research site must include all of the above information.

7.2.4 Physical Examination

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

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

7.2.5 Physical Measurements

The following measurements are to be performed: height (initial screening only) and weight. Height and weight are to be measured without shoes.

All measurements are to be recorded on the Physical Measurements CRF.

7.2.6 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 semi-recumbent position (partial semi-Fowler's position) or supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- 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 min) 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.
- Blood pressure will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at initial screening should then be used for blood pressure determinations throughout the study.
- Neither the subject nor the observer (measurer) should talk during measurement.

The position selected for a subject (ie, semi-recumbent or supine) should be the same that is used throughout the study and documented on the Vital Signs CRF.

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

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

If abnormalities in vital signs are found and they are considered to be adverse events, record on the adverse event summary CRF.

7.2.7 Hepatitis Testing

Hepatitis testing will be performed at initial screening to confirm subject eligibility. Subjects should be excluded if they have a positive Hepatitis B Surface Antigen (HepBsAg) or if polymerase chain reaction (PCR) is positive for hepatitis B or hepatitis C virus. Hepatitis testing will be performed by the central laboratory.

- The following laboratory testing will be performed:
  - Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb)
  - Hepatitis B Virus DNA Real-Time PCR will be only performed if total HepBcAb is positive and HepBsAg is negative
  - Hepatitis C virus antibody
  - Hepatitis C Virus RNA Real-Time PCR will be only performed if hepatitis C virus antibody is positive

7.2.8 Urine Drug Screening

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

7.2.9 Pregnancy Testing for Women of Childbearing Potential

Female subjects of childbearing potential will have a serum pregnancy test at initial screening to confirm subject eligibility. All serum pregnancy testing will be performed by the central laboratory. Please refer to the central laboratory manual for details. All urine pregnancy testing will be performed by the local laboratory.

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

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.

7.2.11 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. The PK samples will be analyzed only for those subjects assigned to an AMG 334 treatment group.

Approximately 5 mL of blood will be collected at each timepoint. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples.

7.2.12 Pharmacokinetic (PK) Substudy Sampling

In addition to PK sampling on all subjects, subjects may elect to participate in a separate PK substudy. Participation in the PK substudy is optional and may not be offered at all study sites. Subjects participating in the PK substudy must have provided informed consent. Approximately 91 subjects (approximately 65 subjects across the AMG 334 treatment groups) will participate in the PK substudy. The PK substudy enrollment will be blinded (as for the main study); however, the PK samples will be analyzed only for those subjects assigned to an AMG 334 treatment group. PK substudy enrollment will close once the target number of PK substudy participants has been reached. Blood samples will be collected and assayed for AMG 334 serum concentration at day 8 and day 64. The PK substudy sampling window is ± 3 consecutive calendar days.

Approximately 5 mL of blood will be collected at each timepoint. Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples.

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

Clinical Outcome Assessments (COAs) will be collected by subjects using a handheld eDiary at various frequencies.

The eDiary will collect the following COAs daily, at home:

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

The eDiary will collect the following patient-reported outcomes (PROs):

- Migraine symptom interference items, daily, at home
- Migraine Physical Function Impact stand-alone item, daily, at home
- Headache Impact Test (HIT-6), monthly, in clinic

Site study staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's eligibility to enter the baseline phase). The site study staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day during the baseline phase and between the day 1 and week 52 study visits**,** between the week 72 and week 76 study visits, **between the week 96 and week 100/ET study visits,** and to bring the eDiary to every study visit during these periods. At the day 1 study visit the investigator will use the subject's eDiary to review all data entered during the baseline phase and confirm the relevant inclusion and exclusion criteria. **During these periods the subject will bring the eDiary to every study visit.**

Please refer to the eDiary manual for additional details.

7.2.13.1 Migraine Symptom Interference Items

Three items will assess the extent to which migraine symptoms interfered with the subject's daily activities and whether the subject spent the day/part of the day in bed or missed work or school due to migraine-related symptoms.

The recall period is the past 24 hours.

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

7.2.13.2 Migraine Physical Function Impact Stand-alone Item

The Migraine Physical Function Impact stand-alone item is a global question which provides an assessment of overall impact of migraine on everyday activities. Subjects respond to the item using a 5-point scale, with difficulty items ranging from "Not difficult" to "Extremely difficult." These are assigned scores from 1 to 5, with 5 representing the greatest burden. The score will be rescaled to a 0 - 100 scale, with higher scores representing greater impact of migraine (ie, higher burden).

The recall period is the past 24 hours.

Subjects will complete the Migraine Physical Function Impact stand-alone item using the eDiary.

7.2.13.3 Headache Impact Test (HIT-6)

The Headache Impact Test (HIT-6) is a short-form self-administered questionnaire based on the Internet-HIT question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and

change in a patient's clinical status over a short period of time. Six items assess the frequency of pain severity, headaches limiting daily activity (household, work, school, and social), wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling "fed up" or irritated because of headache, and headaches limiting ability to concentrate or work on daily activities. Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always."

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

No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.

Subjects will complete the HIT-6 using the eDiary.

7.2.14 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 in 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.

7.2.15 Beck Depression Inventory (BDI)-II

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

7.2.16 Concomitant Medications Recording

Data on all concomitant therapies being taken by the subject during the study should be collected throughout the study.

Subjects will enter individual instances of dosing with acute headache medications. Site study staff will pre-specify the subject's acute headache medications that will appear on the subject's assigned eDiary; the information includes the medication name, dose strength, and route of administration. If the subject takes an acute headache medication during aura or to treat a migraine or non-migraine headache, the subject will select one of the pre-specified medications (or "other" medication) and enter the date of administration and number of times the medication was taken on that date.

The acute headache medications reported in the eDiary also will be collected in the CRF, but data will include only the drug name, indication, and start and stop dates of PRN use (not the individual administration dates). Other concomitant therapies will be collected in the CRF, and data will include the generic drug name/treatment, indication, and dates of administration.

Refer to Section 6.4 regarding concomitant therapy and Section 6.7 for the list of treatments excluded during the study.

7.2.17 Adverse Event, Serious Adverse Event, Adverse Device Effect Collection/Recording/Reporting

Adverse event**, serious adverse event, and adverse device effect** information should be collected throughout the study and recorded at each study visit. Refer to Section 9 for details.

7.2.18 Product Complaint Reporting

Product complaint information should be collected throughout the study and recorded at each study visit, as applicable. Refer to the IPIM for details.

7.2.19 Laboratory Assessments

Sites must use 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 used for parameters such as complete blood count (CBC) with differential, serum chemistry, urine drug screening, and serum pregnancy testing (for women of childbearing potential [WOCBP]). Samples for PK testing, biomarker development, pharmacogenetic studies, 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 locally perform the urine pregnancy testing (for WOCBP) (also indicated as "local laboratory").

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 2**-Table 4**) 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.

See Table 5 for 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):

Table 5. Analyte Listing

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

7.2.20 Initial Screening Phase

The following procedures are to be completed during the initial screening phase as designated in the Schedule of Assessments (Table 2):

- Confirmation that the ICF has been signed
- The investigator is required to explain effective contraception methods to each subject.
- Entry of the subject into the initial screening phase using the IVR/IWR System
- Medical and medication history recording
- Physical examination (including neurologic exam) as per standard of care
- Physical measurements: height and weight
- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Laboratory assessments using the central laboratory: hepatitis testing, urinalysis, urine drug screen, pregnancy testing (serum), chemistry and hematology panels
- ECG
- C-SSRS
- BDI-II
- Prior and concomitant medications recording. For all prior and current migraine prophylactic medications, collect medication name, dose, unit, frequency, start date, stop date, determination of adequate therapeutic trial, and reason(s) for stopping the medication, as applicable.
- Serious adverse event **collection**/recording/**reporting** (Note: Serious adverse events are to be collected after signing of the informed consent through 16 weeks after the last dose of investigational product.)
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers, variability and PK of the investigational product.

The duration of the initial screening phase is up to 3 weeks. Certain initial screening phase procedures may be repeated during the original initial screening phase. These procedures include laboratory assessments due to value(s) out of range due to sampling error or that could be within range with repeat sampling. Amgen may grant an extension to the initial screening phase in rare cases where additional time is required to confirm eligibility.

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

7.2.21 Baseline Phase

7.2.21.1 Week -4 Visit

The following procedures are to be completed at the week -4 visit as designated in the Schedule of Assessments (Table 2):

- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Pregnancy testing (urine)
- Assignment of an eDiary to the subject at the week -4 visit (after confirming the subject's eligibility to enter the baseline phase). The subject is to interact with the eDiary every day throughout the 4-week baseline phase. Refer to Section 7.2.13 and the eDiary manual for details, including information to be addressed during subject training.
- HIT-6. The subject will complete this PRO while in the clinic, using the eDiary. For each study visit, PROs should be completed prior to invasive procedures (eg, blood draws).
- C-SSRS
- Concomitant medications recording
- Serious adverse event collection/recording/reporting

7.2.22 Day 1 Visit (Prior to Randomization)

The following procedures are to be completed at the day 1 visit prior to randomization as designated in the Schedule of Assessments (Table 2):

- Physical measurement: weight
- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Pregnancy testing (urine)
- C-SSRS
- BDI-II
- **Employment status**
- Concomitant medications recording
- Serious adverse event **collection**/recording/**reporting**
- Review of the subject's eDiary data to confirm subject eligibility prior to randomizing the subject. Run the eligibility calculations on the subject's eDiary only after all other eligibility criteria (eg, lab values) have been confirmed.
- Enrollment (ie, randomization) of the subject into the double-blind treatment phase using the IVR/IWR System

7.2.23 Day 1 (After Randomization) and the Double-blind Treatment Phase

The following procedures are to be completed during the 24-week double-blind treatment phase at timepoints designated in the Schedule of Assessments (Table 2):

- Physical examination (including neurologic exam) as per standard of care

- Physical measurement: weight
- **Medical and Medication History**
- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Laboratory assessments using the central laboratory: urinalysis, urine drug screen (performed at the investigator's discretion based on clinical suspicion), chemistry and hematology panels
- Pregnancy testing (urine)
- ECG
- PK sampling (serum)
- PK substudy sampling (serum)
- Biomarker development: blood sampling
- Pharmacogenetic substudy sampling (For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample.)
- Anti-AMG 334 antibody serum sampling
- The subject is to interact with the eDiary every day and bring his/her eDiary to every study visit. Please refer to Section 7.2.13 and the eDiary manual for details.
- COAs, migraine symptom interference items, and the Migraine Physical Function Impact stand-alone item
- HIT-6. The subject will complete the PRO while in the clinic, using the eDiary. For each study visit, PROs should be completed prior to invasive procedures (eg, blood draws).
- C-SSRS
- **Employment status (weeks 12 and 24/end of double-blind treatment phase)**
- Concomitant medications recording
- Administration of double-blind investigational product QM SC. The first dose of investigational product is to be administered only after completion of all day 1 procedures. (Randomization and administration of the first dose of investigational product should occur on day 1.) In general, administration of investigational product should be the last procedure performed at each study visit. Following the first 3 doses of investigational product in the double-blind treatment phase (ie, day 1, week 4, week 8), subjects are to remain in the clinic for approximately 1 hour for observation.
- Serious and non-serious adverse event **collection**/recording/**reporting**. (Note: Serious adverse events are to be collected after signing of the informed consent through 16 weeks after the last dose of investigational product. Non-serious adverse events are to be collected after the first dose of investigational product through 16 weeks after the last dose of investigational product.)
- Product complaints recording
- Phone call to subject approximately 7 and 14 days after the first dose of investigational product and approximately 7 days after each subsequent dose of investigational product. These phone calls are to confirm the safety of the subject. An

additional visit may be needed based on the subject's condition and the investigator judgment.

- Registering the subject's end of investigational product and/or end of study (as relevant) using the IVR/IWR System

A subject who discontinues investigational product during the double-blind treatment phase and remains in the study will complete all remaining procedures and study visits during the double-blind treatment phase and then complete the safety follow-up visit 16 weeks after the last dose of investigational product.

A subject who discontinues the study during the double-blind treatment phase will complete the week 24/ET visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

7.2.24 Open-label Treatment Phase

The following procedures are to be completed during the **OLTP** at time points designated in the Schedule of Assessments (Table 3):

- Confirmation that the subject may enter the **OLTP**: The subject has completed the double-blind treatment phase and did not end double-blind investigational product early, continues to provide informed consent, and is appropriate for continued treatment. The investigator should consider the appropriateness for continued treatment, if the subject:
  - Developed any unstable or clinically significant medical condition, laboratory or ECG abnormality following randomization into the double-blind treatment phase 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 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.
  - Experienced a serious adverse event in the double-blind treatment phase and the investigator determined that there was a reasonable possibility that the event may have been caused by investigational medicinal product.
- Entry of the subject into the **OLTP** using the IVR/IWR System
- Registration of the subject's end of investigational product and/or end of study (as relevant) using the IVR/IWR System
- Body weight measurement
- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Laboratory assessments using the central laboratory: urine drug screen (performed at the investigator's discretion based on clinical suspicion), chemistry and hematology panels
- Pregnancy testing (urine)
- ECG

- PK sampling (serum)
- Anti-AMG 334 antibody serum sampling
- The subject is to interact with the eDiary every day and bring his/her eDiary to every study visit, as noted in the Schedule of Assessments table. Please refer to Section 7.2.13 and the eDiary manual for details.
- COAs, migraine symptom interference items, and the Migraine Physical Function Impact stand-alone item
- HIT-6. The subject will complete these PROs while in the clinic. For each study visit, these PROs should be completed prior to invasive procedures (eg, blood draws).
- C-SSRS
- **Employment status**
- Concomitant medications recording
- Administration of open-label AMG 334 70 mg QM SC or **140 mg QM SC**. The first dose of open-label investigational product is to be administered only after completion of all week 24 procedures. In general, administration of investigational product should be the last procedure performed at each study visit.
- **After IRB approval of Protocol Amendment 2, the 24-week double-blind treatment phase is followed by a 76-week OLTP with dose determined by the subject's week 48 status:**

  (1) Subjects who have already completed the week 48 visit will continue to receive AMG 334 70 mg QM SC (OL70) for a total of 76 weeks, following the open label assessments in Table 3.

  (2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label AMG 334 140 mg QM SC for 76 weeks.

  (3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open-label phase duration of 76 weeks. The dose increase should be done at the first available opportunity, defined as the first visit after IRB approval of Protocol Amendment 2. Refer to Table 3 for assessments to be collected at the visit of the dose increase and 12 weeks after the dose increase. At the time of the dose increase, the End of Open-Label 70 mg eCRF page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.
- Serious and non-serious adverse event collection/recording/reporting. (Note: Serious and non-serious adverse events are to be collected through 16 weeks after the last dose of investigational product)
- **Adverse device effects collection/recording/reporting**
- Product complaints recording

A subject who discontinues open-label investigational product or the study during the **OLTP** will complete the week **100**/ET visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

7.2.25 Clinical Home Use Substudy (Optional)

The following procedures are to be completed during the OLTP at time points designated in the Schedule of Assessments (Table 4). At each CHU substudy visit, any assessments scheduled for the main 20120309 study visit should also be completed.

