NOVARTIS

Global Clinical Development - General Medicine

AMG 334

Clinical Trial Protocol CAMG334A2302 / NCT03333109

A 12-week double-blind, randomized, multi-center study comparing the efficacy and safety of once monthly subcutaneous AMG 334 against placebo in adult episodic migraine patients (EMPOwER)

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Table of contents

[redacted]

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[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

γGT	Gamma-glutamyl transferase
ACE/ARB	Angiotensin-Converting Enzyme inhibitor/Angiotensin-Receptor Blocker
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARS	All randomized set
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical classification
BOCF	Baseline observation carried forward
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
BUN	blood urea nitrogen
CM	Chronic migraine
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	Code of Federal Regulation
CGRP	Calcitonin Gene-related Peptide
CMH	Cochran-Mantel-Haenszel
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcomes Assessment
CPK	creatine phosphokinase
CRA	Clinical research associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Toxicity Criteria
DBTP	Double-Blind Treatment Period
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram

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EDC	Electronic Data Capture
EM	Episodic migraine
EQ-VAS	EuroQual visual analog scale
EU	European Union
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
GCP	Good Clinical Practice
HA	Health authority
HepBcAb	Hepatitis B core antibody
HepBsAg	Hepatitis B surface antigen
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator notification
IPD	Important protocol deviations
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-uterine device
IUS	Intra-uterine system
LDL	low density lipoprotein
LFT	Liver function test
LPLT	Last patient last treatment
LPLV	Last patient last visit
LSM	Least square means
MAR	Missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

[redacted]

MedDRA	Medical dictionary for regulatory activities
mg/ml	milligram(s) per milliliter
MI	Multiple imputation
MNAR	Missing not at random
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)
PFS	Pre-filled syringe
PK	pharmacokinetic(s)
PRO	Patient-reported outcome
QM	Quality management
RBC	red blood cell(s)
RDW	Red cell distribution width
sc	subcutaneous
SAE	serious adverse event
SAP	Statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
SY	Subject years
TIA	Transient ischemic attack
ULN	Upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization

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Glossary of terms

Assessment	A procedure used to generate data required by the study
[redacted]	[redacted]
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (eg 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (ie prior to starting any of the procedures described in the protocol)
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
QTcF	Fridericia QT correction formula
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject

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	withdrawal
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	CAMG334A2302
Full Title	A 12-week double-blind, randomized, multi-center study comparing the efficacy and safety of once monthly subcutaneous AMG 334 against placebo in adult episodic migraine patients
Brief title	Study of efficacy and safety of AMG 334 in adult episodic migraine patients
Sponsor and Clinical Phase	Novartis Phase 3
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to obtain data from regions not adequately represented in the phase 2/3 trials, and to support registration in countries beyond the European Union (EU) and United States (US), particularly those requiring local data for regulatory approval (India, Korea, and Taiwan). It has a similar design to the Phase 3 studies in EM in order to allow bridging to the broader AMG 334 development program encompassing both episodic and chronic migraine patients, and support a broad label of "prophylaxis of migraine in adults".
Primary Objective(s)	The primary objective is to evaluate the effect of AMG 334 compared to placebo by measuring the change in monthly migraine days from baseline to the last month (Month 3) of the double-blind treatment period (DBTP).
Secondary Objectives	Objective 1: To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects as measured by the achievement of at least a 50% reduction from baseline in monthly migraine days at Month 3 Objective 2: To evaluate the effect of AMG 334 compared to placebo as measured by the change from baseline in monthly acute migraine-specific medication treatment days at Month 3 Objective 3: To evaluate the safety and tolerability of AMG 334 as measured by adverse event frequency, clinical laboratory value changes, vital sign changes, and the presences of anti-AMG 334 antibodies Objective 4: To evaluate the effect of AMG 334 compared to placebo on change from baseline in headache impact scores as measured by change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6) at Month 3
Study design	This study uses a single-cohort, 3-treatment arm, randomized (2:3:3 (140 mg: 70 mg: placebo)), double-blind study design in adult patients with episodic migraine. . A screening period of 2 weeks will be used to assess initial eligibility, followed by a 4-week baseline period to assess diary compliance and headache frequency. . Eligible patients will then be randomized to either AMG 334 or placebo for 12 weeks, followed by a 12-week follow-up period.
Population	The study population will consist of male and female patients, ages 18 to 65, with a documented history of episodic migraine as outlined in the inclusion criteria. .

