16.1.1 Protocol and Amendments

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Erenumab (AMG 334)

Amgen Protocol Number 20140254

EudraCT Number 2015-002322-40

Clinical Study Sponsor:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320, USA
Tel: +1 (805) 447-1000

Key Sponsor Contact(s):
PPD
Global Clinical **Trial** Manager
Amgen **Ltd**.
1 Uxbridge Business Park,
Sanderson Road
Uxbridge, UB8 1DH, UK
PPD

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	06 August 2015
Amendment 2 Date:	17 November 2015 (European Union, Voluntary Harmonization Procedure countries only)
Amendment 3 Date:	27 January 2016
Amendment 4 Date:	**28 October 2016**

NCT Number: 2575833
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 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated **28 October** 2016 and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Study Phase: 2a

Indication: Prevention of migraine

Primary Objective: To evaluate the effect of AMG 334 compared to placebo on exercise capacity in subjects with stable angina as measured by total exercise time (TET) during an exercise treadmill test (ETT).

Secondary Objectives: To evaluate the effect of AMG 334 compared to placebo during an ETT on the time to the onset of:

- Exercise-induced angina
- ST-segment depression

Safety Objectives: To evaluate the safety and tolerability of AMG 334 in a population with stable angina.

Hypothesis: The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in exercise duration, compared to placebo, and that the true treatment difference in change from baseline in exercise duration**is less than a 9**0 second **decrease**.

Primary Endpoint:

- Change from baseline in TET

Secondary Endpoints:

- During the ETT
  - Time to onset of exercise-induced angina
  - Time to onset of ≥ 1 mm ST-segment depression

Safety Endpoints:

- Adverse events and Disease Related Events
- Changes in vital signs

Study Design: This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

Sample Size: At least 54 subjects will be randomized

Summary of Subject Eligibility Criteria: The study seeks to enroll adult subjects (≥ 18 to ≤ 85 of age at the time of screening) with a history of chronic stable angina for at least 3 months prior to screening, with at least 1 angina episode/month, on average over that period, with a history of ischemic heart disease. Subjects will experience at least 1 angina episode and are receiving stable doses of cardiac medications (eg, beta blockers, calcium channel blockers, etc.) for at least 30 days prior to randomization and that are not expected to change during the study.

For a full list of eligibility criteria, please refer to Section 4.

Investigational Product: The investigational products used in this study include AMG 334 and placebo.

AMG 334 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated with C mM sodium acetate, C % (w/v) sucrose, CCI % (w/v) polysorbate C, at pH C. Placebo vials will be packaged and formulated to match AMG 334 but will not contain AMG 334.

Amgen Investigational Product Dosage and Administration: Eligible subjects will be randomized into the study and receive an intravenous infusion of investigational product prior to the initiation of the ETT on study day 1. A single dose of 140 mg of AMG 334 or a matching volume of placebo will be mixed in 100 mL of dextrose 5% in water (D5W) and infused over approximately 60 minutes.

See Section 6.2.1.1 for further details.

Procedures: After signing the informed consent form (ICF) subjects will enter the screening phase (up to 6 weeks), serious adverse events will be collected throughout the study including the screening phase, while adverse events and disease related events will start being collected post randomization/post first dose. Screening evaluations will include targeted medical and medication history, physical examination, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, and exercise treadmill test (ETT). Blood samples will be collected for biomarker analysis, hematology, chemistry, and for all females (except females not of childbearing potential, see definition in Exclusion Criteria Section 4.1.2.2) a urine pregnancy test. At the day 1 pre-dose visit, eligible subjects will be enrolled and randomized into the 12-week double-blind on-study period and will receive investigational product. Following investigational product administration, an exercise treadmill test post-randomization (ETTr) will be conducted, and pharmacokinetics (PK) sampling will be performed. Safety follow-up visits will occur every 2-4 weeks after the last dose of investigational product. Subjects will record episodes of angina and antianginal medication use in an angina diary beginning on the day of screening Visit 1 and through the End of Study (EOS)/Early Termination (ET) visit to record angina episodes not occurring during ETT.

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

Statistical Considerations: The primary analysis for the study will be performed after all subjects have completed the ETTr. The final analysis for the study will be performed after all subjects have completed the study.

The primary objective of this study is to evaluate the effect of AMG 334 compared to placebo on exercise capacity in subjects with stable angina as measured by TET during an ETT. The full analysis set (FAS) will be used to tabulate demographic data, baseline disease characteristics, and subject disposition. The efficacy analysis set (EAS) will include all FAS subjects who received investigational product and completed the ETTr and be used to analyze the primary and secondary endpoints (including the change from baseline in TET, time to onset of ≥ 1 mm ST-segment depression, and time to onset of exercise-induced angina). The safety analysis set (SAS) includes all FAS subjects who received investigational product and will be used to analyze safety endpoints.

Summary statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of subjects, mean, median, standard deviation, standard error, lower and upper quartiles, minimum, and maximum. For categorical endpoints, frequency, and percentage will be given.

An independent Data Monitoring Committee (DMC) will review safety data and make recommendations regarding the safety of the study participants throughout the study.

The primary endpoint is the change from baseline in exercise duration **as measured by TET during the ETT**.

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). A two-sided 90% confidence interval (CI) for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than - **9**0 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean

change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

The secondary efficacy endpoints are time to onset of ≥ 1 mm ST-segment depression and time to exercise-induced angina. For each endpoint, Kaplan-Meier estimates of the event-free survival time will be computed and graphically displayed. A stratified (< 7 or ≥ 7 minute randomization strata) log-rank test statistic will be calculated to compare the two treatment groups at a significance level of 0.10.

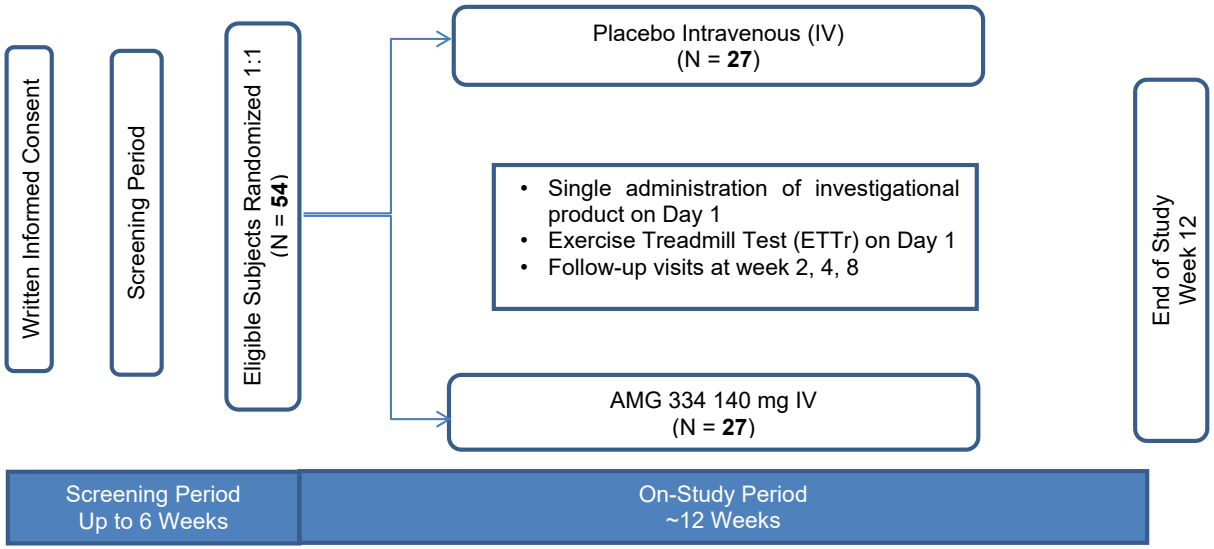
The SAS will be used to analyze safety endpoints based on the actual treatment received. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events. Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product, adverse events of special interest if any, and Disease Related Events also will be provided. Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term. The analyses of selected 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. The analyses of vital signs will include summary statistics over time by treatment group.

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

Sponsor: Amgen, Inc.

Data Element Standards Version/Date:	Version 5/20 March 2015

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AJCC	American Joint Committee on Cancer
CEC	Clinical Events Committee
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
CK-MB	Creatine kinase – myocardial band
C_{max}	maximum concentration
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DRE	Disease Related Event
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
EDC	Electronic Data Capture
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Study (end of trial)	defined as when the last subject is assessed or **participates in study procedures** for evaluation in the study (ie, study week 12)
End of Study (primary completion)	defined as when the last subject completes the on study ETT (ETTr) which is conducted after randomization and administration of investigational product on Day 1
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
EOS	End Of Study
ET	Early Termination
ETT	Exercise Treadmill Test
ETTr	Exercise Treadmill Test post-randomization
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Interactive Voice Response System (IVRS)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information

Abbreviation or Term	Definition/Explanation
Interactive Web Response System (IWRS)	web based technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
PK	pharmacokinetic
POR	Proof of Receipts
Q4W	every 4 weeks
SAS	Safety Analysis Set
SBP	Systolic blood pressure
SC	subcutaneously
Source Data	information from an original record or certified copy of the original record containing subject information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that investigational product is administered to the subject
TIA	Transient ischemic attack
TET	Total Exercise Time
ULN	Upper Limit of Normal

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

To evaluate the effect of AMG 334 compared to placebo on exercise capacity in subjects with stable angina as measured by total exercise time (TET) during an exercise treadmill test (ETT).

1.2 Secondary

To evaluate the effect of AMG 334 compared to placebo during an ETT on the time to the onset of:

- Exercise-induced angina
- ST-segment depression

1.3 Safety Objectives

To evaluate the safety and tolerability of AMG 334 in a population with stable angina.

2. BACKGROUND AND RATIONALE

2.1 AMG 334 Development Rationale

Calcitonin gene-related peptide (CGRP) is a potent vasodilator and nociceptive modulator peptide. It belongs to the calcitonin family of peptides and is widely expressed in the peripheral and central nervous system. Several lines of evidence indicate CGRP is involved in the initiation and progression of migraine pain: 1) it is expressed in the trigeminal system, which is implicated in the pathophysiology of migraines; 2) CGRP levels are elevated in migraineurs during an attack (Bellamy et al, 2006; Ashina et al, 2000; Gallai et al, 1995; Goadsby et al, 1990; Goadsby et al, 1988); 3) acute migraine therapies such as triptans restore CGRP levels to normal after treatment (Juhasz et al, 2005); 4) CGRP infusion triggers the onset of migraine headaches in migraine sufferers (Petersen et al, 2004; Lassen et al, 2002), and 5) CGRP antagonists have demonstrated efficacy in acute migraine reversal (Connor et al, 2009; Hewitt et al, 2009; Ho et al, 2008a; Ho et al, 2008b).

2.2 Study Rationale

During myocardial ischemia, cardiac sensory nerves release neuropeptides, including CGRP, substance P, neurokinin A, and other neurokinins that produce compensatory coronary vasodilation and negative inotropic and chronotropic effects, potentially mitigating the extent and severity of the ischemic response (Burley et al, 2007). The release of CGRP during myocardial ischemia suggests that CGRP blockade may

interfere with homeostatic cardio protective mechanisms that occur in the setting of acute ischemia.

The hypothesis that blockade of CGRP-receptors does not reduce exercise capacity was tested in an ETT with telcagepant, an orally-administered CGRP receptor antagonist previously under development for the treatment of acute migraine (Chaitman et al, 2012).

The ETT is an established methodology for detecting the physiologic effect of vasoactive agents such as antianginal drugs and has also been used in safety studies to assess the potential of vasoactive drugs to reduce exercise time. The effects of supra-therapeutic doses of telcagepant on TET were assessed in a double-blind, randomized, placebo-controlled, two-period, crossover study in 60 subjects with stable angina and reproducible exercise-induced angina. No significant between-treatment differences were found in TET, maximum exercise heart rate, or time to > 1-mm ST-segment depression. The results of this study suggest that CGRP blockade does not exacerbate myocardial ischemia.

2.3 Amgen Investigational Product Background

AMG 334 is a human monoclonal antagonist antibody that interacts with the extracellular domains of the CGRP receptor complex blocking the action of CGRP. AMG 334 dose-dependently inhibited CGRP-induced skin vasodilation measured by laser Doppler in healthy human volunteers, confirming its in vivo potency in blocking this pathway. AMG 334 is being developed for the prevention of migraines based on the observed long serum half-life in humans, the strong rationale for CGRP involvement in migraine pathophysiology, and the clinical data demonstrating CGRP antagonists are effective in acute migraine reversal as well as the prophylaxis of migraine.

The present study will evaluate the hypothesis that AMG 334 does not decrease exercise capacity, as measured by TET during an ETT, in subjects with documented cardiovascular disease and stable angina. Additional endpoints to be measured in this study include time to onset of exercise-induced angina, and time to onset of ≥ 1mm ST-depression during the ETT, incidence of adverse events and Disease Related Events, and changes in vital signs. In addition, the safety and tolerability of AMG 334 in a stable angina population will also be evaluated. Due to the variability of TET, the study design will be double-blind and placebo-controlled. It is expected that AMG 334 administered subcutaneously (SC) once monthly in doses of 70 to 140 mg will be effective in migraine prophylaxis. A dose of 140 mg of AMG 334 administered

intravenously (IV) will be evaluated in this study to ensure adequate coverage of the expected exposure with the intended clinical doses. Pharmacokinetic (PK) simulation indicates that 140 mg administered SC every 4 weeks (Q4W) will result in a mean steady-state maximum concentration (C_{max}) of approximately 25,000 ng/mL in serum. Greater serum concentrations (mean > 28,000 ng/mL) were observed during the first 2 days following a single 140 mg IV dose, which was well tolerated (Study 2010267; Amgen data on file).

2.4 AMG 334 Clinical Safety Summary

As of 10 August 2015, approximately 1,039 subjects have received AMG 334 since the beginning of the clinical development program. Across phase 1 studies, 152 subjects (healthy subjects, subjects with hot flash and migraineurs) have received AMG 334 at doses up to 280 mg SC and 140 mg IV. In the phase 1 studies, 24-hour continuous ambulatory blood pressure (BP) monitoring demonstrated no change in BP circadian rhythm and no increase in BP with increasing doses of AMG 334.

Across ongoing phase 2 clinical studies, approximately 887 subjects have received more than 1 dose of investigational product (IP), including a total of 472 subjects in the double-blind phase of the episodic migraine study (Study 20120178). In both the double-blind and open-label treatment portions of the phase 2 episodic migraine study (Study 20120178), concomitant use of triptan-based migraine medications was reported in 64.8% of subjects. In this study, BP was assessed at each visit. There was no clinically significant difference in either systolic or diastolic BP at any dose group of AMG 334 compared with placebo. Moreover, there was no difference in the frequency of the adverse event of blood pressure increase between placebo and any dose of AMG 334. To date, AMG 334 has demonstrated a favorable safety and tolerability profile that supports further development. Refer to the AMG 334 Investigator's Brochure for details.

2.5 Risk Assessment

There is no direct benefit for individual subjects participating in this study, however there is a potential indirect benefit to participants in this study since they will undergo cardiovascular evaluation and assessments, including ETT, which may provide their treating physician with more detailed information that may improve their care. This study will test the hypothesis that AMG 334 does not significantly decrease exercise capacity in the study population, and, as such, would be supportive of the safe use of AMG 334 as migraine prophylaxis in subjects with, or at risk of, cardiovascular disease.

To date, no evidence of a cardiovascular safety signal has been observed in preclinical, or phase 1, 2, and 3 studies of several investigational products interfering with the CGRP signaling pathway. This body of evidence includes dedicated cardiovascular studies with hemodynamic monitoring.

All subjects participating in the clinical study will be monitored closely for any cardiovascular abnormalities with vital signs assessments, electrocardiograms (ECGs), and physical examinations conducted at screening and before, during, and after the ETT procedures.

2.6 Clinical Hypothesis

The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in **TET**, compared to placebo and that the true treatment difference in change from baseline in exercise duration is **less than a 9**0 second **decrease**.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. **At least 54** subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This is a multicenter study that will be conducted at approximately 40 sites.

3.3 Number of Subjects

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

At least 54 subjects will be enrolled in this study (**27** subjects in the placebo group and **27** in the AMG 334 group). Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The estimated study duration for an individual subject is approximately 18 weeks, consisting of the following:

- Up to 6-week screening period
- 12-week on-study period

3.5.2 End of Study

Primary Completion: The date on which the last subject completes the on-study ETT post-randomization (ETTr) which is conducted after randomization and administration of investigational product on Day 1.

Final completion: The end of study ([EOS], end of trial) is defined as the time when the last subject is assessed or **participates in study procedures** for evaluation in the study (ie, study week 12).

4. SUBJECT ELIGIBILITY

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

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

102 Age ≥ 18 to ≤ 85 at the time of screening.

103 History of chronic stable angina for at least 3 months prior to screening, with at least 1 angina episode/month, on average over that period.