Screening:

- **Obtain consent to CHU substudy**
- **Review of IFU for AI/pen with subject**
- **Register CHU consent date using the IVR/IWR System (via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**

Day 1:

- **After confirming subject eligibility, the following procedures are to be completed:**
- **Register CHU randomization to randomize the subject to two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen self-administration using the IVR/IWR System (via Additional Product Dispensing activity)**
  - **Site to instruct subject on how to self-administer AMG 334 with the AI/pen by reviewing entire IFU**
  - **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 the AI/pen under site supervision**
  - **Review for adverse events/adverse device effects/serious adverse events**
  - **Product complaint recording (if applicable)**
  - **Study coordinator to reconcile IP (AI/pen)**

Day 28:

- **Study coordinator dispenses AI/pen to subject for self-administration on day 29 (IP device assigned using the IVR/IWR system via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Telephone call time scheduled for day 29 (Note, telephone visit must occur after subject has self-administered IP)**

Day 29:

- **Subject self-administers AMG 334 using AI/pen in non-clinic setting**
- **Telephone visit with study coordinator to inquire of subject if the subject 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/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**

Day 56:

- **Subject returns IP for Study Coordinator to reconcile IP (AI/pen)**
- **Study coordinator dispenses AI/pen to subject for self-administration on day 57 (IP device assigned using the IVR/IWR system via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Telephone call time scheduled for day 57 (Note, telephone visit must occur after subject has self-administered IP)**

Day 57:

- **Subject self-administers AMG 334 using AI/pen in the non-clinical setting**
- **Telephone visit with study coordinator to inquire of subject if the subject 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/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Day 85: End of CHU substudy:**
- **Subject returns IP for study coordinator to reconcile IP (AI/pen)**
- **Review adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Subject continues all 20120309 study assessments and IP is administered at site as per the 20120309 protocol**

7.2.26 Safety Follow-up / End of Study Visit

Subjects who complete the **OLTP** or who discontinue investigational product would complete the safety follow-up visit 16 weeks after the last dose of investigational product. The following procedures are to be completed for the safety follow-up as designated in the Schedule of Assessments (Table 3):

- Registration of the subject's end of investigational product and/or end of study using the IVR/IWR System

- Physical examination (including neurologic exam) as per standard of care
- Physical measurement: weight
- Vital signs: systolic/diastolic blood pressure, heart rate, and body temperature
- Laboratory assessments using the central laboratory: urine drug screen (performed at the investigator's discretion based on clinical suspicion), chemistry and hematology panels
- Pregnancy testing (urine, serum)
- PK sampling (serum)
- Anti-AMG 334 antibody serum sampling
- C-SSRS
- Concomitant medications recording
- Serious and non-serious adverse event **collecting/**recording**/reporting**. (Note: Serious and non-serious adverse events are to be collected through 16 weeks after the last dose of investigational product)
- **Adverse device effect/recording/reporting**
- **Product complaint recording**

7.3 Antibody Testing Procedures

Blood samples for antibody testing are to be collected 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. Samples allocated for PK assessment also can be used for immune complex assessment. Additional blood samples may be obtained to rule out anti-AMG 334 antibodies during the study.

Sites will not be notified of positive neutralizing antibody results to the investigational product for a subject prior to that subject's final scheduled study visit. The subjects with a positive neutralizing antibody response will continue to be dosed during the course of study but will be monitored for immunogenicity-related adverse events.

Subjects who test positive for neutralizing antibodies to the investigational product at the final scheduled study visit or following unblinding 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) after the last dose 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

CCI [redacted]

7.5 Pharmacogenetic Studies (Optional)

CCI [redacted]

7.6 Sample Storage and Destruction

Any sample collected according to the Schedule of Assessments (Table 2-**Table 3**) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods

produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis, or storage. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the 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 these analyses 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 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 (or a legally acceptable representative) can decline to continue receiving investigational product and/or other 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 and must discuss with the subject the options for continuation of the Schedule of Assessments (**Table 2-Table 4**) and collection of data, including endpoints**,** adverse events**, adverse device effects (if applicable), and serious adverse events**. The investigator must document the change to the Schedule of Assessments (**Table 2-Table 4**) 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, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, 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 by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request

- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, protocol-specified criteria [eg, hepatotoxicity stopping rules], pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 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 is defined as any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate **IFU**, 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 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 DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

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

The investigator is responsible for ensuring that all adverse events **and adverse device effects (including the OLTP and CHU substudy)** observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up visit (16 weeks after the last dose of investigational product) are reported using the Event 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 and/or toxicity,
- assessment of relatedness to investigational product (**AMG 334/placebo),** and/or **the Amgen medical devices (**pre-filled syringe **or the AI/Pen**), **and/or study-mandated procedure/study activity,** and
- action taken.

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is **available at the following location:**

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

During the double-blind treatment period, the investigator must assess whether the adverse event is possibly related to the investigational **medicinal** product (**AMG 334/placebo**). 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 **medicinal** product (**AMG 334/placebo**)?"

During the OLTP and the CHU substudy, the investigator must assess whether the adverse event is possibly related to AMG 334. 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 AMG 334?"

During the OLTP and the CHU substudy, the investigator must assess whether the adverse event is possibly related to the prefilled syringe or AI/Pen (investigational medical devices used to administer AMG 334). 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 investigational medical devices?

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

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The criteria for grade 4 in the CTCAE grading scale differ 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 single event with the worst severity on the Adverse Event Summary CRF.

The investigator is responsible for reviewing laboratory test results, ECGs, and vital signs 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 values, ECG findings, or vital signs without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory values, ECG findings, or vital signs that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality or ECG 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 **(this includes the CHU substudy)** observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the safety follow-up visit (16 weeks after the last dose of investigational product) are recorded in the subject's medical record and are submitted to Amgen, including serious adverse events that are reported to the Event Adjudication Committee for adjudication. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

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

Contingency Report Form, the data must be entered into the EDC system when the system is again available.

During the double-blind treatment period, the investigator must assess whether the serious adverse event is possibly related to the investigational medicinal product (AMG 334 / placebo). 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 medicinal product (AMG 334 / placebo)?"

During the OLTP and the CHU substudy, the investigator must assess whether the serious adverse event is possibly related to AMG 334. 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 AMG 334?"

During the OLTP and the CHU substudy, the investigator must assess whether the serious adverse event is possibly related to the prefilled syringe or AI/Pen (investigational medical devices used to administer AMG 334). 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 investigational medical devices?

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

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

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.

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

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

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

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 separately. 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.

9.4 Pregnancy and Lactation Reporting

If a **female subject becomes** pregnan**t,** or **a male subject fathers a child**, while the subject is taking investigational product**/product-required therapies**, report the pregnancy to Amgen **Global Patient Safety** as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should **report** pregnancies that occur through 16 weeks after the last dose of investigational product**/protocol-required therapies**.

The pregnancy should be reported to Amgen **G**lobal **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 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 the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

If a female breastfeeds while taking investigational product/protocol-required therapies report the lactation case to Amgen as specified below.

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur 16 weeks after the last dose of investigational product**/protocol-required therapies**.

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.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each of the last three months (months 4, 5, and 6) of the double-blind treatment phase.

10.1.1.2 Secondary Endpoints

Efficacy:

- Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in mean monthly acute migraine-specific medication treatment days over the last three months (months 4, 5, and 6) of the double-blind treatment phase

Safety:

- Adverse events
- Clinical laboratory values and vital signs
- Anti-AMG 334 antibodies

10.1.1.3 Exploratory Endpoints

- Change from baseline in mean headache impact scores as measured by the Headache Impact Test (HIT-6) over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly migraine days at assessment timepoints
- Change from baseline in mean monthly migraine attacks over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly migraine attacks at assessment timepoints
- Change from baseline in mean monthly headache (migraine and non-migraine headache) days over the last three months (months 4, 5, and 6) of the double-blind treatment phase

- Change from baseline in monthly headache (migraine and non-migraine headache) days at assessment timepoints
- Achievement of at least 50% reduction from baseline in monthly migraine days at assessment timepoints
- Achievement of at least 75% reduction from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Achievement of at least 75% reduction from baseline in monthly migraine days at assessment timepoints
- Achievement of 100% reduction from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Achievement of 100% reduction from baseline in monthly migraine days at assessment timepoints
- Change from baseline in mean monthly acute headache medication treatment days over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly acute headache medication treatment days at assessment timepoints
- Change from baseline in monthly acute migraine-specific medication treatment days at assessment timepoints
- Change from baseline in mean monthly hours of migraine headache over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly hours of migraine headache at assessment timepoints
- Change from baseline in mean monthly average severity of migraine pain over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly average severity of migraine pain at assessment timepoints
- Change from baseline in mean monthly migraine days with severe pain over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly migraine days with severe pain at assessment timepoints
- Change from baseline in mean monthly hours of severe migraine pain over the last three months (months 4, 5, and 6) of the double-blind treatment phase
- Change from baseline in monthly hours of severe migraine pain at assessment timepoints
- Change from baseline in migraine pain interference with daily activities as measured by the migraine symptom interference items over the last three months (months 4, 5, and 6) of the double-blind treatment phase at assessment timepoints
- Change from baseline in the overall impact on everyday activities score as measured by the Migraine Physical Function stand-alone item items over the last three months (months 4, 5, and 6) of the double-blind treatment phase

- AMG 334 exposure and PK-PD relationships
- [redacted]

10.1.1.4 Clinical Home Use Substudy

10.1.1.4.1 Primary Endpoint

- **Subject-reported outcome of attempted full-dose administration on day 29 and day 57**

10.1.1.4.2 Secondary Endpoint

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

10.1.1.5 Definitions of Terms Included in Endpoints

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b):

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

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

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

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

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or

- a headache of any duration for which acute headache treatment is administered.

Acute Headache Medication Treatment Day: Any calendar day during which the subject took an acute headache medication (migraine-specific or non-migraine-specific).

Acute Migraine-specific Medication Treatment Day: Any calendar day during which the subject took a migraine-specific medication (ie, triptan or ergotamine).

Monthly eDiary Data: Data collected by the eDiary in any 28-consecutive day interval relative to study day 1 when **at least** 14 days of eDiary data are collected within that 28-consecutive day interval. **Monthly frequency measurements will be prorated to 28-day equivalents.**

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.
b) An attack treated successfully with medication but with relapse within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

10.1.2 Analysis Sets

The full analysis set (FAS) includes all subjects who were randomized in the study. The efficacy analysis set includes subjects in the FAS and who received at least one dose of investigational product and **had** at least one **change from** baseline **measurement in** monthly migraine day**s during** the double-blind treatment phase. In the efficacy analysis set, subjects will be analyzed according to randomized treatment, regardless of the treatment received. The per-protocol set is a subset of the efficacy analysis set that includes subjects who completed the 24-week double-blind treatment phase with no major protocol violations. For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed **according to the randomized treatment unless a subject has received the incorrect dose during the entire double-blind treatment phase**. The open-label analysis set (OLAS) will consist of all subjects receiving at least one dose of AMG 334 in the **OLTP**. This analysis set will be used when summarizing data collected during the **OLTP**.

All subjects enrolled in the CHU substudy will be included in the CHU substudy analysis set.

10.1.3 Covariates and Subgroups

All analyses of efficacy endpoints will be adjusted for the effect of the stratification factor of prior/current treatment with migraine prophylactic medication (current migraine prophylactic medication treatment vs prior migraine prophylactic medication treatment only vs no prior or current migraine prophylactic medication treatment) and the baseline value. The primary, secondary efficacy, and selected safety endpoints will be analyzed in the subgroups defined by the stratification factor as well as **baseline monthly migraine days** (< **8 days** vs ≥ **8 days**), **prior prophylactic failure status (failed any vs not failed any), and** BMI **(**< median vs ≥ median).

10.2 Sample Size Considerations

The primary endpoint is the change from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase. Using the treatment effect compared to placebo of -1.12 and -1.30 for the AMG 334 70 mg and 140 mg dose groups, respectively and a common standard deviation of 2.8 based on a Japan topiramate trial (www.clinicaltrial.gov), the planned sample size of 131 subjects in the placebo, 70 mg and 140 mg dose groups will provide 90% and 96% power for a two-sided test with significance level of 0.05 to show the superiority of AMG 334 70 mg and 140 mg compared to placebo, respectively. The proposed number of subjects in the 28 mg (n=66) dose group with the placebo (n=131), the 70 mg (n=131) and the 140 mg (n=131) dose groups is sufficient to demonstrate a dose-response using MCP-Mod analysis with the minimum power of 95% and provide the estimates of response in a Japanese population, using an assumed treatment effect of -0.55 for the AMG 334 28 mg dose group.

Clinical Home Use Substudy

Approximately 50 subjects will be enrolled in to the CHU substudy. The following assumptions are made based on the minimum sample size of 50 subjects: 5% of subjects per treatment group discontinue IP and 90% of the remaining subjects respond that they administered a full dose. As such, 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 25 subjects per group are

8.5%, 13.8%, and 11.5%, respectively. The anticipated 95% confidence interval half width for the difference between treatment groups in the proportion of subjects administering a full dose is 19.5%. 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 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the unblinding of investigators and subjects may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2).

Individual subject treatment assignments will be maintained by the IVR/IWR System. The independent Biostatistics group external to Amgen will have access to treatment assignments and will provide unblinded results, including aggregate and subject level data, to the DMC for data reviews for safety monitoring. Any unplanned unblinding occurring during the study period will be documented and reported in the final clinical study report.

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

The analysis plan will detail the analyses and describe the timing for unblinding according to Amgen's standard operating procedure.

10.4 Planned Analyses

10.4.1 Data Monitoring Committee (DMC)

An independent DMC will review and make recommendations regarding the safety of the study participants throughout the double-blind treatment phase of the study, and until treatment assignment information is available to the study team for the primary analysis.

The DMC will be composed of external advisors, including at least 2 clinicians and a biostatistician. Summaries of data at the treatment group level will be prepared and presented by an independent biostatistician at the DMC meeting. Additionally the DMC will review pharmacokinetic data and compare the results against pre-defined criteria for observed and predicted data to potentially recommend discontinuation of enrollment into one or more of the AMG 334 treatment groups, in which case randomization of the remaining subjects would continue for the remaining treatment groups.

10.4.2 Interim Analysis

During the **OLTP** of the study, an interim analysis is planned after at least 100 subjects randomized to **140** mg of AMG 334 have completed **26 and** 52 weeks of treatment with investigational product. The purpose of this interim analysis is to evaluate the long-term efficacy and safety of AMG 334 in subjects with episodic migraine after the 24-week double-blind treatment phase.

10.4.3 Primary Analysis

The objective of the primary analysis is to evaluate the efficacy and safety of AMG 334 in subjects with episodic migraine, compared to placebo, and to identify an optimal dose in Japanese population. The following hypothesis for the primary endpoint will be tested for each AMG 334 treatment group (140 mg, 70 mg, and 28 mg) compared to placebo using the linear mixed effects model:

- Clinical Hypothesis: In subjects with episodic migraine, AMG 334 reduces the mean monthly migraine days from baseline, compared to placebo

To maintain a family-wise type I error at 0.05, the pair-wise comparison will be tested in a sequential testing procedure in the order of AMG 334 140 mg vs. placebo, 70 mg vs. placebo and 28 mg vs. placebo. The lower dose group will be tested only when the higher dose group is considered statistically significant.

The primary analysis will be performed when the last subject completes the week 24 assessment or is discontinued from the study.

10.4.4 Final Analysis

The objective of the final analysis is to evaluate the long-term profile of migraine days and adverse events of AMG 334 in subjects with migraine after the 24-week double-blind treatment phase, **OLTP**, and safety follow-up. The final analysis for the study, including all study periods and all data, will be performed at the end of the trial. In addition to the primary analysis, efficacy data and safety data from the **OLTP**, the safety follow-up will

be tabulated by double-blind treatment group as well as by aggregated overall AMG 334 treatment group; no formal testing will be conducted.

Final Analysis activities are commenced based on achieving the End of Trial milestone described in Section **3.6.2**.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

The primary objective of this study is to evaluate the effect of AMG 334 compared to placebo on the change from baseline in mean monthly migraine days, in subjects with episodic migraine.