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	Approximately 880 patients will be randomized in an estimated 100 centers worldwide. Assuming a 40% screening failure rate, approximately 1467 patients are anticipated to be screened.

Key Inclusion criteria	• Adults ≥ 18 to ≤ 65 years of age
	• History of migraine (with or without aura) for ≥ 12 months prior to screening
	• Migraine frequency 4-14 migraine days per month on average across the 3 months prior to screening (refer to Section 6.4.1 for the definition of migraine day)
	• Headache frequency < 15 headache days per month on average across the 3 months prior to screening (refer to Section 6.6.1 for the definition of headache day)
	• Migraine frequency 4-14 migraine days during the baseline phase based on the eDiary calculations
	• Headache frequency < 15 headache days during the baseline phase based on the eDiary calculations
	• At least 80% compliance with the eDiary during the baseline phase
	• Older than 50 years of age at migraine onset
	• No therapeutic response with > 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:
	  • Category 1: Divalproex sodium, sodium valproate
	  • Category 2: Topiramate
	  • Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
	  • Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
	  • Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
	  • Category 6: Flunarizine, verapamil
	  • Category 7: Lisinopril, candesartan

Key Exclusion criteria	• Used a prohibited medication, device, or procedure within 2 months prior to the start of or during the baseline phase, or during the DBTP (Refer to Section 5.5.8 for the list of these excluded treatments)
	• Received botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline phase or during the baseline phase
	• Taken the following for any indication in any month during the 2 months prior to the start of the baseline phase:
	  • Ergotamines or triptans on ≥ 10 days per month, or
	  • Simple analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or
	  • Opioid- or butalbital-containing analgesics on ≥ 4 days per month

Study treatment	• AMG 334 70 mg/1 mL pre-filled syringe • Matching placebo in 1 mL pre-filled syringe, identical in appearance
Efficacy assessments	• Migraine days
Key safety assessments	• Adverse event monitoring • Physical examinations

[redacted]

Other assessments	• Laboratory evaluations, including anti-AMG 334 antibody testing • ECG • Patient reported outcomes (PROs) • Headache Impact Test-6 (HIT-6) 
Data analysis	The primary efficacy endpoint variable will be analyzed using a generalized linear mixed model based on observed monthly data during the DBTP and pairwise comparisons will be conducted. The secondary efficacy endpoints will be analyzed using a linear mixed effects model similar to the primary endpoint. The dichotomous endpoints will be analyzed by Cochran-Mantel-Haenszel (CMH) test with patients who are missing monthly migraine day data at Month 3 of the DBTP imputed as non-responders. Nominal 95% confidence intervals and p-values will be reported. A hierarchical gate-keeping procedure and the Hochberg method will be used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints.
Key words	AMG 334, erenumab, migraine, episodic, headache, CGRP

1 Introduction

1.1 Background

Migraine is a common world-wide occurring neurological disorder throughout all regions and ethnicities with a high global prevalence, significant socio-economic burden and substantial impairment and disability of affected patients. It is mainly characterized by recurrent headache lasting 4-72 hours but is usually accompanied by other neurological disturbances, nausea, vomiting and other nonspecific symptoms. The patient burden and disability as well as the societal impact increase with higher attack frequency, which is why the spectrum of migraine disorders is typically described according to frequency of migraine days per month. "Episodic migraine" (EM) is characterized by the presence of 4 to 14 migraine days per months, while "Chronic migraine" (CM) is defined as 15 or more headache days per months, at least 8 out of which have to be typical migraine days.

Migraineurs are currently being treated for migraine prophylaxis by a variety of drug classes, many of them being used off-label and often based on insufficient or limited evidence. All of these therapies are commonly associated either with variable efficacy and/or substantial tolerability issues that often leads to treatment discontinuation in migraine patients. The standard of care also varies significantly across different geographies and treatment decisions are often made on a case-by-case basis without general consensus on treatment guidelines.