104 Ischemic heart disease documented by any one or more of the following:

a. A history of myocardial infarction (MI) with elevated Creatine kinase - myocardial band (CK-MB), troponin I or T, or the presence of electrocardiogram (ECG) changes consistent with an MI, or

b. Coronary angiography demonstrating at least 1 major epicardial coronary artery (eg, left anterior descending, left circumflex, or right coronary artery) with a stenosis of at least 50% diameter or greater but excluding > 50% or flow-limiting stenosis of the left main coronary artery unless revascularized by coronary artery bypass grafting, or

c. Revascularization procedure (eg, cardiac bypass graft, angioplasty) ≥ 3 months prior to screening

105 Receiving stable doses of cardiac medications (eg, beta blockers, calcium channel blockers, antianginals, etc.) for at least 30 days prior to randomization and that are not expected to change during the study

106 Completes 2 qualifying ETTs during screening period (as described for Screening in Section **7.3.7** **and** **Section** 7.3.8). The following ETT qualifications are required:

a. Limitation of exercise due to symptoms related to myocardial ischemia (such as angina pectoris, chest pain/discomfort, dyspnea, shortness of breath), or ≥ 3 mm ST-segment depression

b. ≥ 1.0 mm ischemic ST-segment depression during exercise performance

c. Exercise duration of ≥ 3 to ≤ 12 minutes, and

d. ≤ 1 minute difference or within 20% duration (using the longest duration qualifying ETT) in TET between the 2 qualifying ETTs

e. ECG tracings from screening ETTs are acceptable to the core ECG laboratory

4.1.2 Exclusion Criteria

4.1.2.1 General

201 Currently participating in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug studies. Other investigational procedures while participating in this study are not allowed.

202 Current or prior malignancy within 5 years of randomization, with the exception of non-melanoma skin cancers, cervical or breast ductal carcinoma in situ, and adenocarcinoma of the prostate Stage I or IIa (defined as T1, T2a or T2b, N0, M0 with documented serum PSA <20 ng/mL and Gleason score ≤7) per the American Joint Committee on Cancer (AJCC) primary tumor, regional lymph nodes, and distant metastasis system.

203 Subject has known sensitivity to any of the components of the investigational product

204 Subject likely to not be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

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

4.1.2.2 Reproductive

206 Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).
- Female subjects not of childbearing potential are defined as: Any female who is has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR are post-menopausal. Post-menopausal women are those who fit into one of the following categories:
    - 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.

207 Females who are pregnant, planning to become pregnant, or breastfeeding during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

208 Subject with a positive pregnancy test at screening

4.1.2.3 Psychiatric and Neurologic

209 Within the 6 months prior to or during screening, report of suicidal ideation with intent, with or without a plan, or suicidal behavior as evidenced by a Columbia-Suicide Severity Rating Scale (C-SSRS) score of 4 or 5 and any behavior during screening

210 Any psychiatric or neurologic conditions that may interfere with the conduct of the study

4.1.2.4 Psychosocial

211 History of alcohol abuse or dependence within 12 months prior to study enrollment, or inability to refrain from alcohol use within 8 hours prior to a scheduled ETT

212 Inability to refrain from use of caffeine or nicotine products within 2 hours prior to a scheduled ETT

213 Unable to refrain from unaccustomed strenuous physical activity from the date of consent through their completion of the trial

4.1.2.5 Cardiovascular

214 History of cardiovascular conditions (including but not limited to severe aortic or mitral stenosis, heart failure New York Heart Association (NYHA) class 3 or 4, Brugada or long QT syndrome) that may interfere with the conduct or interpretation of the study or may constitute a safety risk per the investigator

215 Systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure (DBP) > 90 mmHg (determined by the mean of 3 consecutive measurements at least 5 minutes apart during screening)

216 Within the 3 months prior to or during screening

a. Unstable angina or acute coronary syndrome
b. Transient ischemic attack (TIA) or stroke
c. Revascularization procedure
d. Instability in ST-segment depression between screening ETTs, as assessed by the core ECG laboratory.

217 ECG findings that preclude analysis of the ETT, including but not limited to:

a. Any right or left bundle branch block
b. Pacemaker
c. Resting ST-segment depression ≥ 1.0 mm
d. Left ventricular hypertrophy with repolarization changes
e. Wolf-Parkinson White

218 Digitalis or Implantable defibrillator use

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects

must personally sign and date the informed consent form 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 in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (up to 6 weeks) 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 System (IVRS)/Interactive Web Response System (IWRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. A subject may be rescreened once if there are exclusionary medical conditions (such as elevated blood pressure or abnormal laboratory findings) that may resolve and allow for rescreening. Subjects may also be rescreened once if in the opinion of the investigator the reason for initial screen failure has been resolved or is no longer applicable (eg, due to a protocol amendment). Subjects may not be rescreened if unable to perform at least two ETTs with TET within one minute (or within 20% duration, using the longest duration qualifying ETT) of each other. **If for any other reason a subject should fail screening as a result of technical difficulties while conducting the ETTs during screening these cases should be reviewed, and it will be at Amgen discretion whether re-screening will be permitted.** The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. The randomization number will be different from the subject identification number.

5.1 Randomization/Treatment Assignment

Randomization must occur on day 1 pre-dose and after the completion of procedures associated with the end of the screening phase.

Subjects will be randomized in a 1:1 allocation ratio to a single dose of AMG 334 or placebo prior to completing an ETT with approximately **27** subjects assigned to each treatment group. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. The randomization will be performed by IVRS/IWRS. Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

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

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study (eg, in situations of emergency). Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Products

The Amgen Investigational Product and/or placebo used in this study includes: AMG 334 and placebo.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product AMG 334 and Placebo

AMG 334 will be manufactured and packaged by Amgen Inc., and distributed using Amgen clinical investigational product distribution procedures. AMG 334 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated with C Cl mM sodium acetate, C Cl % (w/v) sucrose, CCl % (w/v) polysorbate C Cl, at pH C Cl.

Placebo vials will be presented in identical containers and stored/packaged the same as AMG 334.

6.2.1.1 Dosage, Administration, and Schedule

Eligible subjects will be randomized into the study and receive an IV infusion of investigational product prior to the initiation of the ETT on study day 1. A single dose of 140 mg of AMG 334 or a matching volume of placebo will be mixed in 100 mL of dextrose 5% in water (D5W) and infused over approximately 60 minutes. Details regarding the storage, preparation, and administration of investigational product may be found in the IPIM, a document separate from this protocol.

Overdose with this product has not been reported.

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.

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 **are randomized but do not receive investigational product or receive partial dose** are to **remain on study and follow** all other study procedures until the end of the -study . If subjects refuse to complete all remaining study visits, they should complete the **early termination (**ET**)** visit.

End of investigational product and early discontinuation from investigational product are to be registered in the IVRS/IWRS.

6.3 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

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

6.4 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(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.

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

Subjects are prohibited from participating in other interventional studies (eg, studies which require medical device use or drug therapy or with protocol required procedures) while participating in this study.

The following are excluded prior to ETT:

- alcohol within 8 hours
- sublingual nitroglycerin within 4 hours
- caffeine and nicotine products within 2 hours

Any cardiac medications taken on a regular schedule (eg, beta blockers, calcium channel blockers, antianginals, etc.) should remain stable and not interrupted throughout the study, unless determined otherwise by the investigator or local regulatory guidance.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 1 can only be performed after obtaining a signed informed consent. This includes any discontinuation of the subject's medication for the purpose of participation in this study.

It is very important to attempt to perform study procedures and obtain samples at the precise timepoints stipulated below. When it is not possible to perform the study visit at the exact timepoint, the visit may be performed within the acceptable visit window as defined in the visit-specific section below.

With the exception of the screening and re-screen visits, all study procedures for a visit should be completed on the same day. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the CRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Table 1. Schedule of Assessments

	Screening Period (up to 6 weeks) Screening Visits				On-Study Period (12 weeks) On-Study Visits[j]					EOS/ET
					Day 1					
Procedure	**Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4[l]**	**Pre-dose[b]**	**Post-dose**	**Week 2[i]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[c]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[d]		X[d]	X[d]	X[d]		X				
Blood Pressure, Heart Rate[e]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[f]	**X**	Record Continuously								**X**
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling					X					
Urine drug screen[k]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.

[a] **Visits 1 and 2 in the Screening period may be combined. In the case where visits 1 and 2 are combined, all visit 1 assessments must be completed prior to the ETT for visit 2. The laboratory assessment results do not need to be reviewed prior to the ETT for visit 2, but must be reviewed prior to subsequent ETT (or before randomization).**

[b] Pre-dose assessments should be conducted on day 1 prior to randomization.

[c] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.

[d] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria**,** and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.

[e] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.

[f] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.

[g] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.

[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).

[i] Visit at week 2 can be done via telephone contact.

[j] Study visit windows are ± 1 week.

[k] Urine drug screen may also be performed as needed throughout the study per investigator judgment.

[l] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

7.2 General Study Procedures

The procedures performed at each study visit are outlined above in Table 1. Details regarding each type of procedure are provided in subsequent sub-sections.

Refer to the applicable supplemental central laboratory, IVRS/IWRS, and study manuals for detailed collection and handling procedures.

7.2.1 Screening

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written informed consent, the site will register the subject in IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is up to 6 weeks. If a subject has not met all eligibility criteria at the end of the 6-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once.

7.2.2 On-Study Period

The following procedures will be completed during the 12 week on-study period at the times designated in the Schedule of Assessments (Table 1). Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled. The date of the first dose of AMG 334 or placebo is defined as day 1. All subsequent study visits will be scheduled based on the day 1 date.

AMG 334 or placebo is to be administered after all pre-dose assessments have been completed on day 1.

7.2.3 End of Study Visit (Week 12/Early Termination Visit)

Subjects who complete the on-study period or who discontinue investigational product would complete the EOS/ET visit 12 weeks after the last dose of investigational product (refer to Table 1).

7.3 Description of Study Procedures

7.3.1 Informed Consent

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

7.3.2 Physical Examination, Height, and Weight

A physical examination will be performed at the initial screening visit (Visit 1) and abnormal findings collected on the medical history CRF. Breast, genital, and rectal examinations are not required unless specific evaluation is warranted. The physical

examination at the EOS/ET visit will consist of a follow-up examination to monitor for any changes from the screening physical examination. Any clinically significant changes in the physical examination per the investigator's opinion should be recorded in the Event CRF. All screening physical examinations are to be conducted per the site's standard of care.

7.3.2.1 Physical Measurements

Height (in centimeters) should be measured with the subject's shoes removed.

Weight (in kilograms) should be measured with the subject wearing light clothing and with shoes removed.

7.3.3 Targeted Medical/Surgical History

The investigator or designee will collect a targeted subject's relevant medical and surgical history and will be reviewed prior to randomization for the purposes of eligibility. The investigator or designee will collect medical and surgical history, including information on the subject's current conditions. The information will be recorded in the medical history CRF for subjects enrolled into the study on study day 1.

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

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items which define 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered 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 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.

7.3.5 Blood Pressure/Heart Rate

The systolic and diastolic BP and heart rate is to be collected at the timepoints outlined in the schedule of assessments (refer to Table 1).

Blood pressure will be measured in the following manner:

- Subjects should be sitting quietly and comfortably, with both feet on the floor, for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- Caffeine, exercise, and nicotine use should be avoided for at least 30 minutes prior to measurement.

- An appropriately-sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least two measurements (separated by at least 5 minutes) should be made and the average recorded. If there is a high value, it is acceptable to wait approximately 30 minutes before the next two blood pressure measurements are taken for the purpose of averaging and recording in the CRF.
- 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, sitting) should be the same that is used throughout the study and documented on the Vital Signs CRF.

7.3.6 Concomitant Medications

All concomitant medications (eg, cardiovascular, psychiatric, central nervous system, endocrine, pain medications), prescribed at the time the subject signs the informed consent will be recorded in the CRF through the completion of the EOS/ET visit .

For cardiovascular medications the name of the medication, dose, route, frequency, and dates of administration will be collected.

For other medications the name of the medication, start and stop dates will be collected.

7.3.7 Exercise Treadmill Test

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study. Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Additional details regarding the ETT procedures, including provision of data to the core ECG laboratory, may be found in the ETT manual.

7.3.8 Exercise Treadmill Test Scheduling

7.3.8.1 Screening

During screening 2 ETTs will be conducted (ETT 1 and ETT 2) to determine the subject's eligibility for the study. ETT 2 will be conducted after acknowledgement of acceptability of ETT1 has been received from the core ECG laboratory, within > 48 hours and ≤ 14 days after ETT 1. Both ETTs must be scheduled between 0600 and 1300 (eg, must begin no earlier than 0600 and no later than 1300 [see Table 2]). In addition, ETT 2 should begin within ± 2 hours of the recorded time at which ETT 1 began (eg, when ETT 1 begins at 0700, ETT 2 must begin no earlier than 0600 and no later than 0900).

If the TET in ETT 1 and ETT 2 differs by > 1 minute or > 20% duration, using the longest duration qualifying ETT, an additional screening ETT (ETT 3) must be conducted; ETT 3 should occur within > 48 hours and ≤ 14 days after ETT 2 and begin within ± 2 hours of the recorded time at which the ETT 2 began. No more than 3 screening ETTs can be conducted. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.

Subjects may enroll in the trial if there is ≤ 1 minute difference and ≤ 20% duration difference in the TET between the 2 qualifying ETTs performed during screening. The qualifying ETTs should have associated ECGs that have been deemed acceptable by the core ECG laboratory before a subject can be randomized.

For further guidance please refer to the EET study manual that outlines site requirements for conduct, tracing requirements, scheduling, and shipping procedures for all ETTs to be performed by a subject.

Table 2. Exercise Treadmill Test Scheduling

If initial[1] ETT begins at:	Follow- up[a] ETT must begin between:
0600	0600 - 0800
0630	0600 - 0830
0700	0600 - 0900
0730	0600 - 0930
0800	0600 - 1000
0830	0630 - 1030
0900	0700 - 1100
0930	0730 - 1130
1000	0800 - 1200
1030	0830 - 1230
1100	0900 - 1300
1130	0930 - 1300
1200	1000 - 1300
1230	1030 -1300
1300	1100 -1300

ETT = exercise treadmill test
[a] Initial ETT refers to the first of 2 qualifying ETTs (ETT1 or 2), follow-up ETT refers to the second qualifying ETT (ETT 2 or 3)

7.3.8.2 On-Study

Eligible subjects will have 1 additional ETT (ETTr) conducted after randomization and administration of investigational product on Day 1. The ETTr must be scheduled between 0600 and 1300 (eg, must begin no earlier than 0600 and no later than 1300) and should begin within ± 2 hours of the recorded time at which the last qualifying ETT began.

7.3.9 Monitoring During Exercise Treadmill Test

7.3.9.1 Blood Pressure

In addition to the standard blood pressure assessments conducted at each visit, during all ETTs blood pressure should be recorded as follows:

- Prior to the ETT
  - In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator.

7.3.9.2 Electrocardiograph

Site staff should visually monitor the subject's ECG during the ETT. The subject's heart rate and rhythm should be monitored in addition to identification of ischemic changes that may occur during the ETT. All ECG tracings should be examined and copies retained in the subject's source notes.

A 12-lead exercise ECG should be collected as follows during all ETTs:

- Prior to the ETT
  - In a sitting position at rest after at least 3 minutes
  - In a standing position after at least 2 minutes of standing
- Every minute
- At the end of each exercise stage, in an upright position
- At peak exercise during the ETT, in an upright position
- Immediately post-exercise, in a standing position
- At 1, 3 and 5 minutes post-exercise, during recovery, in a sitting position, and every 5 minutes thereafter if needed, until heart rate and blood pressure return to baseline or near-baseline values, as judged by the investigator.

If ST-segment changes occur, a printout will be run every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

7.3.9.3 ST-Segment Depression

Definition

ST-segment depression must occur during exercise performance. The depth of the ST-segment depression is measured at 60 msec after the J-point.

A ≥ 1 mm ST-segment depression is defined as:

- Horizontal or down-sloping ST depression
  - If the ST level at baseline is above the isoelectric line, the isoelectric line is the reference point for measurements
  - If the ST level at baseline is below the isoelectric line, the baseline ST level is the reference point for measurements
  - Examples:
    - If the standing at-rest value is +0.2, then a 1 mm ST-segment depression would be reached when the subject's ST value is -1.0 mm
    - If the standing at-rest value is -0.2, then a 1 mm segment depression would be reached when the subject's ST value equals -1.2 mm

Measurement

The measurement of ST-segment depression during exercise should be based on the average of at least 3 consecutive ST-segments. Any computer-generated determination of ST-segment depression should be verified by review of the ECGs to confirm that they meet criteria for ischemic ST-segment depression. ST-segment deviation should be visually monitored throughout the ETT. Frequent 12-lead ECGs (ie, every 30 seconds) must be recorded until resolution of the ST-segment depression.

The ECG tracings are to be properly labeled, with one copy maintained in the subject's source records and one copy provided to the core ECG laboratory, per the instructions provided in the ETT Manual. Analysis of the ETT parameters will be performed by the core ECG laboratory.