Summary descriptive statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and two-sided 95% confidence intervals of the means (except for safety laboratory analyses). For categorical endpoints, the summaries will contain the number and percentage of subjects falling into each category. The number of days on investigational product and the total dose of investigational product will be summarized using descriptive statistics.

For all efficacy endpoints, nominal p-values will be provided for the comparisons between each AMG 334 treatment group vs the placebo group without adjusting for multiple comparisons.

In addition, the dose-response data will be depicted graphically to support a bridging strategy.

The full analysis set (FAS) will be utilized to tabulate demographic data, baseline disease characteristics and subject disposition. The efficacy analysis set will be utilized to analyze efficacy endpoints. The per-protocol analysis set will be used for the sensitivity analyses of primary and secondary endpoints. The safety analysis set will be used to analyze safety endpoints during the double-blind phase. The OLAS will be used to analyze the data collected during the **OLTP**.

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

The proportion of subjects who administer a full dose of AMG 334 in home-use will be summarized by treatment group at CHU day 29 and day 57. 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 2 visits will also be estimated. Ninety-five percent confidence intervals will be provided for each group and the difference in proportions between the groups. Subject incidence of adverse events, serious adverse events, and adverse device effects will be summarized by system organ class and preferred term for subjects enrolled in the CHU substudies. Details of the analysis of the CHU substudy will be described in a separate Statistical Analysis Plan.

10.5.2 Primary Efficacy Endpoint

The primary endpoint, the change from baseline in mean monthly migraine days over the last 3 months (months 4, 5, and 6) of the double-blind treatment phase, will be analyzed using the repeated measures linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The primary endpoint will be tested for each AMG 334 treatment group compared to the placebo group sequentially at a 2-sided significance level of 0.05 in the order of AMG 334 140 mg vs. placebo, 70 mg vs. placebo and 28 mg vs. placebo. The lower dose group will be tested only when the higher dose group is considered statistically significant. The mean change from baseline for each treatment group, and the treatment difference, 95% confidence interval will be reported.

Sensitivity analyses for the primary endpoint include: (1) the same analysis using the per-protocol analysis set, (2) the last observation carried forward (LOCF) to handle missing data **with analysis of covariance (ANCOVA) model**, and (3) **multiple imputation (MI) with assumptions of missing at random (MAR) and missing not at random (MNAR) to handle missing data.**

Once the superiority of AMG 334 70 mg and 140 mg compared to placebo is established, a dose-response model will be assessed using the MCP-Mod approach including all treatment groups. Using linear, log linear, E_{max} and sigmoid E_{max} model as candidate models, a dose response will be tested with type 1 error rate of 0.05 and identify the dose-response model that would establish the dose response relationship with best fit. The minimal effective dose identified and treatment effect at each treatment group will be estimated from the model.

10.5.3 Secondary Efficacy Endpoints

- Achievement of at least a 50% reduction from baseline in mean monthly migraine days over the last three months (months 4, 5, and 6) of the double-blind treatment phase

The 50% responder endpoint will be analyzed using a stratified CMH test after the missing data are imputed as non-response. The odds ratio for each AMG 334 treatment group vs placebo group and associated 95% confidence intervals will be reported. Sensitivity analyses for **the binary endpoint** include: (1) **CMH test** using the per**-**protocol analysis set, and (2) **generalized linear mixed model without imputation of missing data, and (3)** logistic regression model **for each visit after the** missing **data are** imputed as non-responders.

- Change from baseline in mean monthly acute migraine-specific medication treatment days over the last three months (months 4, 5, and 6) of the double-blind treatment phase

The same analysis methods will be used as for the primary endpoint (Section 10.5.2).

10.5.4 Exploratory Endpoints

The exploratory efficacy endpoints at each assessment time will be analyzed using the repeated measures linear mixed effects model (a generalized linear mixed model for dichotomized variables) that includes treatment group, baseline values, stratification factor, scheduled visit, and the interaction of treatment and scheduled visit without any imputation for missing data. The least squares mean (or odds ratio) of treatment group and placebo with associated 95% confidence intervals and p-values will be reported.

10.5.5 Safety Endpoints

For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed **according to the randomized treatment unless a subject has received the incorrect dose during the entire double-blind treatment phase**.

The Medical Dictionary for Regulatory Activities will be used to code all adverse events.

Subject incidence rates (double-blind treatment phase) and **exposure-adjusted** subject incidence rates (**OLTP**) of all treatment-emergent adverse events will be tabulated by treatment groups and by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, treatment-related adverse events, serious treatment-related adverse events, and adverse events of special interest also will be provided.

In addition, summaries of treatment-emergent adverse events and summaries of serious treatment emergent adverse events will be provided by preferred term in descending order of frequency. The analyses of safety laboratory endpoints will include summary statistics over time by treatment group **for selected analytes**. Shift tables of the worst on-study safety laboratory toxicity based on grade relative to baseline will be tabulated by treatment group.

The analyses of vital signs will include summary statistics over time by treatment group.

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.

All safety analyses will be performed for the double-blind treatment phase and **OLTP** separately.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

The investigator also is 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

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB 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 for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB approval throughout the duration of the study. Copies of the investigator's reports and the IRB 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.
- 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 ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency, and the IRB 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

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

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB 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). For example, in this study, the C-SSRS 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 and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Medical device (ie, syringes) documentation, as applicable

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.

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 subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and **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 2**-Table 4**), the investigator can search publically

available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

CRFs must be completed in English. 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

To coordinate dissemination of data from this study, Amgen **may facilitate** the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013**, updated 2014**), 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 subject to the injury section of the Clinical Trial Agreement.

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14. APPENDICES

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

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

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

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

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- **Hepatobiliary tract disease**
- **Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)**
- **Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia**
- **Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms**
- **Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)**
- **Alpha-one antitrypsin deficiency**
- **Alcoholic hepatitis**
- **Autoimmune hepatitis**
- **Wilson's disease and hemochromatosis**
- **Nonalcoholic fatty liver disease including steatohepatitis (NASH)**
- **Non-hepatic causes (eg, rhabdomylosis, hemolysis)**

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

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

Table 6. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

Criteria for Rechallenge of Amgen Investigational Product Therapies 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 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 6) are never to be rechallenged.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

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

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

Additional Clinical Assessments and Observation

All subjects in whom investigational product is withheld (either permanently or conditionally) due to potential DILI as specified in **Table 6** or who experience AST or ALT elevations > 3 x **upper limit of normal (**ULN**) or 2-fold increases above baseline values for subjects with elevated values before drug** are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

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

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product has been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL**. The following are to be considered depending on the clinical situation**:
  - **C**omplete blood count (CBC) with differential to assess for eosinophilia
  - **S**erum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - **S**erum acetaminophen (paracetamol) levels

- **A** more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- **V**iral serologies
- **Creatine phosphokinase (**CPK**)**, haptoglobin, **lactate dehydrogenase (**LDH**)**, and peripheral blood smear
- **A**ppropriate liver imaging if clinically indicated

- **A**ppropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- **H**epatology 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 **or considered stable by the investigator**. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of 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 Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

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

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

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

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

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

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

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

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

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

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

4. **Hospitalization**

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

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

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

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.

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

9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

AMGEN
Study # 20120309
AMG 334

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 334		Prefilled Syringe		Prefilled Autoinjector/ Pen (AIPen)					
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓				
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN
Study # 20120309
AMG 334

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product (01 Still being Administered, 02 Permanently discontinued, 03 Withheld)	Lot # and Serial #
AMG 334	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Prefilled Syringe	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Prefilled Autoinjector/Pen (AI/Pen)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date (Day Month Year)	Test												
	Unit												

AMGEN Study # 20120309 AMG 334	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

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

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: 20120309

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: 20120309

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 2

Protocol Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Migraine Prevention

Amgen Protocol Number AMG 334 20120309

Amendment Date: 05 June 2017

Rationale:

This is Amendment 2 for AMG 334 Study 20120309. Amendment 1 for this protocol was not implemented and therefore, the changes captured in this document reflect changes made in both Amendment 1 and Amendment 2.

The primary change to the protocol is to include a Clinical Home Use (CHU) substudy during the open-label phase. The purpose of the CHU substudy is to assess subject's ability to administer a full dose of AMG 334 in home use, using either 2 pre-filled 70 mg/mL autoinjectors/pens (AIs/pens) or 1 pre-filled 140 mg/mL AI/pen.

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

- Updated the open-label treatment phase to include AMG 334 dose increase to 140 mg/mL.
- Update the number of subjects that have received at least 1 dose of AMG 334 to date.
- Update pregnancy, lactation, and contraception requirements in alignment with Core Risk & Discomforts language.
- To align Section 6 (Treatment Procedures), Section 7 (Study Procedures), and Section 10 (Statistical Considerations) with changes made in the pivotal 20120296 study.
- To align Section 9 (Safety Data Collection, Recording, and Reporting), Section 12.6 (Publication Policy), and End of Study language with new Amgen protocol template language.
- Administration, typographical, and formatting changes were made throughout the protocol.

Description of Changes:

Section: Global

Change: Updated document date from 20 August 2015 to **05 June 2017**.

Section: Global

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

Section: Title Page, Key Sponsor Contact

Replace:

PPD [redacted]

Study Manager, Amgen Inc.

One Amgen Center Drive

Thousand Oaks, CA 91320, USA

PPD [redacted]

[redacted]

With:

PPD [redacted]

Clinical Research Medical Director, Amgen Inc.

One Amgen Center Drive

Thousand Oaks, CA 91320, USA

PPD [redacted]

[redacted]

Section: Title Page

Add:

Amendment 1:	**26 April 2017**
Amendment 2	**05 June 2017**

Section: Protocol Synopsis, Clinical Home Use Substudy (During the Open-label Treatment Phase [OLTP]) Objectives

Add:

Clinical Home Use Substudy (During the Open-label Treatment Phase [OLTP]) Objectives:

- **Primary Objective: To assess users' ability to administer a full dose (140 mg) of AMG 334 in home-use, using either 2 pre-filled 70 mg/mL autoinjectors/pens (AIs/pens) or 1 pre-filled 140 mg/mL AI/pen**
- **Secondary Objective: To assess the safety and tolerability of AMG 334 administered using either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen**

Section: Protocol Synopsis, Hypothesis

Add:

In subjects with episodic migraine, AMG 334 reduces the mean monthly migraine days from baseline, compared to placebo. **In the clinical home use (CHU) substudy, it is hypothesized that users will be able to administer a full dose of AMG 334 comparably using 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. No formal hypotheses will be tested in the CHU substudy.**

Section: Protocol Synopsis, Clinical Home Use Substudy (During the OLTP) Endpoints

Add:

Clinical Home Use Substudy (During the OLTP) Endpoints:

Primary Endpoint: Subject-reported outcome of attempted full-dose administration at day 29 and day 57.

Secondary Endpoint: Subject incidence of adverse events, serious adverse events, and adverse device effects

Section: Protocol Synopsis, Study Design, Paragraph 2

Add:

Approximately 50 subjects will be enrolled in the AMG 334 20120309 CHU substudy to assess the subject's ability to self-administer 140 mg of AMG 334 for in-home use. Subjects will be randomized 1:1 to use either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. Participation in the substudy is optional, and no additional samples will be collected for the substudy.

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration, Paragraph 1

Replace:

Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20) and AMG 334 70 mg will be administered during the 52-week open-label treatment phase (ie, at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72).

With:

Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20). **During the OLTP, AMG 334 70 mg or 140 mg QM SC will be administered, depending on the subject's visit completion status after institutional review board (IRB) approval of Protocol Amendment 2.**

Section: Protocol Synopsis, Procedures, Paragraph 1

Replace:

At the week 24 visit, subjects will be entered into the 52-week open-label treatment phase and will begin to receive open-label AMG 334 70 mg QM SC. A safety follow-up visit occurs 16 weeks after the last dose of investigational product. Subjects will use an electronic diary (eDiary) every day throughout the baseline phase, double-blind treatment phase and for the first 6 months and last month of the open-label treatment phase to report information about their migraine and non-migraine headaches and acute headache medication use. Subjects will have in-clinic study visits monthly after the week 4 visit.

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

With:

At the week 24 visit, subjects will be entered into the **76**-week **OLTP** and will begin to receive open-label AMG 334.

After IRB approval of Protocol Amendment 2, the 24-week double-blind treatment phase is followed by a 76- week OLTP with the dose determined by the subject's week 48 status:

(1) Subjects who have already completed the week 48 visit will continue to receive open-label AMG 334 70 mg QM SC (OL70) for a total of 76 weeks.

(2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label AMG 334 140 mg QM SC for 76 weeks.

(3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open label phase duration of 76 weeks. The dose increase should be done at the first available opportunity, defined as the first visit after IRB approval of Protocol Amendment 2. Refer to Table 3 for assessments to be collected at the visit of the dose increase and 12 weeks after the dose increase. At the time of the dose increase, the End of Open-label 70 mg electronic case report form (eCRF) page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.

As a result of Protocol Amendment 2, there will be 3 possible dose sequences in the open-label phase, depending on completion of week 48 visit as noted above: (1) subjects receiving only AMG 334 70 mg QM SC in the open-label phase (OL70), (2) subjects receiving only AMG 334 140 mg QM SC in the open-label phase (OL140), (3) subjects receiving both AMG 334 70 mg (for up to 24 weeks) and 140 mg QM SC (OL70-OL140).

Subjects assigned to receive AMG 334 140 mg QM SC during the open-label phase will not have the option to decrease open-label AMG 334 from 140 mg QM to 70 mg QM. A safety follow-up visit occurs 16 weeks after the last dose of investigational product. Subjects will use an electronic diary (eDiary) every day throughout the baseline phase **and** double-blind treatment phase and for the first 6 months and **between the week 72 and week 76 study visits and between the week 96 and week 100/early termination (ET) study visits** of the **OLTP** to report information about their migraine

and non-migraine headaches and acute headache medication use. Subjects will have in-clinic study visits monthly after the week 4 visit.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2-**Table 3, and Table 4 for CHU substudy**).

Section: Protocol Synopsis, Statistical Considerations, Paragraph 1

Replace:

The final analysis for the study will occur after all subjects have completed safety follow-up through week 88 or discontinued from the study.

With:

The final analysis for the study will occur after all subjects have completed safety follow-up through week **112** or discontinued from the study.

Section: Protocol Synopsis, Statistical Considerations, Paragraph 3

Replace:

For the open-label treatment phase, follow-up time adjusted subject incidence rate of treatment-emergent adverse events will be tabulated overall.

With:

For the **OLTP**, **exposure-**adjusted subject incidence rate of treatment-emergent adverse events will be tabulated overall.