Nontraditional therapies such as herbal medicines, supplements, acupuncture and other therapies also have some role in migraine prophylaxis. While the evidence supporting their use is minimal and often controversial (Gooriah et al 2015), they are very common in the Asian region, and becoming more widespread and increasingly introduced into mainstream Western healthcare.

Common prophylactic drugs or drug classes being used include beta blockers, topiramate, valproate, antidepressants (mainly amitriptyline and venlafaxine), flunarizine, and certain angiotensin-converting-enzyme inhibitor/angiotensin II receptor blockers (ACE/ARBs) such as lisinopril and candesartan. Botulinum toxin (Botox®) is approved in many countries for CM use, but not for EM.

Based on emerging evidence, Calcitonin Gene-related Peptide (CGRP) is a neuropeptide that prominently contributes to migraine pathophysiology. The potential mechanisms of action of CGRP receptor antagonists involve components of the trigeminal-vascular system and include normalization of CGRP-induced vasodilation, reduction of CGRP-induced neurogenic inflammation, and inhibition of pain transmission at the trigeminal ganglion and trigeminal nucleus (Wang et al 1995, Zimmermann et al 1996, Durham 2006). CGRP is an attractive target for the development of a migraine-specific prophylactic therapy with the aim of minimizing migraine days and improving patient quality of life in this common and often disabling disorder.

AMG 334 is a fully human monoclonal antibody targeting the CGRP receptor under development for migraine prophylaxis in adults. . To date studies have been, or are currently being, conducted in North America, Europe, and Japan.

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Results from the AMG 334 Phase 2 study (Study 20120178) in patients with episodic migraine demonstrated that the 70 mg dose resulted in statistically significant and clinically meaningful reductions in monthly migraine days at Week 12 compared with placebo. The 70 mg dose produced statistically significant improvements in multiple secondary and exploratory outcome measures, including the 50% responder rate, monthly headache days, and monthly migraine-specific medication treatment days. Exposure-response pharmacokinetic (PK) analyses over a large range of PK exposures indicated that 70 mg was the lowest dose resulting in efficacious concentrations and potentially higher efficacy could be achieved with 140 mg. Based on this results, a higher dose of 140 mg was incorporated into the following pivotal studies. Results from the AMG 334 Phase 2 study (Study 20120295) in patients with chronic migraine also showed a positive outcome. Patients randomized to the 70 mg and 140 mg dose groups experienced a mean 6.6-day reduction from baseline in monthly migraine days during Weeks 9-12 in both groups. The results were statistically significant compared with 4.2 days observed in the placebo group. The 50% responder rate was increased to 39.9% and 41.2% with 70 mg and 140 mg AMG 334 respectively compared to 23.5% with placebo (Tepper et al 2016a). Both doses were also effective across various other endpoints including frequency-related outcomes and functional improvement measured by established Patient Reported Outcome (PRO) scales (Tepper et al 2016b).

The results from two recently completed Phase 3 studies (Studies 20120296, 70 and 140 mg, and 20120297, 70 mg) in patients with episodic migraine, also showed positive outcomes for AMG 334. In study 20120297, patients randomized to the 70 mg dose group experienced a 2.9-day reduction from baseline in monthly migraine days compared with 1.8 days observed in the placebo group with the difference being statistically significant. In study 20120296, patients randomized to the 70 and 140 mg dose groups experienced mean 3.2 and 3.7-day reductions from baseline, respectively compared with a 1.8 days observed in the placebo group over weeks 13-24. Results for both of these studies were statistically significant. 50% responder rates were significantly increased with AMG 334 compared to placebo in both of the Phase 3 episodic migraine studies. Treatment effects observed with 140 mg in study 20120296 showed consistently higher values across different parameters and subgroups compared to placebo than the 70 mg group, suggesting additional efficacy in patients with episodic migraine.

The safety and tolerability profile of AMG 334 was similar to placebo in both treatment groups for all studies. No adverse event (AE) occurred with an incidence of > six percent; the most commonly reported adverse events included injection site pain, infection of the upper respiratory tract and nausea. The only potentially dose-related event observed so far was mild/transient cases of constipation. Otherwise, the safety and tolerability profile of both doses is very comparable and overall similar to placebo across the Phase 2/3 study program. In the absence of a clear dose-dependent safety signal and the overall efficacy trend in favor of 140 mg, 140 mg dose is considered to have the best benefit-risk ratio across the entire spectrum of migraine.