Criteria for Stopping

For each ETT, identify a single primary reason for stopping the test. During the on-study ETT , terminate the ETT as soon as the subject experiences symptom-limited exercise (defined below), or if asymptomatic ST-segment depression ≥ 3 mm is observed. The exercise duration is the time required for the subject to reach the exercise-limiting degree of symptoms and no further, thus site staff are not to push, coach or encourage subjects to tolerate symptoms during the ETT which would typically cause them to stop exercise during the course of their usual daily activities.

The following symptoms are reasons for stopping the ETT:

- Unacceptable angina (a condition for which the ETT must be interrupted because of excessive chest pain, rather than because of exercise limitation)
- Shortness of breath or fatigue
- Arrhythmia (eg, sustained ventricular tachycardia, ventricular triplets, high degree of ventricular ectopy, heart block, bradyarrythmia)
- Excessive elevation of blood pressure (eg, systolic pressure > 230 mmHg or diastolic pressure > 115 mmHg)
- Technical difficulties in monitoring ECG or SBP
- Fall in systolic blood pressure during exercise of > 10 mmHg
- Feeling of dizziness or faintness
- Intolerable musculoskeletal pain or discomfort
- ST-segment elevation > 1 mm in leads without diagnostic Q waves (other than V1 or aVR)
- ST-segment depression ≥ 3 mm or marked axis shift

The primary reason for ETT discontinuation should be documented in the CRF.

7.3.10 Adverse Events and Disease Related Events

Serious adverse events that occur in a subject after signing the informed consent through the EOS will be recorded in the CRF. All adverse events and Disease Related Events that occur after randomization through the EOS will be recorded in the event CRF.

Disease Related Events

Exercise induced chest pain should not be reported as an adverse event provided that it is consistent with the subject's previous pattern or level of angina.

7.3.11 Collection of Events for Adjudication

Cardiovascular and cerebrovascular events will be collected from the date of randomization through the end of the study (12 weeks after last dose of IP) and adjudicated in a blinded fashion by an independent clinical events committee (CEC). Data for the specified events will be collected on the event CRF for adjudication and transferred to the CEC for analysis per Amgen instructions.

7.3.12 Laboratory Assessments

All screening and on-study laboratory samples will be processed and sent to the central laboratory, unless otherwise noted. The results of this testing will be maintained in the source documents at the site. The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples. Please refer to the central laboratory manual for the complete listing of analytes run by the central laboratory. Blood samples will be obtained by venipuncture before investigational product administration**,** and PK sampling will be done postdose after ETTr. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, hematology, and other testing to be conducted on blood and urine samples are below (Table 3). Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

Table 3. Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Hematocrit	
Total protein	Platelets	PK
Albumin	WBC Differential	Cardiac biomarkers
Calcium	• Bands/stabs	• Troponin-I
Adjusted calcium	• Eosinophils	• CK
Magnesium	• Basophils	• CK-MB
Phosphorus	• Lymphocytes	
Glucose	• Neutrophils	Urine drug screen
BUN or Urea		Urine pregnancy test (local)
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CK-MB = creatine kinase MB isoenzyme; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

7.3.13 Pharmacokinetic Sampling

The PK sample drawn on day 1 will be collected after the completion of ETTr. 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 on day 1 (refer to Table 1). Please refer to the central laboratory manual for instructions on sample collection, processing, and shipping of PK samples.

7.3.14 Angina Diary

Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs (refer to Table 1).

7.4 Biomarkers

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

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

Blood samples are to be collected at the following time points: day 1 pre-dose for all subjects to enable testing of baseline cardiac markers (eg, troponin) or other safety measures, if needed.

7.5 Sample Storage and Destruction

Any sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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 receive investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 1) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 1).

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

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

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or 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 products or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.3.2 Reasons for Removal From Study

- Reasons for removal of a subject from the study are:
- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's baseline condition. Disease-related events for the purposes of this study include angina pectoris and related symptoms such as chest pain and shortness of breath (refer to

Section 7.3.10). Angina pectoris and related symptoms do not meet the definition of an adverse event unless assessed to be more severe than expected relative to the subject's baseline condition (refer to Section 9.1.3).

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

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

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational products/study treatment protocol required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

9.1.2 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than 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.

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.

9.1.3 Serious Adverse Events

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

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

A disease related event is to be reported as a serious adverse event if:

the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or

if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,

and the event meets at least 1 of the serious criteria above

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

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury ([DILI] see Appendix A for drug-induced liver injury 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 Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator are reported by the subject that occur after the first dose of investigational medicinal products/study treatment/protocol-required therapies through the end of study period (12 weeks after the last dose of IP), are reported using the Event CRF. Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

Events assessed by the investigator to be related to the investigational medicinal products/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational products through the end of study period (12 weeks after the last dose of IP) are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

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

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

The investigator must assess whether the adverse event is possibly related to the investigational products. 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 products?

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”?

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

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the study period (12 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 Event CRF.

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

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

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

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event 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 electronic Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

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

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

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

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

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

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

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

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

A serious adverse event of stable angina will not be reported in an expedited manner as this is anticipated to occur in the study population at some frequency independent of the

protocol-required therapies. The Data Monitoring Committee (DMC) will monitor these events on an ongoing basis. As there are no identified risks for AMG 334, all adverse events are considered 'unexpected' for regulatory reporting purposes.

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 12 weeks after a single dose of investigational product.

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

If a lactation case occurs following a female subject's exposure to 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 through 12 weeks after a single dose of investigational product.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Change from baseline in TET

10.1.1.2 Secondary Endpoints

- During the ETT
  - Time to onset of exercise-induced angina
  - Time to onset of ≥ 1 mm ST-segment depression

10.1.1.3 Safety Endpoints

- Adverse events and Disease Related Events
- Changes in vital signs

10.1.2 Analysis Sets

The full analysis set (FAS) includes all subjects who were randomized in the study.

The efficacy analysis set (EAS) includes subjects in the FAS, who received investigational product and completed the ETTr. In the EAS, subjects will be analyzed according to the randomized treatment, regardless of the treatment received.

The safety analysis set (SAS) includes all subjects in the FAS who received investigational product. In the SAS, subjects will be analyzed based on actual treatment received.

10.2 Sample Size Considerations

The primary endpoint is the change from baseline in TET. Assuming between-subject standard deviation for change from baseline in exercise duration of 130 seconds (Chaitman et al., 2004), with a planned study size of at least **27** subjects in each group and a difference in change from baseline in exercise duration of 0 seconds between AMG 334 group and placebo group, there is an 80% probability (power) that the lower bound of the 90% confidence interval (CI) will exceed **-9**0 seconds. **A margin larger than - 60 seconds between groups was required to accommodate the 60 second or 20% difference allowed in qualifying TETs for each subject. Because of this within-subject TET variation, a maximum TET difference of 90 seconds between the AMG 334 group and placebo group was considered reasonable in this study. As such, a margin of - 90 secs was selected, which corresponds to the margin used in a previous study testing a comparable hypothesis (Patterson, et. al 2005). Twenty-nine** subjects are needed in each group if considering 5% dropout.

When approximately **45** subjects have been enrolled, Amgen may **conduct a blinded sample re-estimation and** choose to alter the sample size based on the blinded variance in the pooled treatment groups.

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 unblinded

except as specified (eg, Section 5.2 and Section 9.2.2.3). **With the exception of site staff and subjects, the study will be unblinded at the time of the primary analysis. Complete unblinding of the study will occur at the final analysis.**

Staff from Clinical Supply Chain, Biological Sample Management, PK and Drug Metabolism, Clinical Immunology, Clinical Pharmacology, 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.

10.4 Planned Analyses

10.4.1 Primary Analysis

The primary analysis **of the primary and secondary endpoints** will be performed after all subjects have completed the ETTr.

10.4.2 Final Analysis

The final analysis for the study will be performed after all subjects have completed the study.

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 exercise capacity in subjects with stable angina as measured by TET during an ETT.

The FAS will be used to tabulate demographic data, baseline disease characteristics, and subject disposition. The EAS will include all FAS subjects who received investigational product and completed the ETTr and will be used to analyze the primary and secondary endpoints (including the change from baseline in TET, time to onset of ≥ 1 mm ST-segment depression, and time to onset of exercise-induced angina). The SAS include all FAS subjects who received investigational product and will be used to analyze safety endpoints.

Summary statistics by each treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include: number of subjects, mean,

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

Missing data will not be imputed.

Baseline value for exercise duration is the average value of the last two measurements in the screening period.

10.5.2 Data Monitoring Committee (DMC)

An independent DMC has been established to oversee the safety of study participants for several AMG 334 Migraine programs, including this study. The DMC will be composed of members with relevant expertise (cardiology, neurology, and statistics). DMC meetings are held approximately every 3 months and ad hoc meetings may be requested at any time by either the DMC or the sponsor. Safety data, including adverse events and laboratory data, will be reviewed frequently throughout the study, and the DMC will advise the study sponsor on findings that may impact the conduct of the study, including a recommendation to terminate the study. All serious unexpected serious adverse reactions will be promptly shared with the DMC.

10.5.3 Primary Efficacy Endpoint

The primary endpoint is the change from baseline in exercise duration **as measured by TET during the ETT**. The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change **in TET** compared to placebo, and that the true treatment difference in change from baseline in exercise duration is **less than a 9**0 second **decrease**.

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). A two-sided 90% CI for the mean difference in change from baseline in exercise duration will be calculated . If the lower bound of the CI of the difference is more than -**9**0 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

10.5.4 Secondary Efficacy Endpoints

For the secondary endpoints of time to onset of ≥ 1 mm ST-segment depression and time to exercise-induced angina Kaplan-Meier estimates of the event-free survival time will be computed and graphically displayed for each endpoint. For each endpoint, a

stratified (< 7 or ≥ 7 minute randomization strata) log-rank test statistic will be calculated to compare the two treatment groups at a significance level of 0.10.

10.5.5 Safety Endpoints

The SAS will be used to analyze safety endpoints based on the actual treatment received.

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

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. Tables of fatal adverse events, serious adverse events, leading to withdrawal from investigational product, adverse events of special interest if any, and Disease Related Events also will be provided.

Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term.

The analyses of selected 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.

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

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such

notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of the 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 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 is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, we will notify investigators of any amendments to the protocol. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

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

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

12.2 Study Documentation and Archive

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

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

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, CRF C-SSRS and angina diary 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 consents, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

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 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 EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 1), the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the 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.

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

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

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Clinical Trial Agreement that is available as a separate document.

13. REFERENCES

Amgen. AMG 334 Investigator Brochure, version 5.0.

Ashina M, Bendtsen L, Jensen R, Schifter S, Olesen J. Evidence for increased plasma levels of calcitonin gene-related peptide in migraine outside of attacks. Pain. 2000;86:133-138.

Bellamy JL, Cady RK, Durham PL. Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. Headache. 2006;46:24-33.

Burley DS, Hamid SA, Baxter GF. Cardioprotective actions of peptide hormones in myocardial ischemia. Heart Fail. Rev. 2007;12:279–291.

Chaitman B, Ho A, Behm M, et al. A randomized, placebo-controlled study of the effects of telcagepant on exercise time in patients with stable angina. Clin Pharmacol Ther. 2012;91(3):459-466.

Chaitman B, Pepine C, Parker J, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina, a randomized controlled trial. JAMA. 2004;291(3):309-316.

Connor KM, Shapiro RE, Diener HC, et al. Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology. 2009;73(12):970-977.

Gallai V, Sarchielli P, Floridi A, et al. Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. Cephalalgia. 1995;15:384-390.

Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol. 1990;28:183-187.

Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurol. 1988;23:193-196.

Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet. 2008a;372:2115-2123.

Ho TW, Mannix LK, Fan X, et al; MK-0974 Protocol 004 study group. Randomized controlled trial of an oral CGRP receptor antagonist, MK-0974, in acute treatment of migraine. Neurology. 2008b;70(16):1304-1312.

Hewitt D, Aurora S, Dodick D, et al. Efficacy and tolerability of the CGRP receptor antagonist MK-3207 for the acute treatment of migraine: a single attack randomized double-blind placebo-controlled adaptive dose ranging trial. Abstract for the 14th Congress of the International Headache Society. 2009; LBOR3.

International Committee of Medical Journal Editors, Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2013. http://www.icmje.org/.

Juhasz G, Zsombok T, Jakab B, Nemeth J, Szolcsanyi J, Bagdy G. Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. Cephalalgia. 2005;25(3):179-183.

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. Cephalalgia. 2002;22:54-61.

Patterson D, Kloner R, Effron M, et al. The effect of tadalafil on the time to exercise-induced myocardial ischaemia in subjects with coronary artery disease. Br J Clin Pharmacol. 2005, 60:459-468.

Petersen KA, Birk S, Doods H, Edvinsson L, Olesen J. Inhibitory effect of BIBN4096BS on cephalic vasodilatation induced by CGRP or transcranial electrical stimulation in the rat. Br J Pharmacol. 2004;143:1074-1075.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

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

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section **9.1.3**.

Additional Clinical Assessments and Observation

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

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

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

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels

  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20140254 AMG 334	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

Protocol specific reason(s):

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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	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? IP No✓ Yes✓ <Pidrug> No✓ Yes✓ <Pidrug> No✓ Yes✓ <Pidrug> No✓ Yes✓	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria: **01** Fatal; **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

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

Page 1 of 3

AMGEN
Study # 20140254
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
<<IP/Drug/Device>>	☐blinded ☐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											
	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

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

Page 2 of 3

AMGEN **Study #** 20140254 **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 -	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.		

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

Page 3 of 3

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

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

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Template Date: 15 December 2014

Version 4.0

Amendment 1

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number 20140254

Version 1.0; Date	12 June 2015
Amendment 1 Date:	06 August 2015

Rationale:

The rationale for this amendment is to clarify language throughout the protocol and to remove references to the storage of future research samples.

Description of Changes:

Section: Global

Change: Removed “adverse” from disease related “adverse” events. Correcting typographical and formatting errors.

Section: Title Page

Replace:

Header: Date: 24 November 2014

With:

Header: Date: **06 August 2015**

Replace:

Version 1.0; Date: 12 June 2015

With:

Version 1.0; Date: 12 June 2015
Amendment 1; Date: 06 August 2015

Section: Investigator’s Agreement

Replace:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated 02 June 2015 and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated **06 August** 2015 and agree to abide by all provisions set forth therein.

Section: Study Glossary

Replace:

End of Study (primary completion)	defined as when the last subject completes the on study ETT (ETTr) which is conducted after randomization and administration of study drug on Day 1

With:

End of Study (primary completion)	defined as when the last subject completes the on study ETT (ETTr) which is conducted after randomization and administration of **investigational product** on Day 1

Section: Protocol Synopsis – Statistical Considerations

Replace:

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and baseline exercise duration. A two-sided 90% confidence interval (CI) for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

With:

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and **randomization strata (< 7 or ≥ 7 minutes)**. A two-sided 90% confidence interval (CI) for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

Section: 3.5.2 End of Study

Replace:

Primary Completion: the date on which the last subject completes the on-study ETT (ETTr) which is conducted after randomization and administration of study drug on Day 1.

With:

Primary Completion: the date on which the last subject completes the on-study ETT (ETTr) which is conducted after randomization and administration of **investigational product** on Day 1.

Section: 4.1.2.2 Reproductive

Replace:

206 Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).

Female subjects not of childbearing potential are defined as: Any female who is has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR are post-menopausal. Post-menopausal women are those who fit into one of the following categories:

- Age 55 years with cessation of menses for 12 or more months, OR

With:

206 Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), **surgical contraceptive methods (vasectomy with medical assessment of the surgical**

success of this procedure or bilateral tubal ligation), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).

- Female subjects not of childbearing potential are defined as: Any female who is has had a hysterectomy, OR bilateral salpingectomy, OR bilateral oophorectomy, OR are post-menopausal. Post-menopausal women are those who fit into one of the following categories:
  - Age **≥** 55 years with cessation of menses for 12 or more months, OR

Section: 4.1.2.3 Psychiatric and Neurologic

Replace:

210 Within the 6 months prior to or during screening, report of suicidal ideation with intent, with or without a plan, or suicidal behavior as evidenced by a Columbia-Suicide Severity Rating Scale (C-SSRS) > 2 during screening

211 Any psychiatric or neurologic conditions that may interfere with the conduct of the study

With:

209 Within the 6 months prior to or during screening, report of suicidal ideation with intent, with or without a plan, or suicidal behavior as evidenced by a Columbia-Suicide Severity Rating Scale (C-SSRS) **score of 4 or 5 and any behavior** during screening

210 Any psychiatric or neurologic conditions that may interfere with the conduct of the study

Section: 4.1.2.5 Cardiovascular

Replace:

291 Digitalis or Implantable defibrillator use

With:

218 Digitalis or Implantable defibrillator use

Section: 6.2.1 Amgen Investigational Product AMG 334 and Placebo

Replace:

AMG 334 will be manufactured and packaged by Amgen Inc., and distributed using Amgen clinical study drug distribution procedures. AMG 334 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted] % (w/v) polysorbate [redacted], at pH [redacted].

With:

AMG 334 will be manufactured and packaged by Amgen Inc., and distributed using Amgen clinical **investigational product** distribution procedures. AMG 334 will be packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL AMG 334 formulated

with [redacted] mM sodium acetate, [redacted] % (w/v) sucrose, [redacted] % (w/v) polysorbate [redacted], at pH [redacted].