Section: Protocol Synopsis, Statistical Considerations, Paragraph 4

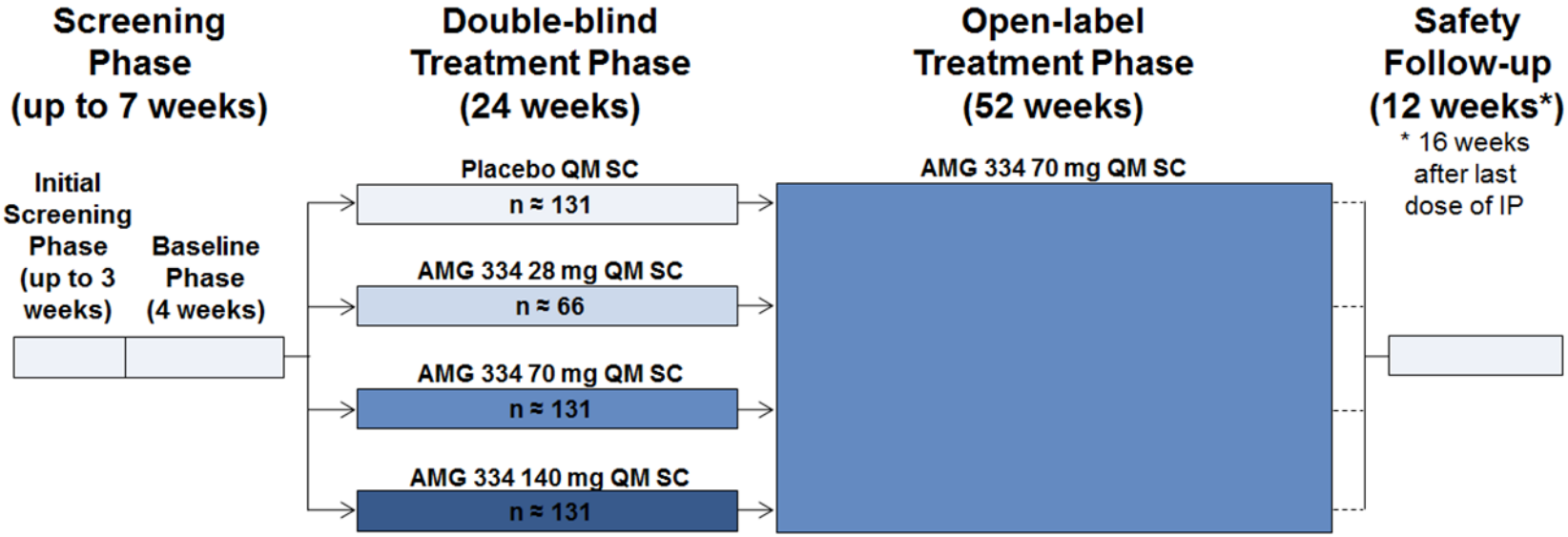
Add:

The proportion of subjects who administer a full dose of AMG 334 in home-use will be summarized by treatment group at CHU day 29 and day 57. Subject incidence of adverse events, serious adverse events, and adverse device effects will be summarized by system organ class and preferred term for subjects enrolled in the CHU substudies.

Section: Protocol Synopsis, Study Design and Treatment Schema,

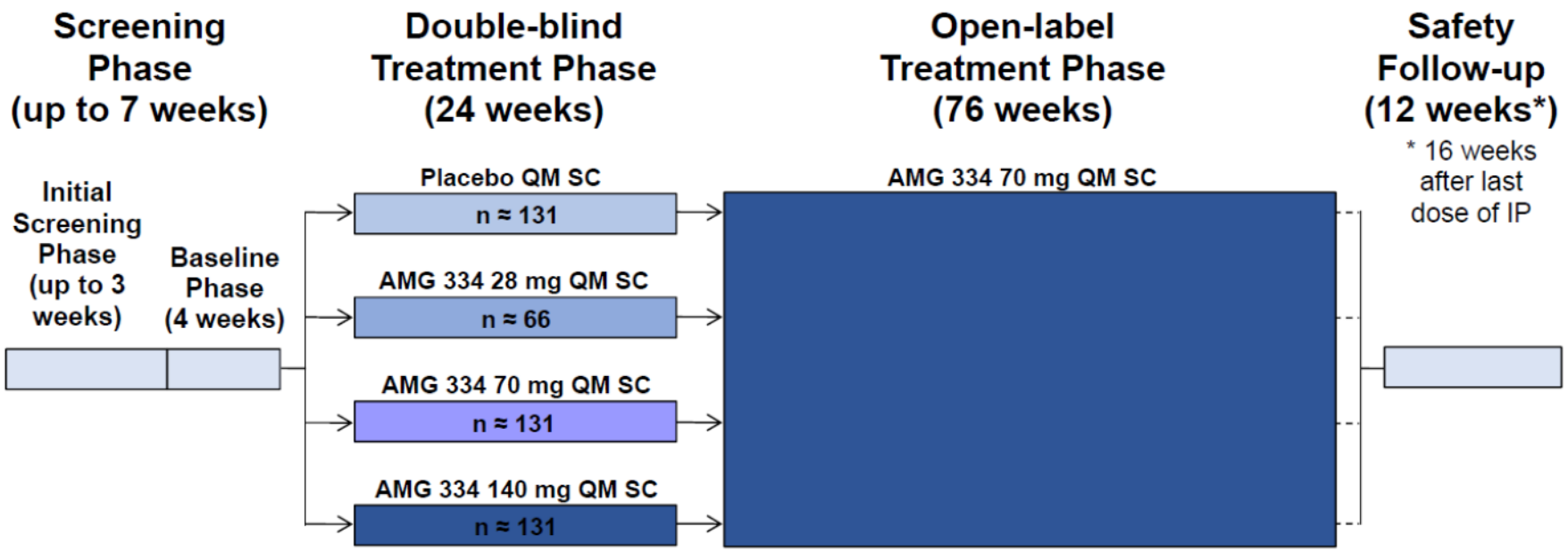
Replace:

Study Design and Treatment Schema



With:

Study Design and Treatment Schema **for Subjects That Completed Week 48 under Protocol Amendment 2 (OL70 subjects)**

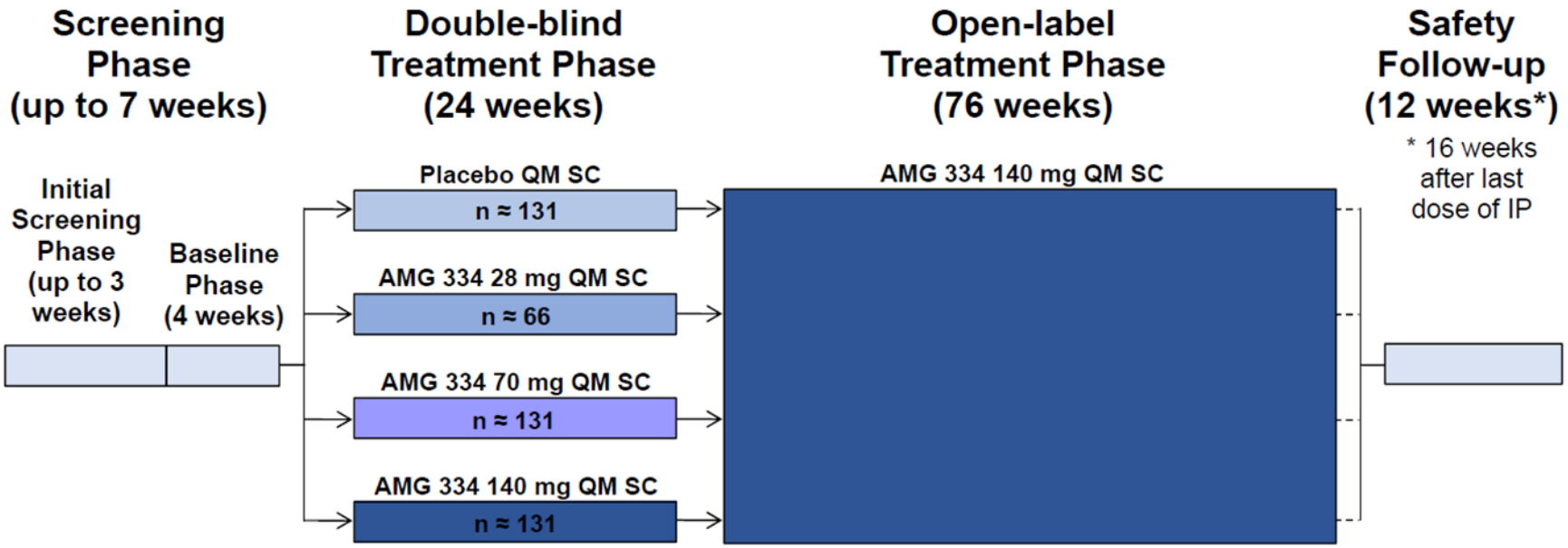


Section: Protocol Synopsis, Study Design and Treatment Schema

Add:

Study Design and Treatment Schema for Subjects Still in the Double-blind Treatment Phase Protocol Amendment 2

(OL140 Subjects)

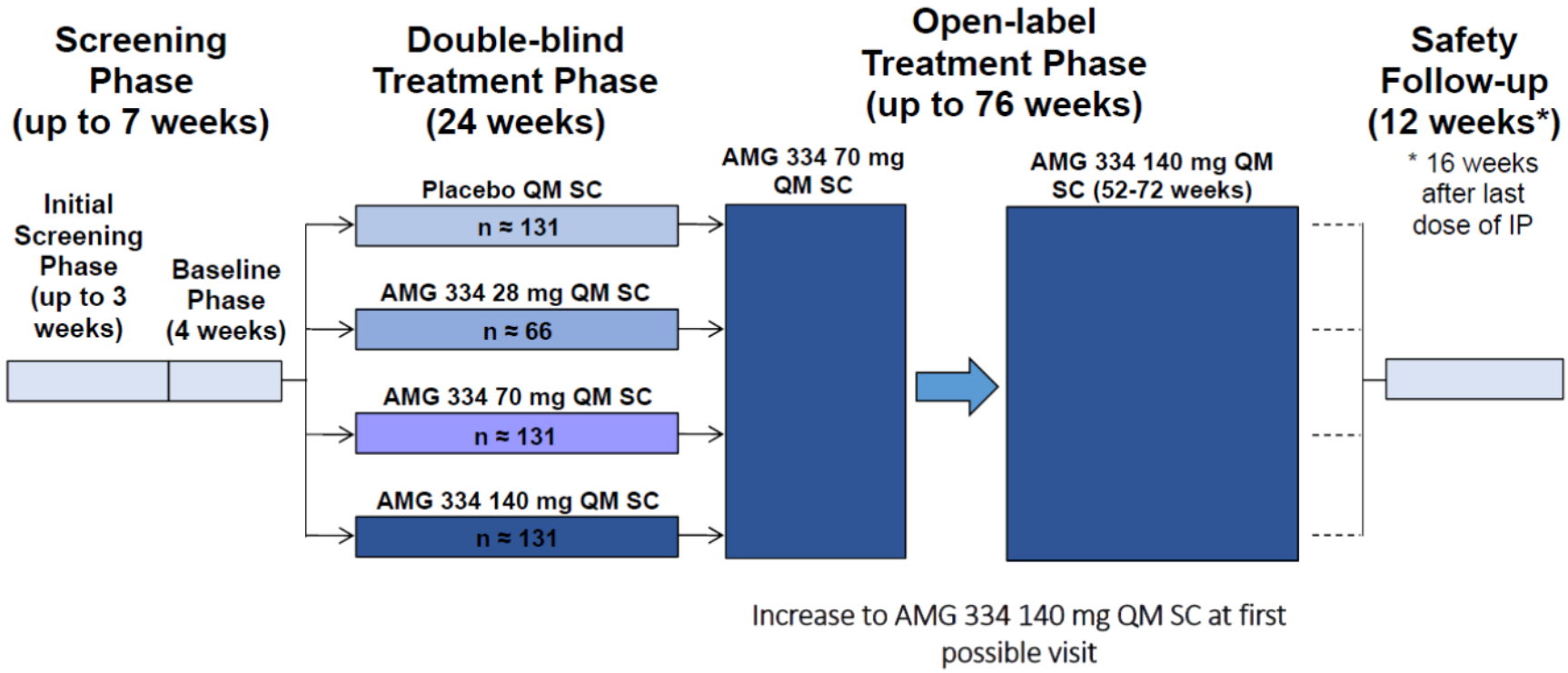


IP = investigational product; QM = monthly; SC = subcutaneous

Section: Protocol Synopsis, Study Design and Treatment Schema

Add:

Study Design and Treatment Schema for Subjects in the Open-label Phase AND Not Yet Completed W48 Under Protocol Amendment 2 (OL70-140 Subjects)



IP = investigational product; QM = monthly; SC = subcutaneous

Section: Study Glossary

Add:

AI/Pen	**Autoinjector/pen**
ANCOVA	**Analysis of covariance**
CHU	**Clinical home use**
CMH	**Cochran-Mantel-Haenszel**
eCRF	**Electronic case report form**
IFU	**Instructions for use**
MAR	**Missing at random**
MI	**Multiple imputation**
MNAR	**Missing not at random**

Section: Study Glossary

Delete:

~~AE~~	~~Adverse event~~

Section: Study Glossary

Replace:

End of Trial	The time when the last subject is assessed or receives an intervention for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit 16 weeks after the last dose of investigational product, or is discontinued from the study)
Primary Completion	The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (ie, when the last subject completes the week 24 assessment or is discontinued from the study)

Women not of childbearing potential	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.

With:

End of **Study**	The **end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (ie, the last subject **last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.**
Primary Completion	**The primary completion date is defined as t**he time when the last subject is assessed or receives an intervention for the final collection of data for the primary **endpoint(s), for the purpose of conducting the primary** analysis**, whether the study concluded as planned in the protocol or was terminated early.** **The primary completion date is the date** when the last subject **has** complete**d** the **assessments for** week 24 or is discontinued from the study**.**

Women not of childbearing potential	• 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 **a** follicle-stimulating hormone level > 40 IU/L or according to the definition of "postmenopausal range" for the laboratory involved. OR • Underwent bilateral oophorectomy OR • Underwent hysterectomy OR • Underwent bilateral salpingectomy.

Section: 1.3 Exploratory, Bullet 18

Replace:

- To evaluate the long-term safety, tolerability and maintenance of effect of AMG 334 after 76 weeks of treatment

With:

- To evaluate the long-term safety, tolerability and maintenance of effect of AMG 334 after **100** weeks of treatment

Section: 1.4 Clinical Home Use Substudy

Add:

1.4 Clinical Home Use Substudy

1.4.1 Primary

The primary objective of the clinical home use (CHU) substudy (during the open-label treatment phase [OLTP]) is to assess users' ability to administer a full dose (140 mg) of AMG 334 in home-use, using either 2 pre-filled 70 mg/mL autoinjectors/pens (AIs/pens) or 1 pre-filled 140 mg/mL AI/pen.

1.4.2 Secondary

Secondary objective of the CHU substudy (OLTP): To assess the safety and tolerability of AMG 334 administered using either 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen.

Section: 2.2 Amgen Investigational Product AMG 334 Background, Paragraph 5

Replace:

As of November 2014, approximately 100 subjects (healthy subjects and migraineurs) had participated in Phase 1 studies, and 103 subjects with hot flashes associated with menopause participated in a Phase 2a study. Approximately 152 subjects had received single or multiple doses of AMG 334 in the Phase 1 and Phase 2a studies. AMG 334 has demonstrated a favorable safety and tolerability profile similar to placebo in these studies. Refer to the AMG 334 Investigator's Brochure for details.

With:

As of **January** 201**7**, approximately **3623** subjects (**2786.43 subject years) have received at least 1 dose of AMG 334. This includes 613** healthy **volunteers and 2917 migraine** subjects. AMG 334 has **to date,** demonstrated a favorable safety and tolerability profile similar to placebo in these studies. Refer to the AMG 334 Investigator's Brochure for details.

Section: 2.3 Rationale, Paragraph 1

Replace:

Migraine prophylaxis is an area of a large unmet medical need, with existing therapies having modest efficacy and being poorly tolerated.

With:

Migraine prophylaxis is an area of a large unmet medical need, with existing therapies having modest efficacy and poor tolera**bility**.

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Paragraph 1

Add:

In the open-label phase, the dose of AMG 334 is being increased to 140 mg in a subset of subjects to provide continuous 1-year safety data for subjects receiving either AMG 334 70 mg or 140 mg.