Overall, the clinical program mainly has been conducted in the US and Europe and includes Caucasian patients and minorities that were primarily included in the US. Ethnic subgroups have been analyzed as appropriately but yield only very small numbers and therefore limited information is available. In the Asian region, only one phase 1 study (Study 20120130) has been conducted in Japan (up to 140 mg in Japanese healthy subjects) and there is an additional

[redacted]

ongoing phase 2 study in Japan (including doses of 28 mg, 70 mg and 140 mg). Based on the available data, PK profiles of erenumab appeared to be similar between Japanese and Caucasians.

In view of limited information on ethnic subgroups beyond Caucasians, this trial will provide additional information about erenumab safety and efficacy in these populations, in addition to providing local data in countries where local exposure is required for regulatory submission.

1.2 Purpose

The purpose of this study is to obtain data from regions not adequately represented in the phase 2/3 trials, and to support registration in countries beyond the EU and US, particularly those requiring local data for regulatory approval (India, Korea, and Taiwan). It has a similar design to the Phase 3 studies in EM in order to allow bridging to the broader AMG 334 development program encompassing both episodic and chronic migraine patients, and support a broad label of "prophylaxis of migraine in adults".

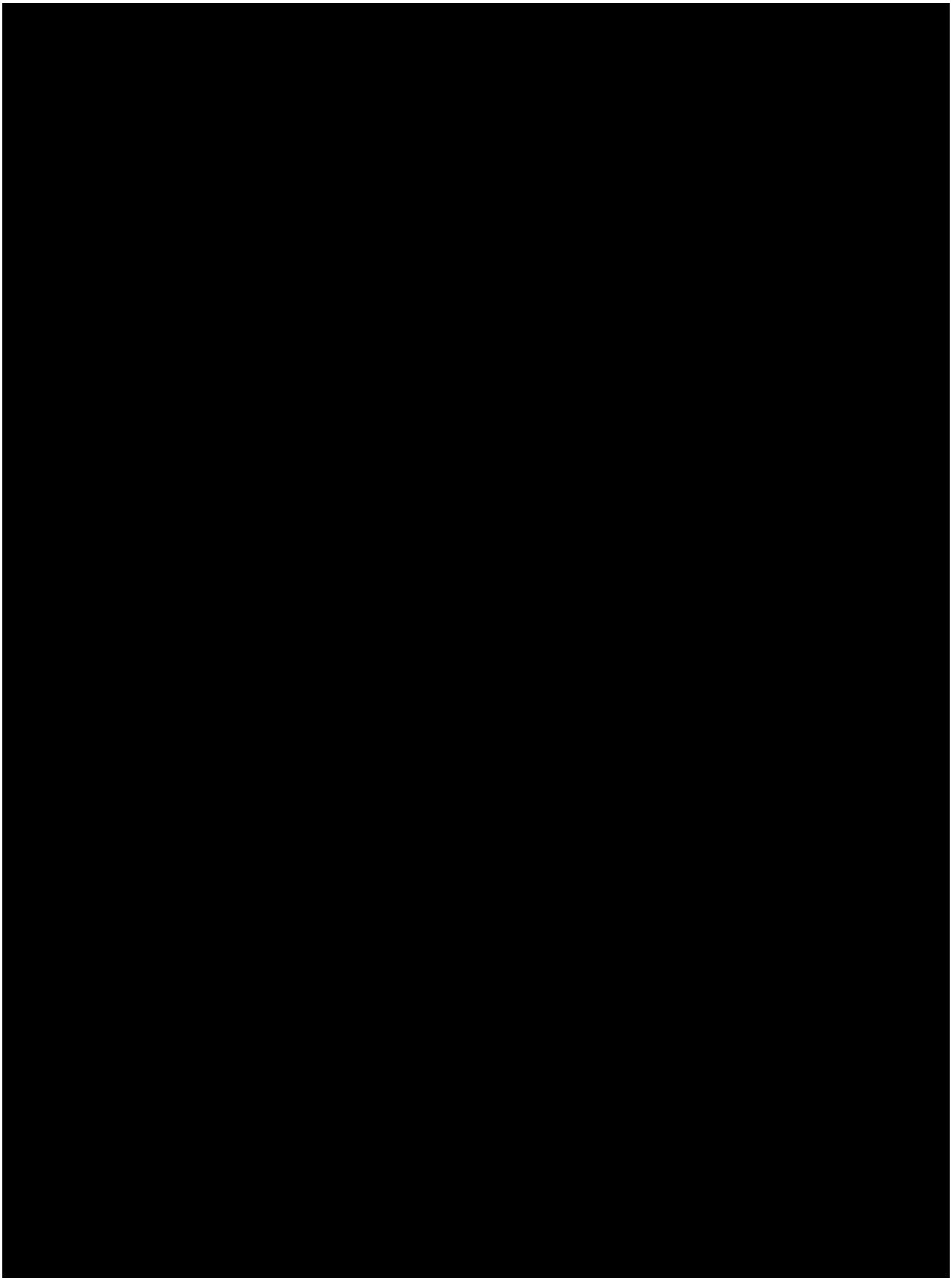
2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	***Endpoint(s) for primary objective(s)***
• To evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly migraine days, in subjects with episodic migraine	• Change from baseline in monthly migraine days at the last month (Month 3) of the double-blind treatment period (DBTP)
Secondary objective(s)	***Endpoint(s) for secondary objective(s)***
• To evaluate the effect of AMG 334 compared to placebo on the proportion of subjects with at least 50% reduction from baseline in monthly migraine days	• Achievement of at least a 50% reduction from baseline in monthly migraine days at Month 3
• To evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly acute migraine-specific medication treatment days	• Change from baseline in monthly acute migraine-specific medication treatment days at Month 3
• To evaluate the safety and tolerability of AMG 334	• Adverse events, clinical laboratory values, vital signs, and anti-AMG 334 antibodies
• To evaluate the effect of AMG 334 compared to placebo on change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6)	• Change from baseline in headache impact scores as measured by the HIT-6 at Month 3