Section: 6.2.1.1 Dosage, Administration, and Schedule

Replace:

Eligible subjects will be randomized into the study and receive an intravenous infusion of investigational product prior to the initiation of the ETT on study day 1. A single dose of 140 mg of AMG 334 or a matching volume of placebo will be mixed in 100 mL of dextrose 5% in water (D5W) and infused over approximately 60 minutes. Details regarding the storage, preparation, and administration of investigational product may be found in the IPIM, a document separate from this protocol. The number of investigational product vials used (2), the volume (2 mL) of investigational product added to the IV bag, the volume of the IV bag (100 mL), start date/time, and stop date/time are to be recorded on each subject's CRF.

With:

Eligible subjects will be randomized into the study and receive an intravenous infusion of investigational product prior to the initiation of the ETT on study day 1. A single dose of 140 mg of AMG 334 or a matching volume of placebo will be mixed in 100 mL of dextrose 5% in water (D5W) and infused over approximately 60 minutes. Details regarding the storage, preparation, and administration of investigational product may be found in the IPIM, a document separate from this protocol. ~~The number of investigational product vials used (2), the volume (2 mL) of investigational product added to the IV bag, the volume of the IV bag (100 mL), start date/time, and stop date/time are to be recorded on each subject's CRF.~~

Section 7.1 Schedule of Assessments

Replace:

Footnote c: During the screening period, two consecutive ETTs are required > 24 hours and ≤ 14 days apart that meet inclusion criteria and were reviewed by a core ECG laboratory to confirm eligibility.

With

Footnote c: During the screening period, two consecutive ETTs are required **> 48 hours** and ≤ 14 days apart that meet inclusion criteria and were reviewed by a core ECG laboratory to confirm eligibility.

Section: 7.3.12 Laboratory Assessments

Replace:

Table 1. Analyte Listing

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	WBC	Hepatitis B surface antigen and Hepatitis B core antibody
Potassium	pH	RBC	Hepatitis C virus antibody
Chloride Bicarbonate	Blood	RBC morphology	Tuberculosis Testing[b]
Total protein	Protein	Absolute neutrophil count	
Albumin	Glucose	Hemoglobin	
Calcium	Bilirubin	Hematocrit	
Adjusted calcium	Microscopic (Reflex testing if > trace)	Platelets	
Magnesium		WBC Differential	
Phosphorus	Pregnancy	• Bands/stabs	
Glucose		• Eosinophils	
BUN or Urea		• Basophils	
Creatinine		• Lymphocytes	
Uric acid		• Neutrophils	
Total bilirubin		• Monocytes	
Direct bilirubin			
Alkaline phosphatase			
AST (SGOT)			
ALT (SGPT)			

With:

Table 2. Analyte Listing

Chemistry	**~~Urinalysis~~**	**Hematology**	**Other Labs**
Sodium	~~Specific gravity~~	WBC	Hepatitis B surface antigen
Potassium	~~pH~~	RBC	Hepatitis B core antibody
Chloride	~~Blood~~	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	~~Protein~~	Hematocrit	**PK**
Total protein	~~Glucose~~	Platelets	**Cardiac biomarkers**
Albumin	~~Bilirubin~~	WBC Differential	• **Troponin-I**
Calcium	~~Microscopic (Reflex testing if > trace)~~	• Bands/stabs	• **CK**
Adjusted calcium	~~Pregnancy~~	• Eosinophils	• **CK-MB**
Magnesium		• Basophils	**Urine drug screen**
Phosphorus		• Lymphocytes	**Urine pregnancy test (local)**
Glucose		• Neutrophils	
BUN or Urea		• ~~Monocytes~~	
Creatinine			
Uric acid			
Total bilirubin			
Direct bilirubin			
Alkaline phosphatase			
AST (SGOT)			
ALT (SGPT)			

Section: 7.5 Sample Storage and Destruction

Replace:

Any sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the coronary artery disease, 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 biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

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

With:
Any sample collected according to the Schedule of Assessments (Table 1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

~~If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the coronary artery disease, 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 biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.~~

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

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

Section: 10.5.3 Primary Efficacy Endpoint

Replace:

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and baseline exercise duration. A two-sided 90% CI for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

With:

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and **randomization strata (< 7 or ≥ 7 minutes)**. A two-sided 90% CI for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

Section: Appendix C. Pregnancy and Lactation Notification Worksheets

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

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® 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® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Template Date: 15 December 2014

Version 4.0

Amendment 2

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number 20140254

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	06 August 2015
Amendment 2 Date:	**17 November 2015**

Rationale:

The rationale for this amendment is to add: a 12-lead electrocardiogram to be conducted 4 hours after the completion of the Exercise Treadmill Test on day 1; an assessment of anti-AMG 334 antibodies at day 1, week 4, and end of study; a summary of clinical safety data to the Background and Rationale; and to clarify language throughout the protocol.

Description of Changes:

Section: Global

Change: Administration, typographical and formatting changes were made throughout the protocol.

Section: Title Page

Replace:

Header: Date: 06 August 2015

With:

Header: Date: **17 November 2015**

Replace:

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	**06 August 2015**

With:

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	06 August 2015
Amendment 2 Date:	**17 November 2015**

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated **06 August** 2015 and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated **17 November** 2015 and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis – Summary of Subject Eligibility Criteria

Replace:

For a full list of eligibility criteria, please refer to Section 4.1.1 through 4.2.2.

With:

For a full list of eligibility criteria, please refer to **Section 4**.

Section: Protocol Synopsis – Amgen Investigational Product Dosage and Administration

Replace:

See Section 6.2.1 for further details.

With:

See **Section 6.2.1.1** for further details.

Section: Protocol Synopsis – Procedures

Replace:

After signing the informed consent form, adverse events and serious adverse events will be collected, and subjects will enter the screening phase (up to 6 weeks). Screening evaluations will include targeted medical and medication history, physical exam, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, and ETT. Blood samples will be collected for pharmacokinetics (PK), biomarker, hematology, chemistry, and for all females (except those at least 2 years post-menopausal or surgically sterile) a urine pregnancy test. At the day 1 pre-dose visit, eligible subjects will be enrolled and randomized into the 12-week double-blind on-study period and will receive investigational product. Following investigational product administration, an ETT (ETTr) will be conducted. Safety follow-up visits will occur every 2-4 weeks after the last dose of investigational product. Subjects will record episodes of angina and antianginal medication use in an angina diary beginning on the day of screening Visit 1 and through the End of Study (EOS)/Early Termination (ET) visit to record angina episodes not occurring during ETT.

With:

After signing the informed consent form, adverse events and serious adverse events will be collected, and subjects will enter the screening phase (up to 6 weeks). Screening evaluations will include targeted medical and medication history, physical exami**nation**,

vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, and ETT. Blood samples will be collected for pharmacokinetics (PK), biomarker **analysis**, hematology, chemistry, and for all females (except those at least 2 years post-menopausal or surgically sterile) a urine pregnancy test. At the day 1 pre-dose visit, eligible subjects will be enrolled and randomized into the 12-week double-blind on-study period and will receive investigational product. Following investigational product administration, an ETT (**exercise treadmill test post-randomization** [ETTr]) will be conducted. Safety follow-up visits will occur every 2-4 weeks after the last dose of investigational product. Subjects will record episodes of angina and antianginal medication use in an angina diary beginning on the day of screening visit 1 and through the End of Study (EOS)/Early Termination (ET) visit to record angina episodes not occurring during ETT.

Section: Protocol Synopsis – Statistical Considerations:

Replace:

The SAS will be used to analyze safety endpoints based on the actual treatment received. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events. Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. 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, adverse events of special interest if any, and Disease Related Events also will be provided. Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term. The analyses of selected 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. Tabulations of grades ≥ 3 laboratory toxicities will be provided. The analyses of vital signs will include summary statistics over time by treatment group.

With:

The SAS will be used to analyze safety endpoints based on the actual treatment received. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events. Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. 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,~~ adverse events of special interest if any, and Disease Related Events also will be provided. Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term. The analyses of selected 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. ~~Tabulations of grades ≥ 3 laboratory toxicities will be provided.~~ The analyses of vital signs will include summary statistics over time by treatment group.

Section: 2.4 AMG 334 Clinical Safety Summary

Add:

As of August 10, 2015, approximately 1,039 subjects have received AMG 334 since the beginning of the clinical development program. Across phase 1 studies, 152 subjects (healthy subjects, subjects with hot flash and migraineurs) have received AMG 334 at doses up to 280 mg SC and 140 mg IV. In the phase 1 studies, 24-hour continuous ambulatory blood pressure (BP) monitoring demonstrated no change in BP circadian rhythm and no increase in BP with increasing doses of AMG 334.

Across ongoing phase 2 clinical studies approximately 887 subjects have received >1 dose of investigational product, including a total of 472 subjects in the double-blind phase of the episodic migraine study (Study 20120178). In both the double-blind and open-label treatment portions of the phase 2 episodic migraine study (Study 20120178) concomitant use of triptan-based migraine medications was reported in 64.8% of subjects. In this study, blood pressure was assessed at each visit. There was no clinically significant difference in either systolic or diastolic blood pressure at any dose group of AMG 334 compared with placebo. Moreover, there was no difference in the frequency of the adverse event of blood pressure increase between placebo and any dose of AMG 334. To date, AMG 334 has demonstrated a favorable safety and tolerability profile that supports further development. Refer to the AMG 334 Investigator's Brochure for details.

Section: 2.5 Risk Assessment

Add:

There is no direct benefit for individual subjects participating in this study, however there is a potential indirect benefit to participants in this study since they will undergo cardiovascular evaluation and assessments, including ETT, which may provide their treating physician with more detailed information that may improve their care. This study will test the hypothesis that AMG 334 does not significantly decrease exercise capacity in the study population, and, as such, would be supportive of the safe use of AMG334 as migraine prophylaxis in subjects with, or at risk of, cardiovascular disease.

To date, no evidence of a cardiovascular safety signal has been observed in preclinical, or phase 1, 2, and 3 studies of several investigational products interfering with the CGRP signaling pathway. This body of evidence includes dedicated cardiovascular studies with hemodynamic monitoring.

All subjects participating in the clinical study will be monitored closely for any cardiovascular abnormalities with vital signs assessments, ECGs, and physical examinations conducted at screening and before, during, and after the ETT procedures.

Section: 3.2 Number of Sites

Replace:

This is a multicenter study that will be conducted at approximately 30 sites.

With:

This is a multicenter study that will be conducted at approximately **40** sites.

Section: 4.1.2.2 Reproductive

Replace:

206. Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods

(oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).

With:

206. Females of reproductive potential who are not willing to use **highly** effective **methods of** birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- **Highly effective** methods of contraception **as per Clinical Trial Facilitation Group recommendations** include:
  - **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **intravaginal**
    - **transdermal**
  - **Progestogen-only hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **injectable**
    - **implantable**
  - **Intrauterine device (IUD)**
  - **Intrauterine hormone-releasing system (IUS)**
  - **Bilateral tubal occlusion**
  - **Vasectomized partner (with medical assessment of the surgical success of this procedure)**
  - **Sexual abstinence**

Section: 5.2 Site Personnel Access to Individual Treatment Assignments

Replace:

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

With:

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject **in** this study **(eg, in situations of emergency)**. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Section: 7.1 Schedule of Assessments

Replace:

Table 1. Schedule of Assessments

	Screening Period (up to 6 weeks) Screening Visits[i]					On-Study Period (12 weeks) On-Study Visits[i]				EOS/ET
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[k]**	**Day 1 Pre-dose[a]**	**Day 1 Post-dose**	**Week 2[h]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Angina diary[e]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Urine pregnancy test[f] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[g]				
Biomarker Sampling					X					
Urine drug screen[j]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, two consecutive ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria and were reviewed by a core ECG laboratory to confirm eligibility.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs through EOS.
[f] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[g] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[h] Visit at week 2 can be done via telephone contact.
[i] Study visit windows are ± 1 week.
[j] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[k] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

With:

Table 1. Schedule of Assessments

	Screening Period (up to 6 weeks) Screening Visits[k]					On-Study Period (12 weeks) On-Study Visits[k]				EOS/ET
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[m]**	**Day 1 Pre-dose[a]**	**Day 1 Post-dose**	**Week 2[j]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X	**X**	**X**	**X**	X		**X**	X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X	**X**	**X**	**X**		**X[e]**	**X**			
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Angina diary[f]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling					**X**	**X[i]**				
Anti-AMG 334 antibodies					**X**			**X**		**X**
Urine drug screen[l]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Day 1 is defined as the date investigational product is received.
[c] During the screening period, 2 consecutive ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria and **will be** reviewed by a core ECG laboratory to confirm eligibility.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT
[e] **ECG will be performed 4 hours after the end of the ETT.**
[f] Angina diary will be completed by subjects beginning on the day of visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs through EOS.
[g] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[i] **Biomarker sampling for troponin I measurement will be performed 4 hours after the end of the ETT.**
[j] Visit at week 2 can be done via telephone contact.
[k] Study visit windows are ± 1 week.
[l] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[m] Optional visit 4 to be performed if ETT 3 is required for eligibility determination.

Section: 7.3.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

Replace:

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items.

With:

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items **which define 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered to study subjects at 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.**

Section: 7.3.7 Exercise Treadmill Test

Replace:

The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Additional details regarding the ETT procedures, including provision of data to the core ECG laboratory, may be found in the ETT manual.

With:

Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Appropriate measures of emergency assistance (including cardiopulmonary resuscitation, access to intensive care unit, and specialized interventions such as coronary catheterization) must be available.

Additional details regarding the ETT procedures, including provision of data to the core ECG laboratory, may be found in the ETT manual.

Section: 7.3.9.1 Blood Pressure

Replace:

- Prior to the ETT
  - In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator.

With:

- Prior to the ETT
  - In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator
- **Maximum SBP during the ETT will be recorded**.

Section: 7.3.9.2 Electrocardiograph

Replace:

If ST-segment changes occur, run a printout every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

With:

If ST-segment changes occur, ~~run a~~ printout **will be run** every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule

as appropriate. **Maximum heart rate and maximum ST-segment depression during ETT will be recorded.**

After the ETTr, all subjects will be followed up at the site for at least 4 hours. At the end of the 4-hour follow-up period, the following procedures will be performed:

- **12-lead rest ECG in a sitting position**
- **Blood pressure measurement in a sitting position**
- **Blood sampling for measurement of troponin I**

Subjects can be kept at the site for longer than 4 hours at the discretion of the investigator.

Section: 7.3.12 Laboratory Assessments

Replace:

Table 2. Analyte Listing

Chemistry	**Hematology**	**Other Labs**
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride		Hepatitis C virus antibody
Bicarbonate	Hemoglobin	
Total protein	Hematocrit	PK
Albumin	Platelets	Cardiac biomarkers
Calcium	WBC Differential	• Troponin I
Adjusted calcium	• Bands/stabs	• CK
Magnesium	• Eosinophils	• CK-MB
Phosphorus	• Basophils	Urine drug screen
Glucose	• Lymphocytes	Urine pregnancy test (local)
BUN or Urea	• Neutrophils	
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

With:

Table 3. Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride		Hepatitis C virus antibody
Bicarbonate	Hemoglobin	
Total protein	Hematocrit	PK
Albumin	Platelets	Cardiac biomarkers
Calcium	WBC Differential	• Troponin I
Adjusted calcium	• Bands/stabs	• ~~CK~~
Magnesium	• Eosinophils	• ~~CK-MB~~
Phosphorus	• Basophils	Urine drug screen
Glucose	• Lymphocytes	Urine pregnancy test (local)
BUN or Urea	• Neutrophils	
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

Section: 7.3.15 Anti-AMG 334 Antibody Analysis

Add:

Blood samples will be collected for the measurement of anti-AMG 334 binding antibodies at the following time points: before dose on day 1, week 4 and EOS, and at additional time points as needed (see Table 1). Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and/or presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 334 antibodies during the study. Subjects who test positive for neutralizing antibodies to AMG 334 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should 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). 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 will not be 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.

Section: 7.4 Biomarkers

Replace:

Blood samples are to be collected at the following time points: day 1 pre-dose for all subjects to enable testing of baseline cardiac markers (eg, troponin) or other safety measures, if needed.

With:

Blood samples are to be collected at day 1 **post-ETT (4 hours)** for all subjects to enable testing of **troponin I** or other safety measures, if needed.

Section: 9.2.2.4 Serious Adverse Events That are not to be Reported in an Expedited Manner

Replace:

A serious adverse event of stable angina will not be reported in an expedited manner as this is anticipated to occur in the study population at some frequency independent of the protocol-required therapies. The Data Monitoring Committee (DMC) will monitor these events on an ongoing basis.

With:

A serious adverse event of stable angina will not be reported in an expedited manner as this is anticipated to occur in the study population at some frequency independent of the protocol-required therapies. The Data Monitoring Committee (DMC) will monitor these events on an ongoing basis. **As there are no identified risks for AMG 334, all adverse events will be considered 'unexpected' for regulatory reporting purposes.**

Section: 10.5.2 Data Monitoring Committee (DMC)
Replace:
A DMC will review and make recommendations regarding the safety of the study participants throughout the study. The DMC will be composed of members with relevant expertise. Safety data will be reviewed and the DMC will advise the study sponsor on findings that may impact the conduct of the study.