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Paragraph 3

Delete:

~~AMG 334 140 mg currently is being evaluated in the ongoing chronic migraine study (Study 20120295) and efficacy data are being collected.~~

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Paragraph 5

Replace:

In the global Phase 2 episodic migraine study (Study 20120178), treatment-emergent adverse events (AEs) were reported by 165 (51.7%) subjects across all AMG 334 arms, and 82 (53.6%) subjects in the placebo arm.

With:

In the **double blind treatment phase of the** global Phase 2 episodic migraine study (Study 20120178), treatment-emergent adverse events were reported by 165 (51.7%) subjects across all AMG 334 arms, and 82 (53.6%) subjects in the placebo arm.

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Paragraph 5

Replace:

The safety and tolerability data generated to date support further evaluation of the 70-mg dose in the Phase 3 studies. The study 20120178 open-label treatment phase is ongoing.

With:

The safety and tolerability data generated to date support**ed** further evaluation of the 70-mg dose in the Phase 3 studies. The study 20120178 **OLTP** is ongoing **and the protocol has been amended to increase the open-label dose from 70 mg to 140 mg**.

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Paragraph 6 and 7

Replace:

The 140 mg of AMG 334 is included in the ongoing chronic migraine study (Study 20120295). As of 13 November 2014, 165 subjects had been randomized 3:2:2 to placebo, AMG 334 70 mg, or AMG 334 140 mg, respectively. Approximately 47 subjects had been randomized to the 140 mg group. Blinded interim safety review did

not reveal any safety signal. Among all subjects who were randomized in study 20120295, four (4) subjects had discontinued investigational product, with two (2) subjects who discontinued investigational product due to adverse event (constipation, gastroesophageal reflux disease). Most commonly reported adverse events (≥ 2% in any group) included fatigue, muscle spasms, and nasopharyngitis. Five serious adverse events (cholecystectomy, non-cardiac chest pain, pancreatitis, parotitis, vomiting) had been reported and all were deemed by the investigator as not related to investigational product.

Overall, the safety data generated to date for both 70 mg and 140 mg of AMG 334 support further evaluation in Phase 3.

With:

AMG 334 140 mg has been evaluated for the prevention of episodic migraine in a global Phase 3 study (20120296) with a 24-week double-blind treatment phase. The study randomized 955 subjects (AMG 334 70 mg [n = 317], AMG 334 140 mg [n = 319], and placebo [n = 319], QM SC) with a history of migraine with or without aura for ≥ 12 months and a monthly migraine frequency of ≥ 4 to < 15 migraine days. For the primary endpoint of change in monthly migraine days from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase, the 70 mg and 140 mg doses were significantly different from placebo (-3.23 days and -3.67 days vs. -1.83 days, p < 0.001). Both doses produced statistically significant improvements in the secondary outcome measures of 50% responder rate and monthly migraine-specific medication treatment days. The results of the other secondary endpoints were consistent with those of the primary endpoint. Across the primary and all secondary endpoints, AMG 334 140 mg showed numerically greater efficacy than 70 mg. At the end of the double-blind treatment phase, subjects in each treatment group are re-randomized 1:1 in a blinded fashion to AMG 334 70 mg or AMG 334 140 mg for the 28-week active treatment phase, which is ongoing.

During the placebo-controlled double-blind treatment phase of the 20120296 study, treatment-emergent adverse events were reported in 57.3%, 55.5%, and 63.0% of subjects in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively, and most were Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2 (mild to moderate in severity). Study drug discontinuations due to adverse events were reported in 7 subjects (2.2%),

6 subjects (1.9%), and 7 subjects (2.2%) in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively. The most frequent adverse events occurring in ≥ 2% of all AMG 334 treated subjects were nasopharyngitis, upper respiratory tract infection, sinusitis, constipation, arthralgia, fatigue, and nausea. Serious adverse events were reported in 2.5%, 1.9%, and 2.2% of subjects in the AMG 334 70 mg, AMG 334 140 mg, and placebo groups, respectively. No serious adverse event occurred in more than 1 subject, except cholelithiasis which was reported by 2 subjects in the AMG 334 70 mg group (one of whom had clear risk factors). Study 20120296 and Study 20120309 are being monitored by the same independent DMC.

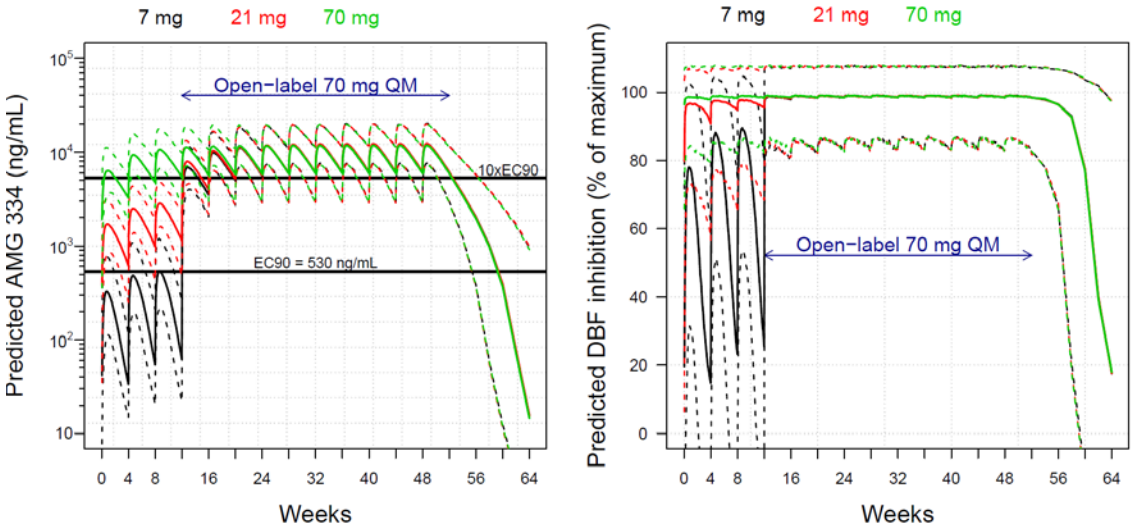
In the global 12-week study 20120295, 667 subjects with chronic migraine (≥ 15 headache days per month, with ≥ 8 migraine days) were randomized to AMG 334 70 mg (n = 191), AMG 334 140 mg (n = 190), or placebo (n = 286), QM SC. For the primary endpoint of change in monthly migraine days from baseline to the last 4 weeks of the 12-week double-blind treatment phase, the 70 mg and 140 mg doses were significantly different from placebo (-6.64 days and -6.63 days vs. -4.18 days, $p < 0.001$). Treatment-emergent adverse events were reported in 39.0%, 43.7%, and 46.8% of subjects in the placebo, AMG 334 70 mg, and AMG 334 140 mg groups, respectively. No apparent dose-response pattern was observed across the most common treatment-emergent adverse events. The most commonly reported adverse events occurring in ≥ 2% of all AMG 334 treated subjects were injection site pain, upper respiratory tract infection, nausea, nasopharyngitis, constipation, muscle spasms, and migraine. Serious adverse events were reported in 2.5%, 3.2%, and 1.1% of subjects in the placebo, AMG 334 70 mg, and AMG 334 140 mg groups, respectively. No individual serious adverse event was reported in more than 1 subject in the placebo, AMG 334 70 mg, or AMG 334 140 mg groups. Subjects from 20120295 were eligible to enroll in an ongoing 52-week open-label extension study (20130255), in which the original dose was 70 mg QM SC, but subsequently the dose was increased to 140 mg QM SC. Of the 609 subjects enrolled, 259 subjects received at least one dose of AMG 334 140 mg. Based on the interim analysis data cut-off of 01 September 2016 with a mean (SD) duration of exposure to AMG 334 140 mg of 176.4 (70.9) days, the reported adverse events were consistent with the known safety profile of AMG 334.

The global Phase 2 study (20120178) in episodic migraine has an ongoing open-label phase of up to 256 weeks. The original dose was 70 mg but a protocol amendment dated 07 April 2016 increased the dose to 140 mg for all subjects. Thus 140 mg has been investigated in the double-blind portions of studies 20120296 and 20120295, as well in open-label or active treatment extension phases (studies 20120296, 20130255, 20120178), and no new safety signal has been detected.

Section: 2.3 Rationale, Rationale for AMG 334 Doses, Figure 2 and Table 1

Delete:

~~Figure 2. Predicted AMG 334 Exposure and Capsaicin-induced Dermal Blood Flow (DBF) Inhibition for the Phase 2 Doses Up to 52 Weeks of Dosing in the Japan Phase 2 Study~~



~~Figure legends: 50th (solid lines), 5th and 95th (lower and upper dashed lines) percentiles of predictions. Estimated mean maximum inhibition in DBF response from Phase 1 study is approximately 93%.~~

~~Table 1. Predicted Safety Margins as Ratios of Exposure After SC Dosing of 70 mg Q4W Compared to Exposure Following the Highest Tested Safe Dose in Studies 20101267 and 20101268~~

	~~Predicted Exposure After Third Dose of 70 mg Q4W SC~~		~~Highest Observed Single Dose Exposure: Predicted Exposure at 70 mg SC Q4W*~~		~~Observed Multiple Dose Exposure at 140 mg SC Q4W: Predicted Exposure at 70 mg SC Q4W#~~	
~~Weight (kg)$~~	~~Mean AUC_{0-28D} (µg•day/mL)~~	~~Mean C_{max} (µg/mL)~~	~~AUC~~	~~C_{max}~~	~~AUC~~	~~C_{max}~~
~~72~~	~~201~~	~~9.4~~	~~2.0~~	~~5.1~~	~~2.4~~	~~2.5~~
~~53~~	~~284~~	~~13~~	~~1.4~~	~~3.7~~	~~1.7~~	~~1.8~~

~~SC = subcutaneous; Q4W = once every 4 weeks; AUC = area under the curve; C_{max} = maximum concentration.~~
~~$: 72 -kg reference weight for non-Japanese subjects and 53 -kg as typical body weight for a Japanese female subject~~
~~*: Ratios of observed 140 mg IV single dose PK to predicted 70 mg SC Q4W PK after third dose; observed mean (%CV) AUC_{0-28D} and C_{max} in Study 20101267 at 140 mg IV SD are 403 µg day/mL (12.8) and 47.8 µg/mL (8.55), N=6, respectively~~
~~#: Ratios of observed 140 mg SC Q4W PK to predicted 70 mg SC Q4W PK after third dose; observed preliminary mean (%CV) AUC_{0-28D} and C_{max} for 140 mg SC Q4W after third dose in Study 20101268 are 475 µg day/mL(33.8) and 23.7 µg/mL (33.3), respectively.~~

Section: 2.4 Clinical Hypothesis, Paragraph 1

Add:

In subjects with episodic migraine, AMG 334 reduces the mean monthly migraine days from baseline, compared to placebo. **In the CHU substudy, it is hypothesized that users will be able to administer a full dose of AMG 334 comparably using 2 pre-filled 70 mg/mL AIs/pens or 1 pre-filled 140 mg/mL AI/pen. No formal hypotheses will be tested in the CHU substudy.**

Section: 3.1 Study Design, Paragraph 1

Replace:

The study is composed of an initial screening phase (up to 3 weeks), a 4-week baseline phase, a 24-week double blind treatment phase, a 52-week open-label treatment phase, and an 12-week safety follow-up phase (16 weeks after the last dose of investigational product).

With:

The study is composed of an initial screening phase (up to 3 weeks), a 4-week baseline phase, a 24-week double-blind treatment phase, a **76**-week **OLTP**, and a 12-week safety follow-up phase (16 weeks after the last dose of investigational product).

Section: 3.2 Clinical Home Use Study Design (Optional) (new section)

Add:

3.2 Clinical Home Use Study Design (Optional)

Approximately 50 subjects will be enrolled in this AMG 334 20120309 CHU substudy to assess subjects' ability to self-administer 140 mg of AMG 334 for in-home use. Subjects will be randomized 1:1 to use either 2 pre-filled 70 mg/mL AIs/pens (for a total dose of 140 mg) or 1 pre-filled 140 mg/mL AI/pen. It is hypothesized that users will be able to self-administer a full dose of AMG 334 comparably using either dosage. No formal hypotheses will be tested.

Safety and tolerability of AMG 334 self-administered using two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen 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 eligibility criteria.

CHU substudy screening (day -28) should occur during or after a subject has received at least 1 dose of open-label AMG 334 140 mg. Subjects should also review the AI/pen instructions for use (IFU) at day -28 of the CHU substudy to determine if they wish to enroll in the substudy at day 1. Subjects must have received at least 1 dose of AMG 334 140 mg by day 1 of the CHU substudy.

Day 1 of the CHU substudy should correspond with any 20120309 study visit up through week 88. At day 1, subjects who meet all eligibility criteria will be randomized via IVR System to self-administer AMG 334 using either two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen (approximately 25 subjects in each arm).

At CHU substudy day 1, areas that may be injected (upper arm, abdomen, or upper thigh) should be examined for any skin abnormalities; adverse events, serious adverse events, and adverse device effects will be collected during the CHU substudy, and will be assessed on CHU screening, day 1, day 28 (at site), and day 56 (at site) and on CHU substudy days 29 and 57 (assessed by telephone visit).

Adverse event, serious adverse event, adverse device effect, concomitant medication therapies, 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 main study. On the CHU substudy day 1 visit, the site should review the IFU with the subject before administration of IP. On day 1 of the substudy, subjects will self-administer IP (two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen) under clinical site supervision.

Subjects will be provided a box containing either two 70 mg/mL AI/pens or one dose of 140 mg AI/pen at the CHU substudy day 28 and day 56 visits and will self-administer IP individually without supervision at home on substudy 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 the AI/pen was injected) and will document the subject's response in the eCRF. 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 adverse device effects.

Day 85 (clinic visit) is the end of the CHU substudy and sites will inquire about adverse events, serious adverse events, and adverse device effects. At day 85 of the CHU substudy, site staff will administer AMG 334 140 mg SC and will continue the scheduled procedures and assessments as per the 20120309 protocol. If a subject terminates the CHU substudy early, the subject may receive administration of AMG 334 140 mg SC at the site as per the 20120309 protocol and will continue 20120309 scheduled procedures and assessments as per the 20120309 protocol.

Section: 3.4 Number of Subjects, Paragraph 4

Add:

Approximately 50 subjects may participate in the CHU substudy.

Section: 3.6.1 Study Duration for Subjects, Paragraph 1

Replace:

The planned length of participation in the study for an individual subject is up to 95 weeks, which includes the following:

With:

The planned length of participation in the study for an individual subject is up to **119** weeks, which includes the following:

Section: 3.6.1 Study Duration for Subjects, Bullet 4

Replace:

- 52-week open-label treatment phase

With:

- **76**-week **OLTP**

Section: 3.6.2 End of Study

Replace:

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis (such as when the last subject completes the week 24 assessment or is discontinued from the study).

End of Trial: The time when the last subject is assessed or receives an intervention for evaluation in the study (ie, when the last subject completes the study, which includes the safety follow-up visit 16 weeks after the last dose of investigational product, or is discontinued from the study).

With:

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

The primary completion date is the date when the last subject **has** complete**d** the **assessments for** week 24 or is discontinued from the study).

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

End of **Study**: The **end of study date is defined as the date** when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (ie, last subject **last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.**

Section: 4.1 Inclusion Criteria, Criterion 109

Add:

CHU Substudy:

- **Subjects must have provided informed consent for the substudy. Subjects enrolling in the CHU substudy must have received open-label 140 mg AMG 334 for at least 1 dose.**

Section: 4.2 Exclusion Criteria, Criterion 221, Bullet 6 Sub-bullet 3

Replace:

- 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.

With:

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

Section: 4.2 Exclusion Criteria, Criterion 227

Add:

CHU Substudy

227 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 an AI/pen after review of the IFU). Subjects receiving AMG 334 70 mg in the open-label phase are not eligible.