[redacted]



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3 Investigational plan

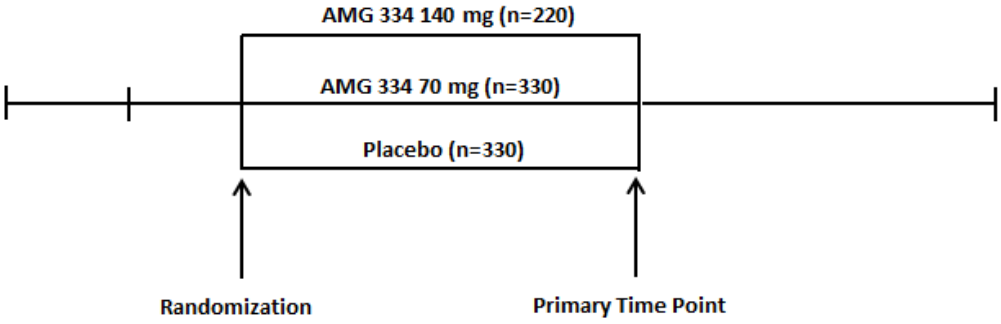
3.1 Study design

This study uses a single-cohort, 3-treatment arm, randomized (2:3:3 [140 mg: 70 mg: placebo]), double-blind study design in adult patients with episodic migraine. . A screening period of 2 weeks will be used to assess initial eligibility, followed by a 4-week baseline period (the maximum duration for the baseline period is 35 days), during which diary compliance and headache frequency will be assessed for a final eligibility assessment prior to randomization and dosing. After randomization/Day 1, visits will occur at four week intervals until Week 12, which is the End of Treatment visit, Last Patient Last Treatment (LPLT). The final visit, Last Patient Last Visit (LPLV), a Safety Follow-Up visit, will occur 12 weeks later, at Week 24.

A blinded interim analysis after approximately 50% patients have completed the DBTP will be conducted to re-estimate the sample size by providing information on the variance for this trial relative to the planning assumptions to account for potential higher variability in Asian countries/new sites.

End of Trial will occur when the last patient completes their last visit (LPLV) of the study.

Figure 3-1 Study Design Schematic



Screen	Baseline	Double-Blind Treatment	Follow-Up
2 weeks	4 weeks	12 weeks	12 weeks

3.2 Rationale for study design

The patient population will be described in more detail in the Section 4 below.