With:

An independent DMC has been established to oversee the safety of study participants for several AMG 334 Migraine programs, including this study. The DMC will be composed of members with relevant expertise **(cardiology, neurology, and statistics). DMC meetings are held approximately every 3 months and ad hoc meetings may be requested at any time by either the DMC or the Sponsor. Safety data including adverse events and laboratory data, will be reviewed frequently throughout the study, and the DMC will advise the study sponsor on findings that may impact the conduct of the study, including a recommendation to terminate the study. All serious unexpected serious adverse reactions will be promptly shared with the DMC.**

Section: 10.5.5 Safety Endpoints

Replace:

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. Tables of fatal adverse events, serious adverse events, leading to withdrawal from investigational product, treatment-related adverse events, serious treatment-related adverse events, adverse events of special interest if any, and Disease Related Events also will be provided.

Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term.

The analyses of selected 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. Tabulations of grades ≥ 3 laboratory toxicities will be provided.

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

With:

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. Tables of fatal adverse events, serious adverse events leading to withdrawal from investigational product, ~~treatment-related adverse events, serious treatment-related adverse events,~~ adverse events of special interest if any, and Disease Related Events also will be provided.

Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term.

The analyses of selected 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. ~~Tabulations of grades ≥ 3 laboratory toxicities will be provided.~~

The analyses of vital signs will include summary statistics over time by treatment group. **Specifically, change from baseline in maximum SBP, maximum heart rate and maximum ST-segment depression (mm) on day 1 post dose will be summarized 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.

Section: 13 References

Added:

Amgen. AMG 334 Investigator Brochure, version 5.0.

Section: Appendix A. Additional Safety Assessment Information

Replace:

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

With:

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 9.1.3**.

Amendment 3

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number 20140254

Amendment 3 Date: 27 January 2016

Rationale:

This protocol is being amended to:

- Increase the number of study centers
- Support decreasing the screen failure rate by:
  - allowing for the use of 2 out of 3 screening exercise treadmill tests (ETTs) to qualify patients for enrollment
  - removing the restriction for antianginal medication on the morning of the ETT
- Clarify the background safety information of AMG 334 use in patients with migraine.
- Clarify the definition of the Columbia-Suicidality Severity Scale (C-SSRS)
- Clarify adverse event, drug related event and serious adverse event reporting instructions
- Align with changes made to the updated standard Amgen protocol template

Description of Changes:

Section: Global

Change: Version dates updated throughout document from 06 August 2015 to **27 January 2016**

Section: Global

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

Section: Global

Change: Corrected abbreviations throughout the protocol (defined on first use, definition removed on subsequent uses).

Section: Title Page

Replace:

Version 1.0; Date:	12 June 2015
Amendment 1; Date:	06 August 2015

With:

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	06 August 2015
Amendment 2 Date:	**17 November 2015 (European Union, Voluntary Harmonization Procedure countries only)**
Amendment 3 Date:	**27 January 2016**

Section: Protocol Synopsis, Study Design

Replace:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average of the 2 final screening ETT (< 7 minutes or ≥ 7 minutes). Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

With:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average **(< 7 minutes or ≥ 7 minutes)** of the 2 **qualifying** ETT**s performed during screening**. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria

Replace:

Subject will experience at least 1 angina episode and are receiving stable doses of cardiac medications (eg, beta blockers, calcium channel blockers, etc.) for at least 30 days prior to randomization and that are not expected to change during the study.

For a full list of eligibility criteria, please refer to Section 4.1.1 through Section 4.1.2.

With:

Subject**s** will experience at least 1 angina episode and are receiving stable doses of cardiac medications (eg, beta blockers, calcium channel blockers, etc.) for at least 30 days prior to randomization and that are not expected to change during the study.

For a full list of eligibility criteria, please refer to Section **4**.

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration

Replace:

See Section 6.2.1 for further details.

With:

See Section **6.2.1.1** for further details.

Section: Protocol Synopsis, Procedures

Replace:

After signing the informed consent form, adverse events and serious adverse events will be collected, and subjects will enter the screening phase (up to 6 weeks). Screening evaluations will include targeted medical and medication history, physical exam, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, and ETT. Blood samples will be collected for pharmacokinetics (PK), biomarker, hematology, chemistry, and for all females (except those at least 2 years post-menopausal or surgically sterile) a urine pregnancy test. At the day 1 pre-dose visit, eligible subjects will be enrolled and randomized into the 12-week double-blind on-study period and will receive investigational product. Following investigational product administration, an ETT (ETTr) will be conducted.

With:

After signing the informed consent form **(ICF) subjects will enter the screening phase (up to 6 weeks),** serious adverse events will be collected **throughout the study including the screening phase, while adverse events and disease related events will start being collected post randomization/post first dose.** Screening evaluations will include targeted medical and medication history, physical exam**ination**, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS) assessment, and **exercise treadmill test (**ETT**)**. Blood samples will be collected for biomarker **analysis**, hematology, chemistry, and for all females (except **females not of childbearing potential, see definition in Exclusion Criteria Section 4.1.2.2**) a urine pregnancy test. At the day 1 pre-dose visit, eligible subjects will be enrolled and randomized into the 12-week double-blind on-study period and will receive investigational product. Following investigational product administration, an **exercise treadmill test post-randomization (**ETTr) will be conducted**, and pharmacokinetics (PK) sampling will be performed**.

Section: Protocol Synopsis, Statistical Considerations, 8th paragraph

Delete:

The SAS will be used to analyze safety endpoints based on the actual treatment received. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events. Subject incidence of all treatment emergent adverse events will be tabulated by treatment groups. 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,~~ adverse events of special interest if any, and Disease Related Events also will be provided. Subject incidence of Disease Related Events and fatal Disease Related Events will be tabulated by system organ class and preferred term. The analyses of selected 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. ~~Tabulations of grades ≥ 3 laboratory toxicities will be provided.~~ The analyses of vital signs will include summary statistics over time by treatment group.

Section: Study Glossary

Add:

Abbreviation or Term	Definition/Explanation
AE	**Adverse Event**
DRE	**Disease Related Event**
SAE	**Serious Adverse Event**

Section: 2.4 AMG 334 Clinical Safety Summary (new section)

Add:

2.4 AMG 334 Clinical Safety Summary

As of 10 August 2015, approximately 1,039 subjects have received AMG 334 since the beginning of the clinical development program. Across phase 1 studies, 152 subjects (healthy subjects, subjects with hot flash and migraineurs) have received AMG 334 at doses up to 280 mg SC and 140 mg IV. In the phase 1 studies, 24-hour continuous ambulatory blood pressure (BP) monitoring demonstrated no change in BP circadian rhythm and no increase in BP with increasing doses of AMG 334.

Across ongoing phase 2 clinical studies, approximately 887 subjects have received more than 1 dose of investigational product (IP), including a total of 472 subjects in the double-blind phase of the episodic migraine study (Study 20120178). In both the double-blind and open-label treatment portions of the phase 2 episodic migraine study (Study 20120178), concomitant use of triptan-based migraine medications was reported in 64.8% of subjects. In this study, BP was assessed at each visit. There was no clinically significant difference in either systolic or diastolic BP at any dose group of AMG 334 compared with placebo. Moreover, there was no difference in the frequency of the adverse event of blood pressure increase between placebo and any dose of AMG 334. To date, AMG 334 has demonstrated a favorable safety and tolerability

profile that supports further development. Refer to the AMG 334 Investigator's Brochure for details.

Section: 2.5 Risk Assessment (new section)

Add:

2.5 Risk Assessment

There is no direct benefit for individual subjects participating in this study, however there is a potential indirect benefit to participants in this study since they will undergo cardiovascular evaluation and assessments, including ETT, which may provide their treating physician with more detailed information that may improve their care. This study will test the hypothesis that AMG 334 does not significantly decrease exercise capacity in the study population, and, as such, would be supportive of the safe use of AMG 334 as migraine prophylaxis in subjects with, or at risk of, cardiovascular disease.

To date, no evidence of a cardiovascular safety signal has been observed in preclinical, or phase 1, 2, and 3 studies of several investigational products interfering with the CGRP signaling pathway. This body of evidence includes dedicated cardiovascular studies with hemodynamic monitoring.

All subjects participating in the clinical study will be monitored closely for any cardiovascular abnormalities with vital signs assessments, electrocardiograms (ECGs), and physical examinations conducted at screening and before, during, and after the ETT procedures.

Section: 3.1 Study Design, 1st paragraph

Replace:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Approximately 120 subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average of the 2 final screening ETT (< 7 minutes or ≥ 7 minutes). Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

With:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Approximately 120 subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average **(< 7 minutes or ≥ 7 minutes)** of the 2 **qualifying** ETT**s performed during screening**. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

Section: 3.2 Number of Sites

Replace:

This is a multicenter study that will be conducted at approximately 30 sites.

With:

This is a multicenter study that will be conducted at approximately **40** sites.

Section: 3.5.2 End of Study, 2nd paragraph

Replace:

The end of study ([EOS]), end of trial) is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, study week 12).

With:

Final completion: The end of study ([EOS], end of trial) is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, study week 12).

Section: 4.1.1 Inclusion Criteria

Delete:

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

Section: 4.1.1 Inclusion Criteria

Replace:

106 Completes 2 consecutive ETTs during screening, performed > 48 hours and ≤ 14 days apart using a standard Bruce ETT protocol, with:

a. Limitation of exercise due to symptoms of angina or ≥ 3 mm ST-segment depression
b. ≥ 1.0 mm ischemic ST-segment depression
c. Exercise duration of ≥ 3 to ≤ 12 minutes , and
d. ≤ 1 minute difference or within 20% duration (using the longest duration qualifying ETT) in TET between the 2 qualifying tests
e. ECG tracings from screening ETTs are acceptable to the core ECG laboratory

With:

106 Completes 2 **qualifying** ETTs during screening period **(as described for Screening in Section 7.3.8). The following ETT qualifications are required:**

a. Limitation of exercise due to symptoms **related to myocardial ischemia (such as angina pectoris, chest pain/discomfort, dyspnea, shortness of breath),** or ≥ 3 mm ST-segment depression
b. ≥ 1.0 mm ischemic ST-segment depression **during exercise performance**
c. Exercise duration of ≥ 3 to ≤ 12 minutes , and
d. ≤ 1 minute difference or within 20% duration (using the longest duration qualifying ETT) in TET between the 2 qualifying **ETTs**
e. ECG tracings from screening ETTs are acceptable to the core ECG laboratory

Section: 4.1.2.5 Exclusion Criteria, Cardiovascular

Replace:

217 ECG findings that preclude analysis of the ETT, including but not limited to:

a. Left bundle branch block
b. Pacemaker
c. Resting ST-segment depression ≥ 1.0 mm
d. Left ventricular hypertrophy with repolarization changes
e. Wolf-Parkinson White

With:

217 ECG findings that preclude analysis of the ETT, including but not limited to:

a. **Any right or left** bundle branch block
b. Pacemaker
c. Resting ST-segment depression ≥ 1.0 mm
d. Left ventricular hypertrophy with repolarization changes
e. Wolf-Parkinson White

Section: 5 Subject Enrollment, 3rd paragraph

Replace:

Each subject who enters into the screening period for the study (up to 6 weeks) 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 System (IVRS)/Interactive Web Response System (IWRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. A subject may be rescreened once if there are exclusionary medical conditions, such as elevated blood pressure or abnormal laboratory findings that may resolve and allow for rescreening. Subjects may not be rescreened if unable to perform two ETT with TET within one minute of each other.

With:

Each subject who enters into the screening period for the study (up to 6 weeks) 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 System (IVRS)/Interactive Web Response System (IWRS). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. A subject may be rescreened once if there are exclusionary medical conditions **(**such as elevated blood pressure or abnormal laboratory findings**)** that may resolve and allow for rescreening. **Subjects may also be rescreened once if in the opinion of the investigator the reason for initial screen failure has been resolved or is no longer applicable (eg, due to a protocol amendment).** Subjects may not be rescreened if unable to perform **at least** two ETT**s** with TET within one minute **(or within 20% duration, using the longest duration qualifying ETT)** of each other.

Section: 5.1 Randomization/Treatment Assignment, 2nd paragraph

Replace:

Subjects will be randomized in a 1:1 allocation ratio to a single dose of AMG 334 or placebo prior to completing an ETT with approximately 60 subjects assigned to each treatment group. Randomization will be stratified by the TET average of the 2 final screening ETT (< 7 minutes or ≥ 7 minutes). The randomization will be performed by IVRS/IWRS. Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

With:

Subjects will be randomized in a 1:1 allocation ratio to a single dose of AMG 334 or placebo prior to completing an ETT with approximately 60 subjects assigned to each treatment group. Randomization will be stratified by the TET average **(< 7 minutes or ≥ 7 minutes)** of the 2 **qualifying ETTs performed during** screening. The randomization will be performed by IVRS/IWRS. Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

Section: 5.2 Site Personnel Access to Individual Treatment Assignments

Add:

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study **(eg, in situations of emergency).** Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

Section: 6.5 Excluded Treatments, Medical Devices, and/or Procedures During Study Period, 2nd paragraph

Replace:

The following are excluded prior to ETT:

- alcohol within 8 hours
- sublingual nitroglycerin within 4 hours
- caffeine and nicotine products within 2 hours
- antianginal medications on the morning (within 4 hours)

Any cardiac medications (eg, beta blockers, calcium channel blockers, antianginals, etc.) should remain stable throughout the study.

With:

The following are excluded prior to ETT:

- alcohol within 8 hours
- sublingual nitroglycerin within 4 hours
- caffeine and nicotine products within 2 hours

Any cardiac medications **taken on a regular schedule** (eg, beta blockers, calcium channel blockers, antianginals, etc.) should remain stable **and not interrupted**

throughout the study**, unless determined otherwise by the investigator or local regulatory guidance**.

Section: 7 Study Procedures, 2nd paragraph

Delete:

With the exception of the screening and re-screen visits, all study procedures for a visit should be completed on the same day. Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the ~~electronic~~ CRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits.

Section: Section 7.1, Table 1 Schedule of Assessments

Add:

Procedure	Screening Period (up to 6 weeks) Screening Visits[l]					On-Study Period (12 weeks) On-Study Visits[l]				EOS/ET
	Visit 1	Visit 2	Visit 3	Visit 4[k]	Day 1 Pre-dose[a]	Day 1 Post-dose	Week 2[h]	Week 4	Week 8	Week 12
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						**X**	**Record Continuously**			**X**
Angina diary[e]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	**X**									

Section: Section 7.1, Table 1 Schedule of Assessments, Footnotes

Replace:

[c] During the screening period, two consecutive ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria and were reviewed by a core ECG laboratory to confirm eligibility.

[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs through EOS.

With:

[c] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria**,** and **they will be** reviewed by a core ECG laboratory to confirm eligibility. **No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.**

[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.

Section: 7.2.1 Screening

Delete:

Informed consent must be obtained before completing any other screening procedure or discontinuation of standard therapy for any disallowed therapy. After signing the written informed consent, the site will register the subject in IVRS/IWRS and screen the subject in order to assess eligibility for participation. The screening window is up to 6 weeks. If a subject has not met all eligibility criteria at the end of the 6-week window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once ~~as described in Section 5~~.

Section: 7.3.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

Add:

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items **which define 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS will be administered 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 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**.

Section: 7.3.7 Exercise Treadmill Test

Delete:

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test ~~and should not take their antianginal medications on the morning of the scheduled ETT (within 4 hours of ETT)~~. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study.

Section: 7.3.8 Exercise Treadmill Test Scheduling, 2nd and 3rd paragraph

Replace:

If the total exercise time (TET) in ETT 1 and ETT 2 differs by > 1 and ≤ 2 minutes, an additional screening ETT (ETT 3) may be conducted; ETT 3 should occur within > 48 hours and ≤ 14 days after ETT 2 and begin within ± 2 hours of the recorded time at which the ETT 2 began. Subjects may enroll in the trial if there is ≤ 1 minute difference in the TET between ETT 2 and ETT 3. The qualifying ETTs should have associated ECGs that have been deemed acceptable by the core ECG laboratory before a subject can be randomized.

With:

If the TET in ETT 1 and ETT 2 differs by > 1 minute **or > 20% duration, using the longest duration qualifying ETT**, an additional screening ETT (ETT 3) **must** be conducted; ETT 3 should occur within > 48 hours and ≤ 14 days after ETT 2 and begin within ± 2 hours of the recorded time at which the ETT 2 began. **No more than 3 screening ETTs can be conducted. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.**

Subjects may enroll in the trial if there is ≤ 1 minute difference **and ≤ 20% duration difference** in the TET between **the 2 qualifying** ETT**s performed during screening**. The qualifying ETTs should have associated ECGs that have been deemed acceptable by the core ECG laboratory before a subject can be randomized.