Section: 5.1 Randomization/Treatment Assignment, Paragraph 5

Add:

For the CHU substudy, after confirming that the optional CHU substudy ICF has been signed, subjects who meet all inclusion/exclusion criteria may be randomized at CHU day 1 via IVR System to self-administer AMG 334 using either two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen (approximately 25 subjects in each arm).

Section: 6.1 Classification of Product(s), Medical Devices and/or Combination Product(s)

Replace:

6.1 Classification of Product and Medical Devices

The Amgen Investigational Product used in this study is AMG 334 and/or placebo, and the pre-filled syringe.

With:

6.1 Classification of Product**(s),** Medical Devices **and/or Combination Product(s)**

The Amgen Investigational Product used in this study is AMG 334 and/or placebo **in a** pre-filled syringe.

For subjects participating in the CHU substudy, Amgen investigational product used is AMG 334 in a pre-filled AI/pen.

Section: 6.2.1 Amgen Investigational Product, Paragraph 2

Replace:

For the pre-filled syringes, AMG 334 will be presented as 70 mg/mL AMG 334 formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate C CI, at pH CC I.

Detailed information regarding the storage, preparation, and administration of investigational product will be provided separately in the IPIM.

With:

For the pre-filled syringes, AMG 334 will be presented as 70 mg/mL AMG 334 formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate C CI, at pH CC I. **If and when available, the AMG 334 140 mg dose in the open-label**

phase may be made available for use as a 140 mg/mL pre-filled syringe formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate CCI, at pH CCI.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, **destruction** and administration of **AMG 334 and placebo**.

Subjects randomized as part of the CHU substudy will be supplied with a sterile, single-use, preservative-free solution(s) for SC injection as either: (1) an AI/pen containing 1 mL AMG 334 at a concentration of 140 mg/mL formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate CCI, pH CCI or (2) two AIs/pens, each containing 1 mL AMG 334 at a concentration of 70 mg/mL formulated with CCI sodium acetate, CCI sucrose, CCI polysorbate CCI, pH CCI.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 1

Replace:

Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20) and open-label AMG 334 70 mg will be administered during the 52-week open label treatment phase (ie, at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72).

With:

Double-blind AMG 334 140 mg, AMG 334 70 mg, AMG 334 28 mg, or placebo will be administered during the 24-week double-blind treatment phase (ie, at day 1 and weeks 4, 8, 12, 16, and 20)**. During the OLTP,** AMG 334 70 mg **or AMG 334 140 mg QM SC** will be administered**, depending on the subject's visit completion status after IRB approval of Protocol Amendment 2**.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 2

Replace:

Investigational product doses are fixed in each phase of the study and will not be adjusted for individual subjects. During the double-blind treatment phase, 3 SC injections are to be given for each investigational product administration (ie, at day 1 and weeks 4, 8, 12, 16, and 20) to maintain the dose-level blinding. The 3 SC injections

should be separated by no more than approximately 1 minute. During the open-label treatment phase, only 1 SC injection is to be given for each investigational product administration (ie, at weeks 24, 28, etc.). The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Please see the IPIM for investigational product details.

With:

During the double-blind treatment phase, 3 SC injections are to be given for each investigational product administration (ie, at day 1 and weeks 4, 8, 12, 16, and 20) to maintain the dose-level blinding. The 3 SC injections should be separated by no more than approximately 1 minute. During the **OLTP**, 1 SC injection is to be given for **AMG 334 70 mg and 2 SC injections for AMG 334 140 mg**. **If and when 140 mg/mL pre-filled syringes become available during the open-label phase, the 140 mg dose may be administered by a single 140 mg/mL SC injection.**

After IRB approval of Protocol Amendment 2, after the 24-week double-blind treatment phase, there is a 76-week OLTP with the dose determined by the subject's week 48 status:

(1) Subjects who have already completed the week 48 visit will continue to receive open-label AMG 334 70 mg QM SC (OL70) for a total of 76 weeks.

(2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label 140 mg QM SC for 76 weeks.

(3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open-label phase duration of 76 weeks. The dose increase to 140 mg should be done at the first available opportunity, defined as the first visit after IRB approval of Protocol Amendment 2. At the time of the dose increase, the End of Open-label 70 mg eCRF page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.

As a result of Protocol Amendment 2, there will be 3 possible dose sequences in the open-label phase, depending on completion of week 48 visit as noted above: (1) subjects receiving only AMG 334 70 mg QM SC in the open-label phase (OL70), (2) subjects receiving only AMG 334 140 mg QM SC in the open-label phase (OL140), and (3) subjects receiving both AMG 334 70 mg (for up to 24 weeks) and 140 mg QM SC (OL70-140). Subjects assigned to receive AMG 334 140 mg QM SC during the open-label phase will not have the option to decrease open-label AMG 334 from 140 mg QM to 70 mg QM.

The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Please see the IPIM for investigational product details.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 7

Add:

During the CHU substudy, the subject will self-administer IP (1 or 2 injections using AI/pen) under site supervision on day 1. On day 28 and day 56 during the CHU substudy, the site will provide IP to the subject to self-administer (1 or 2 injections using AI/pen) on the next day. The anatomical sites for self-administration are the upper thigh or abdomen. The upper arm should only be used if administered by a care-giver. During the CHU substudy the injection site location should be the same for all injections but do not use the same spot on the injection site you used for a previous injection. For further details regarding self-administration procedures, the IFU should be consulted.

Section: 6.2.1.1 Dosage, Administration, and Schedule, Paragraph 11

Add:

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 7.2.25.

Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Paragraph 5

Replace:

Subjects who permanently discontinue investigational product during the open-label treatment phase are to complete the study procedures for the week 76/early termination

(ET) visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

With:

Subjects who permanently discontinue investigational product during the **OLTP** are to complete the study procedures for the week **100**/early termination (ET) visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

Section: 6.3 Hepatoxicity Stopping and Rechallenge Rules

Replace:

6.3 Hepatoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 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, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Nonalcoholic Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

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, and eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product:

- 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 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 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

With:

6.3 Hepatotoxicity Stopping Rules

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

Section: 6.4 Concomitant Therapy, Paragraph 4

Add:

During the initial screening phase, the subject and investigator are to agree on the acute headache medications shown below **(Table 1)** and the appropriate dose(s) that the subject may take on an as-needed basis (PRN) throughout the study.

Section: 6.4 Concomitant Therapy, Table Header

Add:

Table 1. List of Acute Headache Medications

Section: 6.5 Medical Devices, Paragraph 3

Add:

In the CHU substudy, the AMG 334 SureClick AI/pen is a single-use, disposable, handheld mechanical injection device that administers a fixed-dose of AMG 334 into SC tissue. The AMG 334 AI/pen uses the same components as the commercially available Repatha SureClick autoinjector.

Subjects participating in the CHU substudy will return the AIs/pens 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). The investigator will be responsible for obtaining supplies of these devices.

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

Section: 6.6 Product Complaints, Paragraph 1

Replace:

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 or devices provisioned and/or repackaged/modified by Amgen.

With:

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 **for distribution** to **market or** clinic by **either** Amgen or by distributors, and partners with whom Amgen manufactures the material. This includes any products**,** devices**, combination product(s)** provisioned and/or repackaged/modified by Amgen. **Drug(s) or device(s) includes investigational product.**

Section: 6.7 Excluded Therapies Prior to the Start of the Baseline Phase and Throughout the Study, Number 5

Replace:

5. Investigational medications, devices, and procedures are excluded throughout the study. Subjects also must not have used investigational medications, devices or procedures for at least 90 days prior to screening (refer to Exclusion Criterion 222).

With:

5 Investigational medications **and** devices are excluded throughout the study. Subjects also must not have used investigational medications, devices or procedures for at least 90 days prior to screening (refer to Exclusion Criterion 222).

Section: 7 Study Procedures, Paragraph 1

Add:

Refer to the Schedule of Assessments (Table 2-**Table 4**) for an outline of the procedures required at each study visit.

Section: 7 Study Procedures, Paragraph 3, Bullet 3

Replace:

- Each study visit during the 52-week open-label treatment phase has a window of ± 4 consecutive calendar days.

With:

- Each study visit during the **76**-week **OLTP** has a window of ± 4 consecutive calendar days.

Section: 7 Study Procedures, Paragraph 4

Add:

Refer to the Schedule of Assessments (Table 4) for an outline of the procedures required at each study visit in the CHU substudy.

Section: 7.1 Schedule of Assessments, Table 2

Add:

Procedures	Screening Phase (up to 7 wks)			Double-blind Treatment Phase (24 wks) [1]						
	Initial Screening (up to 3 wks) [2]	Baseline Phase (4 wks) [1] Wk -4	Baseline Phase (4 wks) [1] D 1 (pre-rand.)	D 1 (post-rand.)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24 / ET [3]
Medical and Medication History	X							**X**		
Employment Status [15]				**X**			**X**			**X**
Adverse Event/**Serious Adverse Event Collection**/Recording/**Reporting** [16]	X (SAEs only)			X	X	X	X	X	X	X

Section: 7.1 Schedule of Assessments, Table 2, Footnotes

Replace:

Footnotes defined on last page of the second table

With:

Footnotes defined on last page of **Table 4.**

Section: 7.1 Schedule of Assessments, Table 3
Replace:

Procedures	Open-label Treatment Phase (OLTP) (52 wks) [1]														Safety F/U [1] 16 Wks After Last Dose of IP
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76 /ET	
Study Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calls to IVR/IWR System [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Entry into the OLTP [6]	X														
PE														X	
Body Weight Measurement [7]		X			X			X			X			X	X
Vital Signs [8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
UDS	Testing as needed throughout study based on investigator's clinical suspicion														
Pregnancy Testing- Serum [9]															X
Pregnancy Testing- Urine [9]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry, Hematology		X		X				X						X	X
ECG		X		X			X				X			X	
PK Sampling [10]		X		X				X						X	X
Anti-AMG 334 Antibodies; Serum		X		X				X						X	X
COAs [14]				X (Daily)									X (Daily)		
Subject Brings eDiary to Site for Use during Study Visit		X	X	X	X	X	X	X						X	
Migraine Symptom Interference Items [14]				X (Daily)									X (Daily)		
Migraine Physical Function Impact Stand-alone Item [14]				X (Daily)									X (Daily)		
HIT-6 [14]		X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Administration [15]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Event Recording [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Product Complaints Recording	X	X	X	X	X	X	X	X	X	X	X	X	X		

With:

Procedures	Open-label Treatment Phase (OLTP) (**76** wks) [1]																					Safety F/U [1]
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100 /ET[3]**	**Dose increase to 140 mg visit[18]**	**12 wk post increase[18]**	16 Wks After Last Dose of IP
Study Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Calls to IVR/IWR System [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Entry into the OLTP [6]	X																						
PE														X						**X**	**X**	**X**	**X**
Body Weight Measurement [7]		X			X			X			X			X						**X**	**X**		X
Vital Signs [8]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
UDS	Testing as needed throughout study based on investigator's clinical suspicion																						
Pregnancy Testing-Serum [9]																							X
Pregnancy Testing-Urine [9]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry, Hematology		X		X				X						X						**X**	**X**	**X**	X
ECG		X		X			X				X			X			**X**			**X**	**X**	**X**	
PK Sampling [10]		X		X				X						X						**X**	**X**	**X**	X
Anti-AMG 334 Antibodies; Serum		X		X				X						X						**X**	**X**	**X**	X

Footnotes defined on last page of Table 4.

Procedures	Open-label Treatment Phase (OLTP) (**76** wks) [1]																					Safety F/U [1]
	Wk 24 (cont)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	**Wk 80**	**Wk 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100 /ET[3]**	**Dose increase to 140 mg visit[18]**	**12 wk post increase [18]**	16 Wks After Last Dose of IP
COAs [14]	X (Daily)												X (Daily)						**X (Daily)**			
Subject Brings eDiary to Site for Use during Study Visit		X	X	X	X	X	X	X						X						**X**			
Migraine Symptom Interference Items [14]	X (Daily)												X (Daily)						**X (Daily)**			
Migraine Physical Function Impact Stand-alone Item [14]	X (Daily)												X (Daily)						**X (Daily)**			
HIT-6 [14]		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Employment Status [17]								**X**							**X**					**X**			
Concomitant Medications Recording		X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
IP Administration [15]	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	
Adverse Event/**Adverse Device Effects/Serious Adverse Event Collection** /Recording/**Reporting** [16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Product Complaints Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**	

Footnotes defined on last page of Table 4.

Section: 7.1 Schedule of Assessments, Table 4

Add:

Table 4. Clinical Home Use Substudy Assessments

	Screening[19]	Day 1[20]	Day 28 visit	Day 29 Telephone visit	Day 56 visit	Day 57 Telephone visit	Day 85 visit[21]/ ET[22]
Informed Consent	X						
Randomization to AMG 334 70 mg/ml AI/pen x2 or AMG 334 140 mg/ml AI/pen IP self-administration arm		X					
AI/pen Instruction[23]	X	X					
Examination of areas for injection		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 Adverse Device Effects	X	X	X	X	X	X	X
Review for adverse events/serious adverse events	X	X	X	X	X	X	X
Product Complaints Recording (if applicable)		X	X	X	X	X	X

Section: 7.1 Schedule of Assessments, Table 4 Footnotes (moved from Table 3 to Table 4)

Replace:

AE = adverse event; BDI-II = Beck Depression Inventory-II; CGRP = Calcitonin gene-related peptide; COAs = Clinical Outcomes Assessments; cont = continued; C SSRS = Columbia-Suicide Severity Rating Scale; D = day; DBTP = Double-blind Treatment Phase; ECG = electrocardiogram; eDiary = electronic diary; EOS = end of study; EOT = end of treatment; ET = early termination; F/U = follow-up; HIT-6 = Headache Impact Test; IP = investigational product; IVR = interactive voice response; IWR = interactive web response; M = month (end of month x); OLTP = open-label treatment phase; PE = physical exam; per. = period; PK = pharmacokinetics; QM = monthly; rand. = randomized / randomization; SAE = serious adverse event; SC = subcutaneous; UDS = urine drug screen; Wk = week (end of week x); Wkly = weekly

[1] Each study visit during the double-blind treatment phase and safety follow-up has a window of ± 3 consecutive calendar days. The day 1 visit (randomization day) has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. Each study visit during the open-label treatment phase has a window of ± 4 consecutive calendar days. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

[2] Sites to access the Interactive Voice Response (IVR) / Interactive Web Response (IWR) System for the following: to enter the subject into the initial screening phase, to randomize an eligible subject, to obtain the investigational product assignment, to enter the subject into the open-label treatment phase, to register the end of investigational product, and to register study early termination or completion. Subject data will be collected in the IVR/IWR System including, but not limited to reason for screen fail (if applicable).
Sites to access the IVR/IWR System to obtain the investigational product assignment at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72. The IVR/IWR System will automatically assign investigational product when a subject is randomized at day 1 and when a subject is entered into the open-label treatment phase at week 24. Investigational product is dosed QM, SC.

[3] A subject who discontinues the study during the double-blind treatment phase will complete the week 24/early termination (ET) visit. A subject who discontinues open-label investigational product or the study during the open-label treatment phase will complete the week 76/early termination (ET) visit. Subjects also will complete the safety follow-up visit 16 weeks after the last dose of investigational product.

[4] Entry into the baseline phase must occur only after completion of initial screening phase procedures

[6] Enrollment (ie, randomization) into the double-blind treatment phase using the IVR/IWR System must occur only after completion of all baseline phase procedures and prior to the first dose of double-blind investigational product (randomization and administration of the first dose of investigational product should occur on day 1)

[6] Entry into the open-label treatment phase using the IVR/IWR System must occur only after completion of all double-blind treatment phase procedures and prior to
the first dose of open-label AMG 334 70 mg QM SC

[7] Height and weight, measured without shoes. Height to be collected at the initial screening phase visit only.