[redacted]

This study design has been chosen in line with the AMG 334 Phase 3 study designs, which were developed in accordance with the International Headache Society (IHS) guidelines for Controlled Trials of Drugs in Migraine (Tfelt-Hansen 2012), including input from leading clinical migraine experts and regulatory authorities in the US, EU, Canada and Japan. A parallel-group, placebo-controlled design is a standard way of assessing efficacy and safety of new migraine prophylactic agents.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Phase 2 results for AMG 334 in EM patients are available for the doses of 7 mg and 21 mg (both of which have proven to be ineffective compared to placebo) and 70 mg, which has been shown to be effective. The PK of AMG 334 at 70 mg SC were similar for healthy Japanese and white subjects (ratio of geometric means [ie, Japanese/white] for Cmax, AUClast, and AUCinf = 1.02, 1.12, and 1.12, respectively). PK-exposure response modelling suggests that with higher doses, a potential additional benefit in terms of efficacy might be observed. The safety profile of AMG 334 has been investigated up to 280 mg in healthy volunteers in Phase 1 without a difference in safety profile. For these reasons, an additional dose of 140 mg was introduced into the CM Phase 2b trial as well as one of the Phase 3 trials for EM.

Results from the CM Phase 2b trial (Study 20120295) showed statistically significant and comparable results in both dose groups across the majority of endpoints, subgroups and timepoints. In the recently completed 20120296 trial in EM that included both 70 mg and 140 mg AMG 334, consistently higher treatment effects were observed with 140 mg and are considered clinically meaningful across different endpoints in the full population. This was also observed consistently across patient subgroups, suggesting additional efficacy for 140 mg in patients with episodic migraine in general.

The safety and tolerability profile of AMG 334 is comparable across both 70 mg and 140 mg. The only potentially dose-related adverse event observed in the trials completed to date has been constipation, which was observed in 4.3%/3.4% of patients with 140 mg in CM/EM compared to 0%/1.6% of patients with 70 mg in CM/EM. The cases of constipation were usually mild, transient and not clinically relevant.

Both the route of administration (subcutaneous injection) and the investigation of the 70 mg and 140 mg doses of AMG 334 are in line with the phase 2/3 trials and support the “bridging” approach of this trial to the broader AMG 334 development program. The 3-month study duration is endorsed by IHS guidelines as a sufficient duration to assess efficacy in prophylactic migraine treatment clinical trials.

3.4 Rationale for choice of comparator

The choice of a specific therapy for a migraine headache prophylactic often takes into account individual circumstances, comorbidities and patient preferences. Patients are currently being treated by a variety of drug classes that were originally developed for other indications, but were repurposed for migraine prophylaxis. Some drugs have been formally approved for migraine prophylaxis in many countries; the most common approved drugs are propranolol, metoprolol, topiramate and flunarizine. In some countries, additional choices exist that are

[redacted]

only approved and/or available on a national level. Other drugs, while not formally approved, are considered acceptable alternatives and are recommended within national treatment guidelines. Examples with evidence for migraine headache prophylaxis include other drug classes such as antidepressants (mainly amitriptyline and venlafaxine), ACE/ARBs (mainly candesartan and lisinopril) and valproate/divalproex. All of those drugs are occasionally used as migraine prophylactics, but the use is off-label and rests on the individual clinical responsibility of the prescribing physician after an adequate individual benefit-risk assessment.

All of these therapies, regardless if approved or off-label, are commonly associated either with variable migraine efficacy and/or substantial tolerability issues that often lead to treatment discontinuation. The standard of care also varies significantly across different geographies and treatment decisions, particularly in patients that have already failed the standard first line therapies are often made on a case-by-case basis without general consensus on treatment guidelines. Because of the variability of standard of care across different geographies and the potential for functional unblinding due to typical adverse events with any active comparator, placebo was selected as the comparator. The short duration (12 weeks) of placebo treatment, in conjunction with the allowed use of acute migraine treatment, justifies the use of placebo in this study as also suggested in the IHS guidelines (Tfelt-Hansen 2012). All patients continue to receive best supportive care in form of acute abortive medications and other non-pharmacological interventions as appropriate.