Section: 7.3.9.2 Electrocardiograph, 3rd paragraph

Replace:

If ST-segment changes occur, run a printout every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

With:

If ST-segment changes occur, a printout **will be run** every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

Section: 7.3.9.3 ST-Segment Depression, Definition

Replace:

During exercise, the depth of the ST-segment depression is measured at 60 msec after the J-point.

1 mm ST-segment depression is defined as:

- Horizontal or down-sloping ST depression
  - If the ST level at baseline is above the isoelectric line, the isoelectric line is the reference point for measurements
  - If the ST level at baseline is below the isoelectric line, the baseline ST level is the reference point for measurements
  - Examples:
    - If the standing at-rest value is +0.2, then a 1 mm ST-segment depression would be reached when the subject's ST value is -1.0 mm
    - If the standing at-rest value is -0.2, then a 1 mm segment depression would be reached when the subject's ST value equals -1.2 mm

With:

ST-segment depression must occur during exercise performance. The depth of the ST-segment depression is measured at 60 msec after the J-point.

A ≥ 1 mm ST-segment depression is defined as:

- Horizontal or down-sloping ST depression
  - If the ST level at baseline is above the isoelectric line, the isoelectric line is the reference point for measurements
  - If the ST level at baseline is below the isoelectric line, the baseline ST level is the reference point for measurements
  - Examples:
    - If the standing at-rest value is +0.2, then a 1 mm ST-segment depression would be reached when the subject's ST value is -1.0 mm
    - If the standing at-rest value is -0.2, then a 1 mm segment depression would be reached when the subject's ST value equals -1.2 mm

Section: 7.3.9.3 ST-Segment Depression, Criteria for Stopping

Replace:

The following symptoms are reasons for stopping the ETT:

- Unacceptable angina, shortness of breath, or fatigue
- Arrhythmia (eg, sustained ventricular tachycardia, ventricular triplets, high degree of ventricular ectopy, heart block, bradyarrythmia)

With:

The following symptoms are reasons for stopping the ETT:

- Unacceptable angina **(a condition for which the ETT must be interrupted because of excessive chest pain, rather than because of exercise limitation)**
- **S**hortness of breath or fatigue
- Arrhythmia (eg, sustained ventricular tachycardia, ventricular triplets, high degree of ventricular ectopy, heart block, bradyarrythmia)

Section: 7.3.11 Collection of Events for Adjudication

Add:

Cardiovascular and cerebrovascular events will be collected from the date of randomization through the end of the study **(12 weeks after last dose of IP)** and adjudicated in a blinded fashion by an independent clinical events committee (CEC).

Section: 7.3.12 Laboratory Assessments

Add:

All screening and on-study laboratory samples will be processed and sent to the central laboratory**, unless otherwise noted**. The results of this testing will be maintained in the source documents at the site.

Section: 7.3.12, Table 3 Analyte Listing, footnotes

Add:

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CK-MB = creatine kinase MB isoenzyme; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell

Section: 7.3.14 Angina Diary

Replace:

7.3.13.1 Angina Diary

Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs through EOS (refer to Table 1).

With:

7.3.**14** Angina Diary

Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs (refer to Table 1).

Section: 8.3.1 Reasons for Removal From Treatment

Add:

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern**, lost to follow-up**)

Section: 9.1.1 Disease Related Events, 1st paragraph

Add:

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. **Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's baseline condition. Disease-related events for the purposes of this study include angina pectoris and related symptoms such as chest pain and shortness of breath (refer to Section 7.3.10). Angina pectoris and related**

symptoms do not meet the definition of an adverse event unless assessed to be more severe than expected relative to the subject's baseline condition (refer to Section 9.1.3).

Section: 9.1.1 Disease Related Events, 2nd paragraph

Delete:

- Death due to the disease under study is to be recorded on the Event CRF

~~Angina pectoris does not meet the definition of an adverse event unless assessed to be more severe than expected relative to the subject's baseline condition.~~

Section: 9.1.3 Serious Adverse Events

Add:

A disease related event is to be reported as a serious adverse event if:

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

Section: 9.2.1 Reporting Procedures for Disease Related Events

Add:

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator are reported by the subject that occur after the first dose of investigational medicinal products/study treatment/protocol-required therapies through the end of study period **(12 weeks after the last dose of IP)**, are reported using the Event CRF. Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

Section: 9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria, 1st and 2nd paragraph

Add:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational products through the end of study period **(12 weeks after the last dose of IP)** are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

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

Section: 9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria, 4th paragraph

Add:

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** products?

Section: 9.2.2.2 Reporting Procedures for Serious Adverse Events

Add:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of the study **period** (12 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.

Section: 9.2.2.4 Serious Adverse Events That Are Not To Be Reported In An Expedited Manner

Add:

A serious adverse event of stable angina will not be reported in an expedited manner as this is anticipated to occur in the study population at some frequency independent of the protocol-required therapies. The Data Monitoring Committee (DMC) will monitor these events on an ongoing basis. **As there are no identified risks for AMG 334, all adverse events are considered 'unexpected' for regulatory reporting purposes.**

Section: 9.3 Pregnancy and Lactation Reporting

Add:

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

If a lactation case occurs following a female subject's exposure to 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 through 12 weeks after a single dose of investigational product.

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

Section: 10.5.2 Data Monitoring Committee (DMC)

Replace:

10.5.2 Data Monitoring Committee

A DMC will review and make recommendations regarding the safety of the study participants throughout the study. The DMC will be composed of members with relevant expertise. Safety data will be reviewed and the DMC will advise the study sponsor on findings that may impact the conduct of the study.

With:

10.5.2 Data Monitoring Committee **(DMC)**

An independent DMC has been established to oversee the safety of study participants for several AMG 334 Migraine programs, including this study. The DMC will be composed of members with relevant expertise (cardiology, neurology, and statistics). DMC meetings are held approximately every 3 months and ad hoc meetings may be requested at any time by either the DMC or the sponsor. Safety data, including adverse events and laboratory data, will be reviewed frequently throughout the study, and the DMC will advise the study sponsor on findings that may impact the conduct of the study, including a recommendation to terminate the study. All serious unexpected serious adverse reactions will be promptly shared with the DMC.

Section: 10.5.5 Safety Endpoints, 3rd paragraph

Delete:

Subject incidence of all treatment-emergent adverse events will be tabulated by treatment groups. Tables of fatal adverse events, serious adverse events, leading to withdrawal from investigational product, ~~treatment-related adverse events, serious treatment-related adverse events,~~ adverse events of special interest if any, and Disease Related Events also will be provided.

Section: 10.5.5 Safety Endpoints, 5th paragraph

Delete:

The analyses of selected 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. ~~Tabulations of grades ≥ 3 laboratory toxicities will be provided.~~

Section: 12.6 Publication Policy, 2nd paragraph

Replace:

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

With:

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**.

Section: 13 References

Add:

Amgen. AMG 334 Investigator Brochure, version 5.0.

Section: Appendix A, Additional Safety Assessment Information

Replace:

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

With:

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 **9.1.3**.

Section: Appendix B. Sample Serious Adverse Event Report Form

Delete:

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 hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

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

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

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

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

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

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen

FORM-056006 *Instructions Page 1 of 2* *Version 6.0 Effective Date 07 JUL 2014*

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.

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

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

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

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

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

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

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

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

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

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

FORM-056006 *Instructions Page 2 of 2* *Version 6.0 Effective Date 07 JUL 2014*

Country-specific protocol supplement for the European Union, Voluntary Harmonization Procedure Countries

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number (AMG 334) 20140254

Supplement version # 1: 28 January 2016

AMGEN®

1. Explanation of Country-specific Changes to the Protocol

This supplement to the protocol, dated 28 January 2016, provides language for the European Union (EU) Voluntary Harmonization Procedure (VHP) country-specific regulatory requirements and other procedures to follow in the execution of the global study in the EU VHP countries. These changes are being made in response to specific requests from the VHP coordinator.

The requests and changes made are as follows:

- Include a summary of clinical safety data (added to Section 2, Background and Rationale)
- Require highly effective methods of contraception (updated Exclusion Criteria 206)
- Add exclusionary criterion regarding hepatic function (added Exclusion Criteria 219)
- Add additional safety assessments and measures (added to Section 7, Study Procedures):
    - A 12-lead electrocardiogram conducted and blood pressure measurement collected 4 hours after the completion of the Exercise Treadmill Test (ETT) on day 1
    - During the ETT, record: (1) maximum systolic blood pressure, (2) maximum heart rate, and (3) maximum ST-segment depression
    - Biomarker sampling for troponin I measurement performed 4 hours after the end of the ETT
    - An assessment of anti-AMG 334 antibodies at day 1, week 4, and end of study
    - Appropriate measures of emergency assistance (including cardiopulmonary resuscitation, access to intensive care unit, and specialized interventions such as coronary catheterization) must be available

2. Summary of Text Changes to Protocol for EU VHP Countries

The summary of changes outlined below is used to specify the differences from the global protocol amendment 3 (27 January 2016) for the EU VHP countries.

Section: 4.1.2.2 Reproductive (Exclusion Criteria)

Text in global protocol:

206 Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).

New text for EU VHP Countries:

206 Females of reproductive potential who are not willing to use **highly** effective **methods of** birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- **Highly effective** methods of contraception **as per Clinical Trial Facilitation Group recommendations** include:
  - **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **intravaginal**
    - **transdermal**
  - **Progestogen-only hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **injectable**
    - **implantable**

- **Intrauterine device (IUD)**
- **Intrauterine hormone-releasing system (IUS)**
- **Bilateral tubal occlusion**
- **Vasectomized partner (with medical assessment of the surgical success of this procedure)**
- **Sexual abstinence**

Section: 4.1.2.6 Hepatic (Exclusion Criteria, new section)

Add text for VHP countries:

4.1.2.6 Hepatic

219 Hepatic disease by history or total bilirubin ≥ 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.

Section: 7.1 Schedule of Assessments, Table 1

Text in global protocol:

Procedure	Screening Period (up to 6 weeks) Screening Visits[l]					On-Study Period (12 weeks) On-Study Visits[l]				EOS/ET
	Visit 1	Visit 2	Visit 3	Visit 4[k]	Day 1 Pre-dose[a]	Day 1 Post-dose	Week 2[h]	Week 4	Week 8	Week 12
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[e]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[f] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[g]				
Biomarker Sampling					X					
Urine drug screen[j]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page.

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria, and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[f] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[g] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[h] Visit at week 2 can be done via telephone contact.
[i] Study visit windows are ± 1 week.
[j] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[k] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

Section: 7.1 Schedule of Assessments, Table 1

New text for EU VHP Countries:

Procedure	Screening Period (up to 6 weeks) Screening Visits[k]					On-Study Period (12 weeks) On-Study Visits[k]				EOS/ET
	Visit 1	Visit 2	Visit 3	Visit 4[m]	Day 1 Pre-dose[a]	Day 1 Post-dose	Week 2[j]	Week 4	Week 8	Week 12
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X					**X**[e]				
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[f]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling						**X**[i]				
Anti-AMG 334 antibodies					**X**			**X**		**X**
Urine drug screen[l]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page.

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, 2 ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria, and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] **ECG will be performed 4 hours after the end of the ETT.**
[f] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[g] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[i] **Biomarker sampling for troponin I measurement will be performed 4 hours after the end of the ETT.**
[j] Visit at week 2 can be done via telephone contact.
[k] Study visit windows are ± 1 week.
[l] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[m] Optional Visit 4 to be performed if ETT 3 is required for eligibility determination.

Section: 7.3.7 Exercise Treadmill Test

Text in global protocol:

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study. Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Add text for EU VHP countries:

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study. Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety. **Appropriate measures of emergency assistance (including cardiopulmonary resuscitation, access to intensive care unit, and specialized interventions such as coronary catheterization) must be available.**

Section: 7.3.9.1 Blood Pressure

Text in global protocol:

In addition to the standard blood pressure assessments conducted at each visit, during all ETTs blood pressure should be recorded as follows:

- Prior to the ETT
- In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator.

Add text for EU VHP countries:

In addition to the standard blood pressure assessments conducted at each visit, during all ETTs blood pressure should be recorded as follows:

- Prior to the ETT
- In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator
- **Maximum SBP during the ETT will be recorded**

Section: 7.3.9.2 Electrocardiograph, 3rd paragraph

Text in global protocol:

If ST-segment changes occur, a printout will be run every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

Add text for EU VHP countries:

If ST-segment changes occur, a printout will be run every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate. **Maximum heart rate and maximum ST-segment depression during ETT will be recorded.**

After the ETTr, all subjects will be followed up at the site for at least 4 hours. At the end of the 4-hour follow-up period, the following procedures will be performed:

- **12-lead rest ECG in a sitting position**
- **Blood pressure measurement in a sitting position**
- **Blood sampling for measurement of troponin I**

Subjects can be kept at the site for longer than 4 hours at the discretion of the investigator.

Section: 7.3.12 Laboratory Assessments, Table 3

Text in global protocol:

Chemistry	**Hematology**	**Other Labs**
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Hematocrit	
Total protein	Platelets	PK
Albumin	WBC Differential	Cardiac biomarkers
Calcium	• Bands/stabs	• Troponin-I
Adjusted calcium	• Eosinophils	• CK
Magnesium	• Basophils	• CK-MB
Phosphorus	• Lymphocytes	Urine drug screen
Glucose	• Neutrophils	Urine pregnancy test (local)
BUN or Urea		
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

New text for EU VHP countries:

Chemistry	Hematology	Other Labs
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Hematocrit	
Total protein	Platelets	PK
Albumin	WBC Differential	Cardiac biomarkers
Calcium	• Bands/stabs	• Troponin-I
Adjusted calcium	• Eosinophils	Urine drug screen
Magnesium	• Basophils	Urine pregnancy test (local)
Phosphorus	• Lymphocytes	**Anti-AMG 334 antibodies (Amgen/designee)**
Glucose	• Neutrophils	
BUN or Urea		
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

Section: 7.3.15 Anti-AMG 334 Antibody Analysis

Text in global protocol:

Not applicable.

Text for EU VHP countries:

7.3.15 Anti-AMG 334 Antibody Analysis

Blood samples will be collected for the measurement of anti-AMG 334 binding antibodies at the following time points: before dose on day 1, week 4, EOS, and at additional time points as needed (see Table 1). Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and/or presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 334 antibodies during the study. Subjects who test positive for neutralizing antibodies to AMG 334 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should 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). 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 will not be 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.

Section: 7.4 Biomarkers, 3rd paragraph

Text in global protocol:

Blood samples are to be collected at the following time points: day 1 pre-dose for all subjects to enable testing of baseline cardiac markers (eg, troponin) or other safety measures, if needed.

New text for EU VHP countries:

Blood samples are to be collected at day 1 **post-ETT (4 hours)** for all subjects to enable testing of **troponin I** or other safety measures, if needed.

Section: 10.5.5 Safety Endpoints, 6th paragraph

Text in global protocol:

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

Add text for EU VHP countries:

The analyses of vital signs will include summary statistics over time by treatment group. **Specifically, change from baseline in maximum SBP, maximum heart rate, and maximum ST-segment depression (mm) on day 1 post dose will be summarized 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.

Country-specific Protocol Supplement for Specific European Union Countries

Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number (AMG 334) 20140254

Supplement version # 1:	28 January 2016
Supplement version # 2:	28 October 2016
Supplement version # 3:	14 November 2016

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN, Canadian sites, 1-866-50-AMGEN*; <<for all other countries, insert the local toll-free Medical Information number>>* Amgen's general number in the US (1-805-447-1000*).*

AMGEN®

1. Overview of Country-specific Changes to the Protocol

This supplement (dated 14 November 2016) to the protocol amendment 4, dated 28 October 2016, provides language for European Union (EU) country-specific procedures to follow in the execution of the global study in the specified EU countries.

Three supplements have been prepared:

Supplement version # 1, protocol amendment 3:	28 January 2016
Supplement version # 2, protocol amendment 4:	28 October 2016
Supplement version # 3, protocol amendment 4:	14 November 2016

1.1 Supplement #1

1.1.1 Explanation of Country-specific Changes to the Protocol (Supplement #1)

Protocol amendment 3 was amended primarily to include the requested Voluntary Harmonization Procedure (VHP) changes as a supplement to the study protocol, ensuring the core body of the protocol remains the same for all participating countries including those outside of the VHP. Supplement version number 1 incorporated those changes which were made in response to specific requests during the VHP procedure.

The requests and changes made are as follows for supplement version # 1 dated 28 January 2016 as previously provided with protocol amendment 3:

- Include a summary of clinical safety data (added to Section 2, Background and Rationale)
- Require highly effective methods of contraception (updated Exclusion Criteria 206)
- Add exclusionary criterion regarding hepatic function (added Exclusion Criteria 219)
- Add additional safety assessments and measures (added to Section 7, Study Procedures):
    - A 12-lead electrocardiogram conducted and blood pressure measurement collected 4 hours after the completion of the Exercise Treadmill Test (ETT) on day 1
    - During the ETT, record: (1) maximum systolic blood pressure, (2) maximum heart rate, and (3) maximum ST-segment depression
    - Biomarker sampling for troponin I measurement performed 4 hours after the end of the ETT
    - An assessment of anti-AMG 334 antibodies at day 1, week 4, and end of study
    - Appropriate measures of emergency assistance (including cardiopulmonary resuscitation, access to intensive care unit, and specialized interventions such as coronary catheterization) must be available

1.1.2 Summary of Text Changes to Protocol for EU VHP Countries for Supplement #1

The summary of changes outlined below is used to specify the differences from the global protocol amendment 3 (27 January 2016) for the EU VHP countries.