[8] Systolic/diastolic blood pressure, heart rate and body temperature. Blood pressure to be obtained after the subject has been in a semi-recumbent position (partial semi- Fowler's position) or supine position in a rested and calm state for at least 5 minutes. At least 2 measurements (separated by at least 5 min) should be made and the average recorded. The position selected for a subject should be used for all blood pressure measurements throughout the study.

[9] Pregnancy testing for women of childbearing potential (WOCBP)

[10] Samples for PK assessment will be serum

[11] PK samples collected at a study visit during which investigational product will be administered should be collected before dosing with investigational product (trough)

[12] Only subjects participating in the optional PK substudy (must have provided informed consent for the PK substudy) will have blood samples collected on day 8 and day 64. The PK substudy sampling window is ± 3 consecutive calendar days.

[13]For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample. Therefore, additional sampling is not required.
[14]Clinical Outcomes Assessments (COAs) and Patient-reported Outcomes (PROs) to be collected by subjects using eDiaries. The HIT-6 is to be completed during applicable study visits before invasive procedures (eg, blood draws) and investigational product administration.
[15]Site study staff to administer investigational product to subjects on day 1 (only after randomization and completion of all day 1 procedures) and at weeks 4, 8, 12, 16, 20, 24 (only after entering the open-label treatment phase and completion of all week 24 procedures), 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72. Investigational product administration should occur after any trough PK sampling. Sites are to record the time of investigational product administration. Following the first 3 doses of investigational product in the double-blind treatment phase (ie, day 1, week 4, week 8), subjects are to remain in the clinic for approximately 1 hour for observation.
[16] SAEs are to be collected after signing of the informed consent through end of study (16 weeks after the last dose of investigational product). Non-serious AEs are to be collected after the first dose of investigational product through end of study (16 weeks after the last dose of investigational product).

With:

ADE = adverse device effect; AE = adverse event; **AI = autoinjector;** BDI-II = Beck Depression Inventory-II; CGRP = Calcitonin gene-related peptide; **CHU = clinical home use;** COAs = Clinical Outcomes Assessments; cont = continued; C-SSRS = Columbia-Suicide Severity Rating Scale; D = day; DBTP = Double-blind Treatment Phase; ECG = electrocardiogram; eDiary = electronic diary; EOS = end of study; EOT = end of treatment; ET = early termination; F/U = follow-up; HIT-6 = Headache Impact Test; IP = investigational product; IVR = interactive voice response; IWR = interactive web response; M = month (end of month x); OLTP = open-label treatment phase; PE = physical exam; per. = period; PK = pharmacokinetics; **PROs = Patient-reported Outcomes;** QM = monthly; rand. = randomized / randomization; SAE = serious adverse event; SC = subcutaneous; UDS = urine drug screen; Wk = week (end of week x); Wkly = weekly**; WOCBP = women of childbearing potential**

[1] Each study visit during the double-blind treatment phase and safety follow-up has a window of ± 3 consecutive calendar days. The day 1 visit (randomization day) has a window of 0, +7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. Each study visit during the open-label treatment phase has a window of ± 4 consecutive calendar days. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.
[2] Sites to access the Interactive Voice Response (IVR) / Interactive Web Response (IWR) System for the following: to enter the subject into the initial screening phase, to randomize an eligible subject, to obtain the investigational product assignment, to enter the subject into the open-label treatment phase, to register the end of investigational product, and to register study early termination or completion. Subject data will be collected in the IVR/IWR System including, but not limited to reason for screen fail (if applicable).
Sites to access the IVR/IWR System to obtain the investigational product assignment at weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72. The IVR/IWR System will automatically assign investigational product when a subject is randomized at day 1 and when a subject is entered into the open-label treatment phase at week 24. Investigational product is dosed QM, SC.
[3] A subject who discontinues the study during the double-blind treatment phase will complete the week 24/early termination (ET) visit. A subject who discontinues open-label investigational product or the study during the open-label treatment phase will complete the week **100**/early termination (ET) visit. Subjects also will complete the safety follow-up visit 16 weeks after the last dose of investigational product.
[4] Entry into the baseline phase must occur only after completion of initial screening phase procedures
[5]Enrollment (ie, randomization) into the double-blind treatment phase using the IVR/IWR System must occur only after completion of all baseline phase procedures and prior to the first dose of double-blind investigational product (randomization and administration of the first dose of investigational product should occur on day 1)
[6] Entry into the open-label treatment phase using the IVR/IWR System must occur only after completion of all double-blind treatment phase procedures and prior to the first dose of open-label AMG 334
[7] Height and weight, measured without shoes. Height to be collected at the initial screening phase visit only.

[8] Systolic/diastolic blood pressure, heart rate and body temperature. Blood pressure to be obtained after the subject has been in a semi-recumbent position (partial semi- Fowler's position) or supine position in a rested and calm state for at least 5 minutes. At least 2 measurements (separated by at least 5 min) should be made and the average recorded. The position selected for a subject should be used for all blood pressure measurements throughout the study.

[9] Pregnancy testing for women of childbearing potential (WOCBP) **Note: Additional on treatment pregnancy testing may be performed at the investigator's discretion or per local laws and regulation.**

[10] Samples for PK assessment will be serum**.**

[11] PK samples collected at a study visit during which investigational product will be administered should be collected before dosing with investigational product (trough)

[12] Only subjects participating in the optional PK substudy (must have provided informed consent for the PK substudy) will have blood samples collected on day 8 and day 64. The PK substudy sampling window is ± 3 consecutive calendar days.

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

[14] Clinical Outcomes Assessments (COAs) and Patient-reported Outcomes (PROs) to be collected by subjects using eDiaries. The HIT-6 is to be completed during applicable study visits before invasive procedures (eg, blood draws) and investigational product administration.

[15] Site study staff to administer investigational product to subjects on day 1 (only after randomization and completion of all day 1 procedures) and at weeks 4, 8, 12, 16, 20, 24 (only after entering the open-label treatment phase and completion of all week 24 procedures), 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, **76, 80, 84, 88, 92, and 96.** Investigational product administration should occur after any trough PK sampling. Sites are to record the time of investigational product administration. Following the first 3 doses of investigational product in the double-blind treatment phase (ie, day 1, week 4, week 8), subjects are to remain in the clinic for approximately 1 hour for observation.

[16] S**erious adverse events** are to be collected after signing of the informed consent through end of study (16 weeks after the last dose of investigational product). Non-serious **adverse events and adverse device effects (for OLTP only)** are to be collected after the first dose of investigational product through end of study (16 weeks after the last dose of investigational product).

[17] Current employment status will be collected at D1 (pre-rand.), week 12, week 24, and during the open label phase; the status should be collected retrospectively if needed.

[18] Visit for Dose Increase to 140 mg and 12Wk Post Increase to 140 mg apply only to subjects in the open-label phase who have not completed W48 after IRB approval of Protocol Amendment 2.

[19] Screening must occur 4 weeks prior to the planned start of the CHU substudy (day 1). IVR System will be adjusted to accommodate CHU substudy screening and randomization information as required.

[20] Day 1 of the CHU substudy may occur at any visit as long as subject has received at least 1 open-label dose of AMG 334 140 mg in the 20120309 main study.

[21] At day 85 of the CHU substudy, subject will receive AMG 334 140 mg SC administered by site staff using PFS formulation and will continue scheduled procedures and assessments as per 20120309 main study.

[22] ET: If a subject early terminates the CHU substudy, he/she may receive administration of AMG 334 140 mg SC at the site as per 20120309 main study and will continue 20120309 scheduled procedures and assessments as per 20120309 main study.

[23] Study coordinator will review AI/pen training materials (Instructions for Use) with subject at screening and will review AI/pen training materials at day 1 of the CHU substudy.

Section: 7.2.3 Medical and Medication History, Paragraph 1

Add:

A review of medical and medication history will be performed at initial screening to confirm subject eligibility **and at week 16**.

Section: 7.2.13 Clinical Outcomes Assessments (COAs) and Electronic Diaries (eDiaries), Paragraph 4

Replace:

The subject will be instructed to interact with the eDiary every day during the baseline phase and between the day 1 and week 52 study visits and between the week 72 and week 76/early termination (ET) study visits, and to bring the eDiary to every study visit during these periods. At the day 1 study visit the investigator will use the subject's eDiary to review all data entered during the baseline phase and confirm the relevant inclusion and exclusion criteria.

With:

The subject will be instructed to interact with the eDiary every day during the baseline phase and between the day 1 and week 52 study visits**,** between the week 72 and week 76/ study visits, **between the week 96 and week 100/early termination (ET) study visits,** and to bring the eDiary to every study visit during these periods. At the day 1 study visit the investigator will use the subject's eDiary to review all data entered during the baseline phase and confirm the relevant inclusion and exclusion criteria. **During these periods the subject will bring the eDiary to every study visit.**

Section: 7.2.17 Adverse Event, Serious Adverse Event, Adverse Device Effect Collection/Recording/Reporting

Add:

7.2.17 Adverse Event**, Serious Adverse Event, Adverse Device Effect Collection/Recording/**Reporting

Adverse event**, serious adverse event, and adverse device effect** information should be collected throughout the study and recorded at each study visit. Refer to Section 9 for details.

Section: 7.2.19 Laboratory Assessments, Paragraph 3

Add:

Any sample collected according to the Schedule of Assessments (Table 2**-Table 4**) may be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure subject safety.

Section: 7.2.19 Laboratory Assessments, Paragraph 4

Add:

See Table 5 for 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):

Section: 7.2.19 Laboratory Assessments, Table 5 Header

Add:

Table 5. Analyte Listing

Section: 7.2.20 Initial Screening Phase, Bullet 13

Add:

Serious adverse event **collection/**recording**/reporting** (Note: Serious adverse events are to be collected after signing of the informed consent through 16 weeks after the last dose of investigational product.)

Section: 7.2.21.1 Week -4 Visit, Bullet 7

Add:

Serious adverse event **collection/**recording**/reporting**

Section: 7.2.22 Day 1 Visit (Prior to Randomization), Bullet 6

Add:

- **Employment status**

Section: 7.2.22 Day 1 Visit (Prior to Randomization), Bullet 8

Add:

- Serious adverse event **collection/**recording**/reporting**

Section: 7.2.23 Day 1 (After Randomization) and the Double-blind Treatment Phase, Bullet 3

Add:

- **Medical and Medication History**

Section: 7.2.23 Day 1 (After Randomization) and the Double-blind Treatment Phase, Bullet 17

Add:

- **Employment status (weeks 12 and 24/end of double-blind treatment phase)**

Section: 7.2.23 Day 1 (After Randomization) and the Double-blind Treatment Phase, Bullet 20

Add:

- Serious and non-serious adverse event **collection/**recording**/reporting**. (Note: Serious adverse events are to be collected after signing of the informed consent through 16 weeks after the last dose of investigational product. Non-serious adverse events are to be collected after the first dose of investigational product through 16 weeks after the last dose of investigational product.)

Section: 7.2.24 Open-label Treatment Phase, Bullet 15

Add:

- **Employment status**

Section: 7.2.24 Open-label Treatment Phase, Bullets 17, 18, 19, and 20

Add:

- Administration of open-label AMG 334 70 mg QM SC **or 140 mg QM SC**. The first dose of open-label investigational product is to be administered only after completion of all week 24 procedures. In general, administration of investigational product should be the last procedure performed at each study visit.
- **After IRB approval of Protocol Amendment 2, the 24-week double-blind treatment phase is followed by a 76-week OLTP with dose determined by the subject's week 48 status:**
  - **(1) Subjects who have already completed the week 48 visit will continue to receive AMG 334 70 mg QM SC (OL70) for a total of 76 weeks, following the open label assessments in Table 3.**
  - **(2) Subjects who have not yet completed the double-blind treatment phase and are not yet in the open-label phase will receive AMG 334 140 mg QM SC (OL140) upon entering the open-label phase and continue receiving open-label AMG 334 140 mg QM SC for 76 weeks.**

- **(3) Subjects who have not yet completed the week 48 visit but are in the open-label phase receiving AMG 334 70 mg QM SC must increase their dose to AMG 334 140 mg QM SC and continue receiving open-label AMG 334 140 mg QM SC until the week 100 visit (OL70-140) for a total open label phase duration of 76 weeks. The dose increase should be done at the first available opportunity, defined as the first visit after IRB approval of Protocol Amendment 2. Refer to Table 3 for assessments to be collected at the visit of the dose increase and 12 weeks after the dose increase. At the time of the dose increase, the End of Open Label 70 mg eCRF page will need to be completed as subjects will be transitioning from 70 mg to 140 mg.**

- Serious and non-serious adverse event **collection/**recording**/reporting**. (Note: Serious and non-serious adverse events are to be collected through 16 weeks after the last dose of investigational product)
- **Adverse device effects collection/recording/reporting**

Section: 7.2.24 Open-label Treatment Phase, Paragraph 2

Replace:

A subject who discontinues open-label investigational product or the study during the open-label treatment phase will complete the week 76/early termination (ET) visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

With:

A subject who discontinues open-label investigational product or the study during the **OLTP** will complete the week **100**/early termination (ET) visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

Section: 7.2.25 Clinical Home Use Substudy (Optional)

Add:

7.2.25 Clinical Home Use Substudy (Optional)

The following procedures are to be completed during the OLTP at time points designated in the Schedule of Assessments (Table 4). At each CHU substudy visit, any assessments scheduled for the main 20120309 study visit should also be completed.

Screening:

- **Obtain consent to CHU substudy**
- **Review of IFU for AI/pen with subject**

- **Register CHU consent date using the IVR/IWR System (via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**

Day 1:

- **After confirming subject eligibility, the following procedures are to be completed:**
- **Register CHU randomization to randomize the subject to two 70 mg/mL AIs/pens or one 140 mg/mL AI/pen self-administration using the IVR/IWR System (via Additional Product Dispensing activity)**
  - **Site to instruct subject on how to self-administer AMG 334 with the AI/pen by reviewing entire IFU**
  - **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 the AI/pen under site supervision**
  - **Review for adverse events/adverse device effects/serious adverse events**
  - **Product complaint recording (if applicable)**
  - **Study coordinator to reconcile IP (AI/pen)**

Day 28:

- **Study coordinator dispenses AI/pen to subject for self-administration on day 29 (IP device assigned using the IVR/IWR system via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Telephone call time scheduled for day 29 (Note, telephone visit must occur after subject has self-administered IP)**

Day 29:

- **Subject self-administers AMG 334 using AI/pen in non-clinic setting**
- **Telephone visit with study coordinator to inquire of subject if the subject 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/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**

Day 56:

- **Subject returns IP for Study Coordinator to reconcile IP (AI/pen)**
- **Study coordinator dispenses AI/pen to subject for self-administration on day 57 (IP device assigned using the IVR/IWR system via Additional Product Dispensing activity)**
- **Review for adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Telephone call time scheduled for day 57 (Note, telephone visit must occur after subject has self-administered IP)**

Day 57:

- **Subject self-administers AMG 334 using AI/pen in the non-clinical setting**
- **Telephone visit with study coordinator to inquire of subject if the subject 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/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**

Day 85: End of CHU substudy

- **Subject returns IP for study coordinator to reconcile IP (AI/pen)**
- **Review adverse events/adverse device effects/serious adverse events**
- **Product complaint recording (if applicable)**
- **Subject continues all 20120309 study assessments and IP is administered at site as per the 20120309 protocol**

Section: 7.2.26 Safety Follow-up / End of Study Visit, Bullet 11 and 12

Add:

- Serious and non-serious adverse event **collecting/**recording**/reporting**. (Note: Serious and non-serious adverse events are to be collected through 16 weeks after the last dose of investigational product)
- **Adverse device effect/recording/reporting**
- **Product complaint recording**

Section: 7.6 Sample Storage and Destruction, Paragraph 1

Add:

Any sample collected according to the Schedule of Assessments (Table 2**-Table 3**) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects.

Section: 8.1 Subjects' Decision to Withdraw, Paragraph 1

Replace:

If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 3) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 3) 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).

With:

If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product and must discuss with the subject the options for continuation of the Schedule of Assessments (**Table 2-Table 4**) and collection of data, including endpoints**,** adverse events**, adverse device effects (if applicable), and serious adverse events**. The investigator must document the change to the Schedule of Assessments (**Table 2**-**Table 4**) 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).

Section: 9.2.1 Reporting Procedures for Adverse Events and Adverse Device Effects That do not Meet Serious Criteria, Header and Paragraph 1

Replace:

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 the first dose of investigational

product through the end of the safety follow-up visit (16 weeks after the last dose of investigational product) are reported using the Event CRF (eg, Adverse Event Summary), including events that are reported to the Event Adjudication Committee for adjudication.

With:

9.2.1 Reporting Procedures for Adverse Events **and Adverse Device Effects** That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events **and adverse device effects (including the OLTP and CHU substudy)** observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up visit (16 weeks after the last dose of investigational product) are reported using the Event CRF (eg, Adverse Event Summary), including events that are reported to the Event Adjudication Committee for adjudication.

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

- **Replace:**
- assessment of relatedness to investigational product (medicine and/or pre-filled syringe), and

With:

- assessment of relatedness to investigational product (**AMG 334 /** placebo), and/or the **Amgen medical devices (**pre-filled syringe **or the AI/Pen**), **and/or study-mandated procedure/study activity,** and

Section: 9.2.1 Reporting Procedures for Adverse Events and Adverse Device Effects That do not Meet Serious Criteria, Paragraph 3

Replace:

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product (medicine and/or pre-filled syringe). 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 (medicine and/or pre-filled syringe)?"

With:

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is **available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.**

During the double-blind treatment period, the investigator must assess whether the adverse event is possibly related to the investigational **medicinal** product (**AMG 334/placebo**). 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 **medicinal** product (**AMG 334/placebo**)?"

During the OLTP and the CHU substudy, the investigator must assess whether the adverse event is possibly related to AMG 334. 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 AMG 334?"

During the OLTP and the CHU substudy, the investigator must assess whether the adverse event is possibly related to the prefilled syringe or AI/Pen (investigational medical devices used to administer AMG 334). 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 investigational medical devices?

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

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events

Add:

The investigator is responsible for ensuring that all serious adverse events **(this includes the CHU substudy)** observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the safety follow-up

visit (16 weeks after the last dose of investigational product) are recorded in the subject's medical record and are submitted to Amgen, including serious adverse events that are reported to the Event Adjudication Committee for adjudication.

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

During the double-blind treatment period, the investigator must assess whether the serious adverse event is possibly related to the investigational medicinal product (AMG 334 / placebo). 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 medicinal product (AMG 334 / placebo)?"

During the OLTP and the CHU substudy, the investigator must assess whether the serious adverse event is possibly related to AMG 334. 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 AMG 334?"

During the OLTP and the CHU substudy, the investigator must assess whether the serious adverse event is possibly related to the prefilled syringe or AI/Pen (investigational medical devices used to administer AMG 334). 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 investigational medical devices?

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

have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device(s)), and/or procedure"?

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

Section: 9.2.2 Reporting Procedures for Serious Adverse Events (unamended text was moved from Section 9.2.3 to the end of Section 9.2.2)

Add:

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.

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

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

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

Section: 9.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period, Paragraph 2 and 3

Delete:

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

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

Section: 9.4 Pregnancy and Lactation Reporting

Replace:

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 16 weeks after the last dose of investigational product.

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

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur 16 weeks after the last dose of investigational product.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

With:

If a **female subject becomes** pregnan**t,** or **a male subject fathers a child**, while the subject is taking investigational product**/product-required therapies**, report the pregnancy to Amgen **Global Patient Safety** as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should **report** pregnancies that occur through 16 weeks after the last dose of investigational product**/protocol-required therapies**.

The pregnancy should be reported to Amgen **G**lobal **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 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 the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

If a female breastfeeds while taking investigational product/protocol-required therapies report the lactation case to Amgen as specified below.

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur 16 weeks after the last dose of investigational product**/protocol-required therapies**.

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.

Section: 10.1.1.4 Clinical Home Use Substudy

Add:

10.1.1.4 Clinical Home Use Substudy

10.1.1.4.1 Primary Endpoint

- **Subject-reported outcome of attempted full-dose administration on day 29 and day 57**

10.1.1.4.2 Secondary Endpoint

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

Section: 10.1.1.5 Definitions of Terms Included in Endpoints, Acute Headache Medication Treatment Day

Add:

Acute Headache Medication Treatment Day: Any calendar day during which the subject took an acute headache medication (migraine-specific or non-migraine-specific).

Section: 10.1.1.5 Definitions of Terms Included in Endpoints, Monthly eDiary Data

Replace:

Data collected by the eDiary in any 28-consecutive day interval relative to study day 1 when more than 14 days of eDiary data are collected within that 28-consecutive day interval.

With:

Data collected by the eDiary in any 28-consecutive day interval relative to study day 1 when **at least** 14 days of eDiary data are collected within that 28-consecutive day interval. **Monthly frequency measurements will be prorated to 28-day equivalents.**

Section: 10.1.2 Analysis Sets, Paragraph 1

Replace:

The efficacy analysis set includes subjects in the FAS and who received at least one dose of investigational product and completed at least one post-baseline monthly migraine day measurement in the double-blind treatment phase.

With:

The efficacy analysis set includes subjects in the FAS and who received at least one dose of investigational product and **had** at least one **change from** baseline **measurement in** monthly migraine day**s during** the double-blind treatment phase.

Section: 10.1.2 Analysis Sets, Paragraph 1

Replace:

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

With:

For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed **according to the randomized treatment unless a subject has received the incorrect dose during the entire double-blind treatment phase**.

Section: 10.1.2 Analysis Sets, Paragraph 2

Add:

All subjects enrolled in the CHU substudy will be included in the CHU substudy analysis set.

Section: 10.1.3 Covariates and Subgroups

Replace:

The primary, secondary efficacy, and selected safety endpoints will be analyzed in the subgroups defined by the stratification factor as well as age (< median vs ≥ median), sex, race, body mass index (BMI; < median vs ≥ median), and duration of disease (< median vs ≥ median).

With:

The primary, secondary efficacy, and selected safety endpoints will be analyzed in the subgroups defined by the stratification factor as well as **baseline monthly migraine days** (< **8 days** vs ≥ **8 days**), **prior prophylactic failure status (failed any vs not failed any), and** BMI **(**< median vs ≥ median).

Section: 10.2 Sample Size Considerations, Paragraph 2

Add:

Clinical Home Use Substudy

Approximately 50 subjects will be enrolled in to the CHU substudy. The following assumptions are made based on the minimum sample size of 50 subjects: 5% of subjects per treatment group discontinue IP and 90% of the remaining subjects respond that they administered a full dose. As such, 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 25 subjects per group are 8.5%, 13.8%, and 11.5%, respectively. The anticipated 95% confidence interval half width for the difference between treatment groups in the proportion of subjects administering a full dose is 19.5%. 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.

Section: 10.4.2 Interim Analysis, Paragraph 1

Replace:

During the open-label treatment phase of the study, an interim analysis is planned after at least 100 subjects randomized to 70 mg of AMG 334 have completed 52 weeks of treatment with investigational product.

With:

During the **OLTP** of the study, an interim analysis is planned after at least 100 subjects randomized to **140** mg of AMG 334 have completed **26 and** 52 weeks of treatment with investigational product.

Section: 10.4.4 Final Analysis, Paragraph 1

Replace:

The objective of the final analysis is to evaluate the long-term profile of migraine days and adverse events of AMG 334 in subjects with migraine after the 24-week double-blind treatment phase, 52-week open-label treatment phase, and safety follow up.

With:

The objective of the final analysis is to evaluate the long-term profile of migraine days and adverse events of AMG 334 in subjects with migraine after the 24-week double-blind treatment phase, **OLTP**, and safety follow-up.

Section: 10.4.4 Final Analysis, Paragraph 2

Replace:

Final Analysis activities are commenced based on achieving the End of Trial milestone described in Section 3.5.2.

With:

Final Analysis activities are commenced based on achieving the End of Trial milestone described in Section **3.6.2**.

Section: 10.5.1 General Considerations, Paragraph 7

Add:

The proportion of subjects who administer a full dose of AMG 334 in home-use will be summarized by treatment group at CHU day 29 and day 57. 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 2 visits will also be estimated. Ninety-five percent confidence intervals will be provided for each group and the difference in proportions between the groups. Subject incidence of adverse events, serious adverse events, and adverse device effects will be summarized by system organ class and preferred term for subjects enrolled in the CHU substudies. Details of the analysis of the CHU substudy will be described in a separate Statistical Analysis Plan.

Section: 10.5.2 Primary Efficacy Endpoint, Paragraph 2

Replace:

Sensitivity analyses for the primary endpoint include: (1) the same analysis using the per-protocol analysis set, (2) the last observation carried forward (LOCF) to handle missing data, and (3) the inverse probability weighted (IPW) method using generalized estimate equation (GEE) to handle missing data.

With:

Sensitivity analyses for the primary endpoint include: (1) the same analysis using the per-protocol analysis set, (2) the last observation carried forward (LOCF) to handle missing data **with analysis of covariance (ANCOVA) model**, and (3) **multiple imputation (MI) with assumptions of missing at random (MAR) and missing not at random (MNAR) to handle missing data.**

Section: 10.5.3 Secondary Efficacy Endpoints, Paragraph 1

Replace:

The odds ratio for each AMG 334 treatment group vs placebo group and associated 95% confidence intervals will be reported. Sensitivity analyses for response include: (1) the same analysis using the per-protocol analysis set, and (2) the logistic regression model adjusting for baseline values where missing values will be imputed as non-responders.

With:

The odds ratio for each AMG 334 treatment group vs placebo group and associated 95% confidence intervals will be reported. Sensitivity analyses for **the binary endpoint** include: (1) **CHM test** using the per-protocol analysis set, and (2) **generalized linear mixed model without imputation of missing data, and (3)** logistic regression model **for each visit after the** missing **data are** imputed as non-responders.

Section: 10.5.5 Safety Endpoints, Paragraph 1

Replace:

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

With:

For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, safety analysis set) will be analyzed **according to the randomized treatment unless a subject has received the incorrect dose during the entire double-blind treatment phase**.

Section: 10.5.5 Safety Endpoints, Paragraph 3

Replace:

Subject incidence rates (double-blind treatment phase) and subject incidence rates adjusted for follow-up time (open-label treatment phase) of all treatment-emergent adverse events will be tabulated by treatment groups and by system organ class and preferred term.

With:

Subject incidence rates (double-blind treatment phase) and **exposure-adjusted** subject incidence rates (**OLTP**) of all treatment-emergent adverse events will be tabulated by treatment groups and by system organ class and preferred term.

Section: 10.5.5 Safety Endpoints, Paragraph 4

Replace:

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group. Shift tables of the worst on-study safety laboratory toxicity based on grade relative to baseline will be tabulated by treatment group. Subject listing of grades ≥ 3 laboratory toxicities will be provided.

Add:

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group **for selected analytes**. Shift tables of the worst on-study safety laboratory toxicity based on grade relative to baseline will be tabulated by treatment group.

Section: 12.4 Investigator Responsibilities for Data Collection

Add:

For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2**-Table 4**), the

investigator can search publically available records (where permitted) to ascertain survival status.

Section: 12.6 Publication Policy, Paragraph 1

Replace:

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter.

With:

To coordinate dissemination of data from this study, Amgen **may facilitate** the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter.

Section: 12.6 Publication Policy, Paragraph 2

Add:

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013**, updated 2014**), which states:

Section: 13 References, Reference 19

Add:

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2013**, updated 2014**. http://www.icmje.org/. Accessed 19 September 2013.

Section: 14 Appendices, Appendix A

Replace:

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.3 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 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 is 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), 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 has been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain viral serologies
- Obtain CPK, haptoglobin, LDH, and peripheral blood smear
- Perform appropriate liver imaging if clinically indicated

- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of investigational product.

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

With:

Appendix A. **Hepatoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines**

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

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

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

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- **Hepatobiliary tract disease**
- **Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)**
- **Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia**
- **Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms**
- **Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)**
- **Alpha-one antitrypsin deficiency**
- **Alcoholic hepatitis**
- **Autoimmune hepatitis**
- **Wilson's disease and hemochromatosis**
- **Nonalcoholic fatty liver disease including steatohepatitis (NASH)**
- **Non-hepatic causes (eg, rhabdomylosis, hemolysis)**

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

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

Table 6. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

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

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

Criteria for Rechallenge of Amgen Investigational Product Therapies 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 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 6) are never to be rechallenged.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

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

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

Additional Clinical Assessments and Observation

All subjects in whom investigational product is withheld (either permanently or conditionally) due to potential DILI as specified in **Table 6** or who experience AST or ALT elevations > 3 x **upper limit of normal (**ULN**) or 2-fold increases above baseline values for subjects with elevated values before drug** are to undergo a period of "close observation" until abnormalities return to normal or to the subject's baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve**.**
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. **The following are to be considered depending on the clinical situation:**
  - **C**omplete blood count (CBC) with differential to assess for eosinophilia
  - **S**erum total immunoglobulin IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis
  - **S**erum acetaminophen (paracetamol) levels
  - **A** more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents

  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- **V**iral serologies
- **Creatine phosphokinase (**CPK**)**, haptoglobin, **lactate dehydrogenase (**LDH**)**, and peripheral blood smear
- Appropriate liver imaging if clinically indicated

- **A**ppropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- **H**epatology consult (liver biopsy may be considered in consultation with a hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal **or considered stable by the investigator**. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product**(s) and protocol-required therapies**.

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

Section: 14 Appendices, Appendix B

Replace:

Appendix B. Sample Serious Adverse Event Report Form

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

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

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

Definitions:

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

What types of events to report on this form:

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

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Adverse Event**

   Provide the date the Investigator became aware of this Information

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

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

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

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

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

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

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

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device,**

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

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

this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)

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

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

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

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

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

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

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

AMGEN Study # 20120309 AMG 334	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

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

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

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20120309 AMG 334	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 334/Placebo	☒ blinded							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
AMG 334/Prefilled syringe	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

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AMGEN Study # 20120309 AMG 334	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

With:

Appendix B. Sample Serious Adverse Event **Contingency** Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

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

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

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

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

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

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

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

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

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

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

4. **Hospitalization**

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

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

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

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

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.

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

9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

AMGEN
Study # 20120309
AMG 334

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome **If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report** *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 334		Prefilled Syringe		Prefilled Autoinjector/ Pen (AIPen)					
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓				
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN
Study # 20120309
AMG 334

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

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

IP/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product (01 Still being Administered 02 Permanently discontinued 03 Withheld)	Lot # and Serial #
AMG 334	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Prefilled Syringe	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Prefilled Autoinjector/Pen (AI/Pen)	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

AMGEN Study # 20120309 AMG 334	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

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)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

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

Section: 14 Appendices, Appendix C

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: _____

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: 20120309

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: 14 Appendices, Appendix D

Replace:

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

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

With:

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: 20120309

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