Section: 4.1.2.2 Reproductive (Exclusion Criteria)

Text in global protocol:

206 Females of reproductive potential who are not willing to use acceptable method(s) of effective birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- Acceptable methods of effective contraception include: true sexual abstinence when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception], or use of hormonal birth control methods (oral, implantable, injectable, transdermal, intravaginal), intrauterine devices (IUDs), intrauterine hormonal-releasing system (IUS), surgical contraceptive methods (vasectomy with medical assessment of the surgical success of this procedure or bilateral tubal ligation), or two (2) barrier methods (one by each partner and at least one of the barrier methods must include spermicide (unless spermicide is not approved in the country or region) - the male must use a condom and the female must choose either a diaphragm OR cervical cap, OR contraceptive sponge (a male and female condom cannot be used together due to the risk of tearing).

New text for EU VHP Countries:

206 Females of reproductive potential who are not willing to use **highly** effective **methods of** birth control during treatment with AMG 334 and for an additional 12 weeks after receiving a single dose of AMG 334

- **Highly effective** methods of contraception **as per Clinical Trial Facilitation Group recommendations** include:
  - **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **intravaginal**
    - **transdermal**
  - **Progestogen-only hormonal contraception associated with inhibition of ovulation:**
    - **oral**
    - **injectable**
    - **implantable**

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (with medical assessment of the surgical success of this procedure)
- Sexual abstinence

Section: 4.1.2.6 Hepatic (Exclusion Criteria, new section)

Add text for VHP countries:

4.1.2.6 Hepatic

219 Hepatic disease by history or total bilirubin ≥ 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.

Section: 7.1 Schedule of Assessments, Table 1

Text in global protocol:

	Screening Period (up to 6 weeks)					On-Study Period (12 weeks)				EOS/ET
	Screening Visits[l]					On-Study Visits[l]				
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[k]**	**Day 1 Pre-dose[a]**	**Day 1 Post-dose**	**Week 2[h]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[e]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[f] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[g]				
Biomarker Sampling					X					
Urine drug screen[j]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page.

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria, and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[f] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[g] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[h] Visit at week 2 can be done via telephone contact.
[i] Study visit windows are ± 1 week.
[j] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[k] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

Section: 7.1 Schedule of Assessments, Table 1

New text for EU VHP Countries:

	Screening Period (up to 6 weeks) Screening Visits[k]					On-Study Period (12 weeks) On-Study Visits[k]				EOS/ET
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[m]**	**Day 1 Pre-dose[a]**	**Day 1 Post-dose**	**Week 2[j]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X					**X**[e]				
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[f]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling						**X**[i]				
Anti-AMG 334 antibodies					**X**			**X**		**X**
Urine drug screen[l]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page.

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, 2 ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria, and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] **ECG will be performed 4 hours after the end of the ETT.**
[f] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[g] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[i] **Biomarker sampling for troponin I measurement will be performed 4 hours after the end of the ETT.**
[j] Visit at week 2 can be done via telephone contact.
[k] Study visit windows are ± 1 week.
[l] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[m] Optional Visit 4 to be performed if ETT 3 is required for eligibility determination.

Section: 7.3.7 Exercise Treadmill Test

Text in global protocol:

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study. Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety.

Add text for EU VHP countries:

The ETT will be conducted using the standard Bruce protocol. A motor-driven treadmill should be utilized under uniform conditions, optimally by the same technician and supervising physician for each ETT. The subject should wear comfortable clothing and shoes suitable for exercise (eg, no boots or flip flops) for all ETTs. On the day of the treadmill test subjects may consume a light breakfast > 2 hours prior to the ETT. Subjects should not use sublingual nitroglycerin ≤ 4 hours prior to the test. All ETTs for a given subject should be performed in approximately the same conditions (time, temperature, food intake and caffeine and nicotine consumption before the exercise test) with the same investigator who should supervise the ETT performance in the same way throughout the study. Subjects may touch the treadmill bars or handles lightly to assist with balance, however they must not be allowed to hold onto or lean on the treadmill bars or handles during the ETT. The appropriate site staff should examine all ECG tracings and ETT records to ensure subject safety. **Appropriate measures of emergency assistance (including cardiopulmonary resuscitation, access to intensive care unit, and specialized interventions such as coronary catheterization) must be available.**

Section: 7.3.9.1 Blood Pressure

Text in global protocol:

In addition to the standard blood pressure assessments conducted at each visit, during all ETTs blood pressure should be recorded as follows:

- Prior to the ETT
- In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator.

Add text for EU VHP countries:

In addition to the standard blood pressure assessments conducted at each visit, during all ETTs blood pressure should be recorded as follows:

- Prior to the ETT
- In a standing position after 2 minutes of standing
- Within 30 seconds prior to each change in stage and at peak exercise during the ETT, in a standing position
- At the end of the ETT in a sitting position
- During recovery in a sitting position, every minute for 5 minutes after the end of the ETT, then every 5 minutes, as needed, until values return to near baseline values, per the judgment of the investigator
- **Maximum SBP during the ETT will be recorded**

Section: 7.3.9.2 Electrocardiograph, 3rd paragraph

Text in global protocol:

If ST-segment changes occur, a printout will be run every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate.

Add text for EU VHP countries:

If ST-segment changes occur, a printout will be run every 30 seconds until resolution. Additional exercise ECGs will be obtained per the recovery period schedule as appropriate. **Maximum heart rate and maximum ST-segment depression during ETT will be recorded.**

After the ETTr, all subjects will be followed up at the site for at least 4 hours. At the end of the 4-hour follow-up period, the following procedures will be performed:

- **12-lead rest ECG in a sitting position**
- **Blood pressure measurement in a sitting position**
- **Blood sampling for measurement of troponin I**

Subjects can be kept at the site for longer than 4 hours at the discretion of the investigator.

Section: 7.3.12 Laboratory Assessments, Table 3

Text in global protocol:

Chemistry	Hematology	Other Labs
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Hematocrit	
Total protein	Platelets	PK
Albumin	WBC Differential	Cardiac biomarkers
Calcium	• Bands/stabs	• Troponin-I
Adjusted calcium	• Eosinophils	• CK
Magnesium	• Basophils	• CK-MB
Phosphorus	• Lymphocytes	Urine drug screen
Glucose	• Neutrophils	Urine pregnancy test (local)
BUN or Urea		
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

New text for EU VHP countries:

Chemistry	Hematology	Other Labs
Sodium	WBC	Hepatitis B surface antigen
Potassium	RBC	Hepatitis B core antibody
Chloride	Hemoglobin	Hepatitis C virus antibody
Bicarbonate	Hematocrit	
Total protein	Platelets	PK
Albumin	WBC Differential	Cardiac biomarkers
Calcium	• Bands/stabs	• Troponin-I
Adjusted calcium	• Eosinophils	Urine drug screen
Magnesium	• Basophils	Urine pregnancy test (local)
Phosphorus	• Lymphocytes	**Anti-AMG 334 antibodies (Amgen/designee)**
Glucose	• Neutrophils	
BUN or Urea		
Creatinine		
Uric acid		
Total bilirubin		
Direct bilirubin		
Alkaline phosphatase		
AST (SGOT)		
ALT (SGPT)		

Section: 7.3.15 Anti-AMG 334 Antibody Analysis

Text in global protocol:

Not applicable.

Text for EU VHP countries:

7.3.15 Anti-AMG 334 Antibody Analysis

Blood samples will be collected for the measurement of anti-AMG 334 binding antibodies at the following time points: before dose on day 1, week 4, EOS, and at additional time points as needed (see Table 1). Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and/or presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 334 antibodies during the study. Subjects who test positive for neutralizing antibodies to AMG 334 at the final scheduled study visit will be asked to return for additional follow-up testing. This testing should 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). 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 will not be 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.

Section: 7.4 Biomarkers, 3rd paragraph

Text in global protocol:

Blood samples are to be collected at the following time points: day 1 pre-dose for all subjects to enable testing of baseline cardiac markers (eg, troponin) or other safety measures, if needed.

New text for EU VHP countries:

Blood samples are to be collected at day 1 **post-ETT (4 hours)** for all subjects to enable testing of **troponin I** or other safety measures, if needed.

Section: 10.5.5 Safety Endpoints, 6th paragraph

Text in global protocol:

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

Add text for EU VHP countries:

The analyses of vital signs will include summary statistics over time by treatment group. **Specifically, change from baseline in maximum SBP, maximum heart rate, and maximum ST-segment depression (mm) on day 1 post dose will be summarized 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.

1.2 Supplement #2

1.2.1 Explanation of Country-specific Changes to the Protocol for Supplement #2

The changes made are as follows for supplement version # 2 dated 28 October 2016 provided with global protocol amendment 4 (dated 28 October 2016):

- Day 1 visits moved to occur within “On-study visits” as predose was incorrectly placed within the screening period.

1.2.2 Summary of Text Changes to Protocol for Specific EU Countries for Supplement #2

The summary of changes outlined below is used to specify the differences from the global protocol amendment 4 (28 October 2016) for the following EU countries: Bulgaria, Czech Republic, Latvia, Poland, and Romania.

Section 7.1, Schedule of Assessments, Table 1

Text in global protocol:

Procedure	Screening Period (up to 6 weeks) Screening Visits				On-Study Period (12 weeks) On-Study Visits[j]					EOS/ET
	Visit 1[a]	Visit 2[a]	Visit 3	Visit 4[i]	Day 1 Predose[b]	Day 1 Post-dose	Week 2[i]	Week 4	Week 8	Week 12
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[c]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[d]	X[d]	X[d]		X				
Blood Pressure, Heart Rate[e]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[f]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling					X					
Urine drug screen[k]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Visits 1 and 2 in the screening period may be combined. In the case where visits 1 and 2 are combined, all visit 1 assessments must be completed prior to the ETT for visit 2. The laboratory assessment results do not need to be reviewed prior to the ETT for visit 2, but must be reviewed prior to subsequent ETT (or before randomization).
[b] Predose assessments should be conducted on day 1 prior to randomization.
[c] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[d] During the screening period, 2 ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria, and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[e] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[f] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[g] Results of predose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[i] Visit at week 2 can be done via telephone contact.
[j] Study visit windows are ± 1 week.
[k] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[l] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

Section:7.1, Schedule of Assessments, Table 1

Added text for Specific EU countries:

Procedure	Screening Period (up to 6 weeks) Screening Visits				On-Study Period (12 weeks) On-Study Visits[l]					EOS/ET
	Visit 1[a]	Visit 2[a]	Visit 3	Visit 4[n]	Day 1 Predose[b]	Day 1 Post-dose	Week 2[k]	Week 4	Week 8	Week 12
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[c]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[d]		X[d]	X[d]	X[d]		X[d]				
Blood Pressure, Heart Rate[e]	X				X	X		X	X	X
ECG	X					**X**[f]				
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[g]	X	Record Continuously								X
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[h] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[i]				
Biomarker Sampling						**X**[j]				
Anti-AMG 334 Antibodies					**X**			**X**		**X**
Urine drug screen[m]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Visits 1 and 2 in the screening period may be combined. In the case where visits 1 and 2 are combined, all visit 1 assessments must be completed prior to the ETT for visit 2. The laboratory assessment results do not need to be reviewed prior to the ETT for visit 2, but must be reviewed prior to subsequent ETT (or before randomization).
[b] Predose assessments should be conducted on day 1 prior to randomization.
[c] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[d] During the screening period, 2 ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria**,** and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[e] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[f] ECG will be performed 4 hours after the end of ETT.
[g] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[h] Results of predose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[i] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[j] Biomarker sampling for troponin I measurement will be performed 4 hours after the end of the ETT.
[k] Visit at week 2 can be done via telephone contact.
[l] Study visit windows are ± 1 week.
[m] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[n] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

1.3 Explanation of Country-specific Changes to the Protocol for Supplement #3

This supplement is only being submitted to the EU specific countries referenced in this combined supplement.

The changes made are as follows for supplement version # 3 dated 14 November 2016 provided with global protocol amendment 4 (dated 28 October 2016):

- Supplement 1 and 2 are combined in one document and named supplement version #3. This was done to clarify that the previous supplement was not superseded and that both supplements are to be used in the conduct of the study per the latest amendment.

Amendment 4

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina

Amgen Protocol Number 20140254

Version 1.0 Date:	12 June 2015
Amendment 1 Date:	06 August 2015
Amendment 2 Date:	17 November 2015 (European Union, Voluntary Harmonization Procedure countries only)
Amendment 3 Date:	27 January 2016
Amendment 4 Date:	**28 October 2016**

Rationale:

The following changes are being made to the study for the reasons indicated:

- Change in primary hypotheses, specifically that the true difference in change from baseline in exercise duration, if any, is not as much as a 90 second decrease, not 60 seconds. There is no established non-inferiority margin for TET. Two previous studies testing a comparable hypothesis used margins of 60 seconds and 90 seconds, respectively (Chaitman et al, 2012; Patterson et al, 2005). Per protocol, a qualifying TET must be ≥ 3 to ≤ 12 minutes, and the difference between 2 qualifying ETTs must be ≤ 1 minute different or within 20% duration (using the longest duration qualifying ETT). In some cases (when the TET is >5 minutes), a 20% difference in TET will exceed 60 seconds. As such, 60 seconds is not considered to be a clinically meaningful difference, and therefore a non-inferiority margin of -90 sec was selected (Patterson, et. al, 2005).
- Sample size was changed from 120 subjects to at least 54 based on the revised margin of 90 seconds while maintaining 80% power.
- Clarification of rescreening of screen failures due to technical difficulties will be reviewed by Amgen to determine if rescreening is permitted.
- Clarification of text regarding dosage adjustments, delays, rules for withholding or restarting, or permanent discontinuation
- Clarification of timing use of antianginals post ETT
- Clarification of who will be blinded and timing of unblinding
- Clarification of primary analysis
- Clarification of primary efficacy endpoint
- Schedule of Assessments: Day 1 visits moved to occur within on study visits, as these were previously shown incorrectly within the screening period. An instructional footnote was also added for screening visits.

Description of Changes:

Section: Global

Change: Minor corrections were made throughout the protocol correcting typographical and formatting errors.

Section: Header

Replace:

Product: AMG 334

With:

Product: **Erenumab (**AMG 334**)**

Section: Title page

Replace:

AMG 334

With:

Erenumab (AMG 334)

Replace:

Key Sponsor Contact(s):

PPD

Global Clinical Research Study Manager

Amgen Inc.

One Amgen Center Drive

Thousand Oaks, CA 91320, USA

PPD

With:

PPD

Global Clinical Trial Manager

Amgen Ltd.

1 Uxbridge Business Park,

Sanderson Road

Uxbridge, UB8 1DH, UK

PPD

Add:

Amendment 4 Date: 28 October 2016

Section: Investigator's Agreement

Replace:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated 27 January 2016 and agree to abide by all provisions set forth therein.

With:

I have read the attached protocol entitled A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of AMG 334 on Exercise Time During a Treadmill Test in Subjects With Stable Angina, dated **28 October 2016** and agree to abide by all provisions set forth therein.

Section: Protocol Synopsis, Hypothesis

Replace:

Hypotheses: The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in exercise duration, compared to placebo, and that the true treatment difference in change from baseline in exercise duration is -60 seconds or more.

With:

Hypothesis: The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in exercise duration, compared to placebo, and that the true treatment difference in change from baseline in exercise duration is **less than a 9**0 second **decrease**.

Section: Protocol Synopsis, Sample Size

Replace:

Approximately 120 subjects will be randomized

With:

At least 54 subjects will be randomized

Section: Protocol Synopsis, Statistical Considerations

Replace:

The primary endpoint is the change from baseline in exercise duration.

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). A two-sided 90% confidence interval (CI) for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

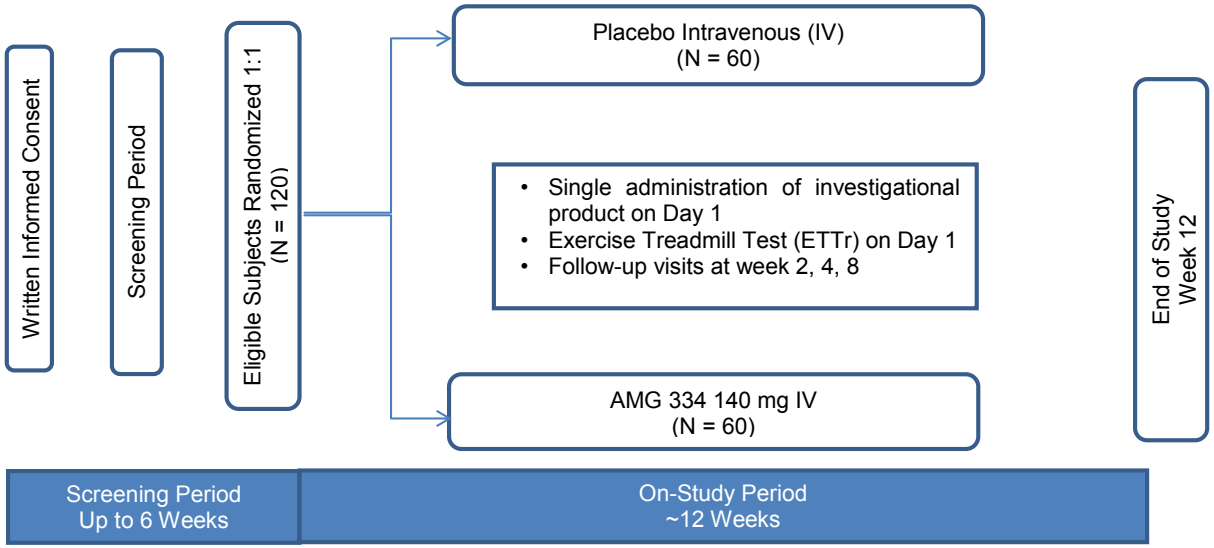
With:

The primary endpoint is the change from baseline in exercise duration **as measured by TET during the ETT**.

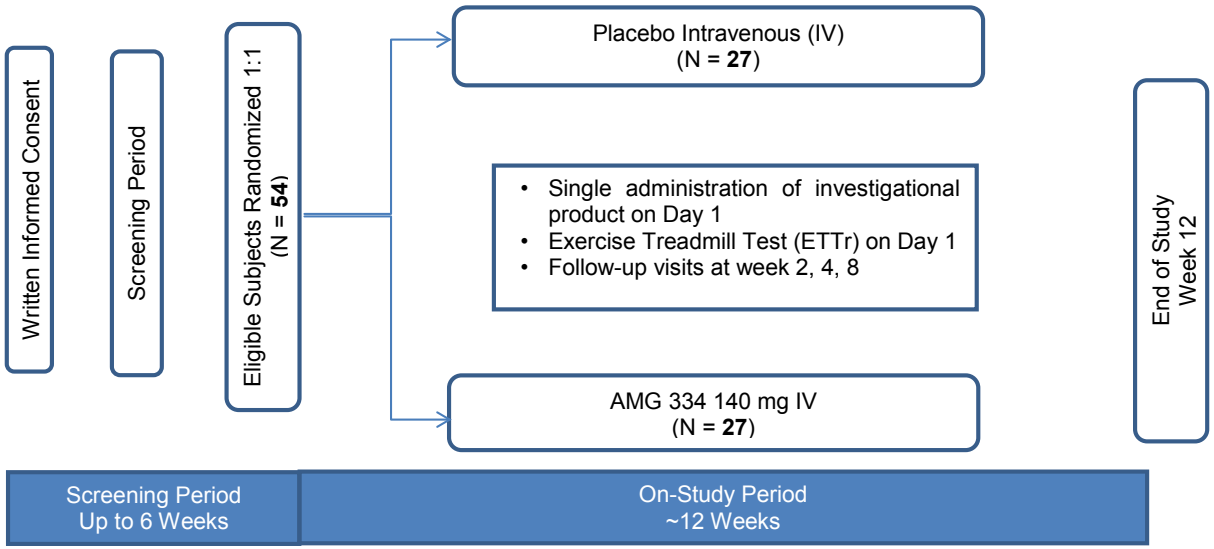
In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). A two-sided 90% confidence interval (CI) for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -**9**0 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

Section: Study Design and Treatment Schema

Replace:



With:


Written Informed Consent
Screening Period
Eligible Subjects Randomized 1:1 (N = 54)
Placebo Intravenous (IV) (N = 27)
• Single administration of investigational product on Day 1
• Exercise Treadmill Test (ETTr) on Day 1
• Follow-up visits at week 2, 4, 8
AMG 334 140 mg IV (N = 27)
End of Study Week 12
Screening Period Up to 6 Weeks
On-Study Period ~12 Weeks

Section: Study Glossary

Delete:

Abbreviation or Term	Definition/Explanation
~~AE~~	~~Adverse Event~~
~~SAE~~	~~Serious Adverse Event~~

Replace:

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study (ie, study week 12)

With:

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	defined as when the last subject is assessed or **participates in study procedures** for evaluation in the study (ie, study week 12)

Section: 2.6 Clinical Hypothesis

Replace:

The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in exercise duration, compared to placebo and that the true treatment difference in change from baseline in exercise duration is -60 seconds or more.

With:

The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in **TET**, compared to placebo and that the true treatment difference in change from baseline in exercise duration is **less than a 9**0 **second decrease**.

Section: 3.1 Study Design

Replace:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. Approximately 120 subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes)

of the 2 qualifying ETTs performed during screening. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

With:

This is a phase 2a, multicenter, randomized, double-blind, placebo-controlled study in subjects with stable angina. **At least 54** subjects will be randomized in a 1:1 ratio to receive either a single dose of AMG 334 or placebo prior to completing an ETT. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. Treatment group will be blinded to the investigator, subjects, and the Amgen study team.

Section: 3.3 Number of Subjects

Replace:

Approximately 120 subjects will be enrolled in this study (60 subjects in the placebo group and 60 in the AMG 334 group). Refer to Section 10.2 for sample size considerations.

With:

At least 54 subjects will be enrolled in this study (**27** subjects in the placebo group and **27** in the AMG 334 group). Refer to Section 10.2 for sample size considerations.

Section: 3.5.2 End of Study

Replace:

Final completion: The end of study ([EOS], end of trial) is defined as the time when the last subject is assessed or receives an intervention for evaluation in the study (ie, study week 12).

With:

Final completion: The end of study ([EOS], end of trial) is defined as the time when the last subject is assessed or **participates in study procedures** for evaluation in the study (ie, study week 12).

Section: 4.1.1 Inclusion Criteria

Replace:

106 Completes 2 qualifying ETTs during screening period (as described for Screening in Section 7.3.8). The following ETT qualifications are required:

a. Limitation of exercise due to symptoms related to myocardial ischemia (such as angina pectoris, chest pain/discomfort, dyspnea, shortness of breath), or ≥ 3 mm ST segment depression
b. ≥ 1.0 mm ischemic ST-segment depression during exercise performance
c. Exercise duration of ≥ 3 to ≤ 12 minutes, and
d. ≤ 1 minute difference or within 20% duration (using the longest duration qualifying ETT) in TET between the 2 qualifying ETTs
e. ECG tracings from screening ETTs are acceptable to the core ECG laboratory

With:

106 Completes 2 qualifying ETTs during screening period (as described for Screening in Section **7.3.7 and Section** 7.3.8). The following ETT qualifications are required:

a. Limitation of exercise due to symptoms related to myocardial ischemia (such as angina pectoris, chest pain/discomfort, dyspnea, shortness of breath), or ≥ 3 mm ST segment depression
b. ≥ 1.0 mm ischemic ST-segment depression during exercise performance
c. Exercise duration of ≥ 3 to ≤ 12 minutes, and
d. ≤ 1 minute difference or within 20% duration (using the longest duration qualifying ETT) in TET between the 2 qualifying ETTs
e. ECG tracings from screening ETTs are acceptable to the core ECG laboratory

Section: 5 Subject Enrollment, Paragraph 4

Add:

If for any other reason a subject should fail screening as a result of technical difficulties while conducting the ETTs during screening these cases should be reviewed, and it will be at Amgen discretion whether re-screening will be permitted.

Section: 5.1 Randomization/Treatment Assignment

Replace:

Randomization must occur on day 1 pre-dose and after the completion of procedures associated with the end of the screening phase.

Subjects will be randomized in a 1:1 allocation ratio to a single dose of AMG 334 or placebo prior to completing an ETT with approximately 60 subjects assigned to each treatment group. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. The randomization will be performed by IVRS/IWRS. Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

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

With:

Randomization must occur on day 1 pre-dose and after the completion of procedures associated with the end of the screening phase.

Subjects will be randomized in a 1:1 allocation ratio to a single dose of AMG 334 or placebo prior to completing an ETT with approximately **27** subjects assigned to each treatment group. Randomization will be stratified by the TET average (< 7 minutes or ≥ 7 minutes) of the 2 qualifying ETTs performed during screening. The randomization will be performed by IVRS/IWRS. Treatment groups will be blinded to the investigator, subjects, and the Amgen study team.

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

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

Replace:

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

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 on-study period are to return for all other study procedures until the end of the double-blind on-study period and study procedures for early termination (ET) visit, 12 weeks after the last dose of investigational product. If subjects refuse to complete all remaining study visits, then they should complete the ET visit.

End of investigational product and early discontinuation from investigational product are to be registered in the IVRS/IWRS.

With:

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

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 **are randomized but do not receive investigational product or receive partial dose** are to **remain on study and follow** all other study procedures until the end of the study. If subjects refuse to complete all remaining study visits, they should complete the **early termination (**ET**)** visit.

End of investigational product and early discontinuation from investigational product are to be registered in the IVRS/IWRS.

Section: 7.1 Schedule of Assessments

Replace:

Table 1. Schedule of Assessments

Procedure	Screening Period (up to 6 weeks) Screening Visits[l]					On-Study Period (12 weeks) On-Study Visits[l]				EOS/ET
	Visit 1	Visit 2	Visit 3	Visit 4[k]	Day 1 Pre-dose[a]	Day 1 Post-dose	Week 2[h]	Week 4	Week 8	Week 12
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[b]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[c]		X[c]	X[c]	X[c]		X				
Blood Pressure, Heart Rate[d]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[e]		Record Continuously								
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[f] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[g]				
Biomarker Sampling					X					
Urine drug screen[j]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.
[a] Pre-dose assessments should be conducted on day 1 prior to randomization.
[b] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.
[c] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria**,** and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.
[d] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.
[e] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.
[f] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.
[g] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).
[h] Visit at week 2 can be done via telephone contact.
[i] Study visit windows are ± 1 week.
[j] Urine drug screen may also be performed as needed throughout the study per investigator judgment.
[k] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

With:

Table 1. Schedule of Assessments

	Screening Period (up to 6 weeks) Screening Visits				On-Study Period (12 weeks) On-Study Visits[j]					EOS/ET
					Day 1					
Procedure	**Visit 1[a]**	**Visit 2[a]**	**Visit 3**	**Visit 4[l]**	**Pre-dose[b]**	**Post-dose**	**Week 2[i]**	**Week 4**	**Week 8**	**Week 12**
General and Safety Assessments										
Informed Consent	X									
Physical Examination, including weight	X									X
Targeted Medical/Surgical History	X									
Height	X									
Randomization[c]					X					
Columbia-Suicide Severity Rating Scale	X				X			X	X	X
ETT[d]		X[d]	X[d]	X[d]		X				
Blood Pressure, Heart Rate[e]	X				X	X		X	X	X
ECG	X									
Concomitant Medications	X	Record Continuously								X
Serious Adverse Events	X	Record Continuously								X
Adverse Events and Disease Related Events						X	Record Continuously			X
Collection of Events for Adjudication						X	Record Continuously			X
Angina diary[f]	**X**	Record Continuously								**X**
Laboratory Assessments										
Hematology, Chemistry (central laboratory)	X				X					X
Hepatitis Sample Collection	X									
Urine pregnancy test[g] (females of reproductive potential)	X				X					X
Pharmacokinetic Sampling						X[h]				
Biomarker Sampling					X					
Urine drug screen[k]	X									
Dosing										
AMG 334 or Placebo						X				

Footnotes defined on next page

ECG = electrocardiogram; EOS = end of study; ET = early termination; ETT = Exercise Treadmill Test; PK = pharmacokinetic.

[a] **Visits 1 and 2 in the Screening period may be combined. In the case where visits 1 and 2 are combined, all visit 1 assessments must be completed prior to the ETT for visit 2. The laboratory assessment results do not need to be reviewed prior to the ETT for visit 2, but must be reviewed prior to subsequent ETT (or before randomization).**

[b] Pre-dose assessments should be conducted on day 1 prior to randomization.

[c] Week 1 begins on the date of randomization. Study day 1 is defined as the date investigational product is received.

[d] During the screening period, two ETTs are required > 48 hours and ≤ 14 days apart that meet inclusion criteria**,** and they will be reviewed by a core ECG laboratory to confirm eligibility. No more than 3 ETTs can be performed during the screening period. Each ETT should occur within 14 days of each other and the total screening period for ETTs should not exceed 28 days.

[e] Blood pressure and heart rate should be assessed at all visits following the standard procedure. During ETT visits, the standard procedure will be conducted prior to the ETT; blood pressure assessments will also be conducted following the monitoring procedure described for the ETT.

[f] Angina diary will be completed by subjects beginning on the day of Visit 1 and through the EOS/ET visit to record angina episodes not occurring during ETTs.

[g] Results of pre-dose pregnancy test must be reviewed prior to administration of investigational product on day 1.

[h] PK sample to be drawn on day 1 after completion of exercise treadmill test post-randomization (ETTr).

[i] Visit at week 2 can be done via telephone contact.

[j] Study visit windows are ± 1 week.

[k] Urine drug screen may also be performed as needed throughout the study per investigator judgment.

[l] Optional Visit 4 to be performed if ETT3 is required for eligibility determination.

Section: 7.3.8.1 Screening

Add:

For further guidance please refer to the EET study manual that outlines site requirements for conduct, tracing requirements, scheduling, and shipping procedures for all ETTs to be performed by a subject.

Section: 10.2 Sample Size Considerations

Replace:

The primary endpoint is the change from baseline in TET. Assuming between-subject standard deviation for change from baseline in exercise duration of 130 seconds (Chaitman et al., 2004), with a planned study size of at least 59 subjects in each group and a difference in change from baseline in exercise duration of 0 seconds between AMG 334 group and placebo group, there is an 80% probability (power) that the lower bound of the 90% confidence interval (CI) will exceed -60 seconds (Chaitman et al., 2012). Sixty-two subjects are needed in each group if considering 5% dropout.

When approximately 80 subjects have been enrolled, Amgen may choose to alter the sample size based on the blinded variance in the pooled treatment groups.

With:

The primary endpoint is the change from baseline in TET. Assuming between-subject standard deviation for change from baseline in exercise duration of 130 seconds (Chaitman et al., 2004), with a planned study size of at least **27** subjects in each group and a difference in change from baseline in exercise duration of 0 seconds between AMG 334 group and placebo group, there is an 80% probability (power) that the lower bound of the 90% confidence interval (CI) will exceed -**9**0 seconds. **A margin larger than - 60 seconds between groups was required to accommodate the 60 second or 20% difference allowed in qualifying TETs for each subject. Because of this within-subject TET variation, a maximum TET difference of 90 seconds between the AMG 334 group and placebo group was considered reasonable in this study. As such, a margin of - 90 secs was selected, which corresponds to the margin used in a previous study testing a comparable hypothesis (Patterson, et. al 2005). Twenty-nine** subjects are needed in each group if considering 5% dropout.

When approximately **45** subjects have been enrolled, Amgen may **conduct a blinded sample re-estimation and** choose to alter the sample size based on the blinded variance in the pooled treatment groups.

Section: 10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Replace:

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2.3).

Staff from Clinical Supply Chain, Biological Sample Management, PK and Drug Metabolism, Clinical Immunology, Clinical Pharmacology, 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.

With:

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 unblinded except as specified (eg, Section 5.2 and Section 9.2.2.3). **With the exception of site staff and subjects, the study will be unblinded at the time of the primary analysis. Complete unblinding of the study will occur at the final analysis.**

Staff from Clinical Supply Chain, Biological Sample Management, PK and Drug Metabolism, Clinical Immunology, Clinical Pharmacology, 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.

Section: 10.4.1 Primary Analysis

Replace:

The primary analysis for the study will be performed after all subjects have completed the ETTr.

With:

The primary analysis **of the primary and secondary endpoints** will be performed after all subjects have completed the ETTr.

Section: 10.5.3 Primary Efficacy Endpoint

Replace:

The primary endpoint is the change from baseline in exercise duration. The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change from baseline in exercise duration, compared to placebo, and that the true treatment difference in change from baseline in exercise duration is -60 seconds or more.

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or ≥ 7 minutes). A two sided 90% CI for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -60 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

With:

The primary endpoint is the change from baseline in exercise duration **as measured by TET during the ETT**. The primary hypothesis is that AMG 334 does not significantly decrease exercise capacity, as measured by change **in TET** compared to placebo, and that the true treatment difference in change from baseline in exercise duration is **less than a 9**0 second **decrease**.

In the primary analysis, the primary endpoint will be analyzed using an analysis of variance model with terms for treatment group and randomization strata (< 7 or

≥ 7 minutes). A two sided 90% CI for the mean difference in change from baseline in exercise duration will be calculated. If the lower bound of the CI of the difference is more than -**9**0 seconds, then the hypothesis that AMG 334 does not decrease exercise duration will be supported. The mean change from baseline in exercise duration for each treatment group and the 90% CIs will be reported.

Section: References

Add:

Patterson D, Kloner R, Effron M, et al. The effect of tadalafil on the time to exercise-induced myocardial ischaemia in subjects with coronary artery disease. Br J Clin Pharmacol. 2005, 60:459-468.