3.5 Purpose and timing of interim analyses/design adaptations

A blinded interim assessment is planned after about 50% of subjects have completed their DBTP, including early withdrawals, to provide additional information on the variance of the primary endpoint in this trial. The purpose of this blinded interim analysis is to account for potential higher variability in new countries and sites and possibly modify the initially planned sample size as outlined in Section 9.7.

3.6 Risks and benefits

Key risks and benefits are briefly summarized below. For further information, please refer to the current Investigator Brochure.

As of 08-May-2017, the safety of AMG 334 in migraine prophylaxis was assessed from integrated safety analyses of 2537 migraine patients exposed to at least one dose of AMG 334, with a cumulative exposure of 2310.3 subject-years (SY). Overall, the safety and tolerability profile of AMG 334 was similar between the 140 mg and 70 mg doses and also comparable to placebo. Adverse drug reactions include injection site reactions, constipation, muscle spasms, and pruritus. The majority were mild or moderate in severity and rarely led to treatment discontinuation. To date, no important risk has been identified for AMG 334.

Overall, to date, there is no evidence from nonclinical and clinical data of risk of cardiovascular effects. On the theoretical basis of the mechanism of action of AMG 334, CGRP receptor blockade may reduce compensatory vasodilation, particularly under ischemic conditions. Therefore, cardiovascular effects continue to be monitored, and patients with pre-existing cardiovascular disease will be excluded from participation.

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All biologicals, including fully human proteins, have the potential to induce immunogenicity leading to the development of specific anti-drug antibodies. So far, the development of anti-AMG 334 antibodies has only been observed with low incidence and was not associated with specific adverse events or a clinically relevant reduction in AMG 334 plasma levels. Patients in clinical studies will continue to be monitored for the development of anti-AMG 334 antibodies and associated clinical sequelae.

Plasma levels of CGRP increase with advancement of pregnancy up to the time of delivery, followed by a sharp decline at term and postpartum in rats and humans. Endogenous CGRP may play an important role in maintaining normal fetoplacental development, fetal survival, and vascular adaptation during pregnancy. Women who are breastfeeding, pregnant, or planning to become pregnant are excluded from study participation, as well as patients who are unwilling to comply with the protocol-specified contraception requirements. All women of child bearing potential will be screened for pregnancy at each study visit.

An external data monitoring committee was established to review the AMG 334 safety data for Phase 2b and Phase 3a studies, and based on these data, recommended continuation of the program. The need for a data monitoring committee (DMC) for this study was assessed, and deemed not necessary because the safety profile of AMG 334 has already been well-characterized from 4 double-blind, placebo-controlled trials in over 2500 patients, and the ability to establish the DMC and meetings is limited due to the anticipated short patient recruitment duration and the double-blind duration of the study (12 weeks). The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and use of rescue medications.

Initial benefits for AMG 334 as a migraine prophylactic have been demonstrated in a Phase 2b trial (Amgen Study 20120178), in which 70 mg was established as the minimally effective dose in EM (Sun et al 2016) with a significant placebo-corrected reduction of 1.1 monthly migraine days compared to baseline, as well as positive results on most secondary endpoints, including 50% responder rate, reduction of acute medication use and overall headache hours.

Initial long-term data are available from the open-label extension of the Phase 2b EM Study 20120178. In the latest interim data cut (28-Jan-2016), efficacy data from 383 patients were included who received at least one dose of AMG 334 in the open-label treatment phase and had ≥ 4 migraine days at baseline of the double-blind treatment period. Sustained efficacy was observed in the open-label extension through Week 64 for reduction in monthly migraine days, responder rates and PRO endpoints (Ashina et al 2016).

Three additional Phase 2/3 studies, including 2 studies in EM, have been completed with AMG 334, which have established 70 mg and 140 mg as being effective and safe in patients with EM or CM, with a favorable benefit/risk profile. Positive treatment effects in general were observed in a robust way across typical migraine endpoints such as change in mean monthly migraine days, > 50% (and higher) responder rates, change in migraine-specific medication use and functional improvement by established PRO scales. Results were in general highly statistically significant and clinically meaningful. As described in Section 3.3, in episodic migraine a dose-dependent increase in efficacy has been observed for the 140 mg dose. Retention rates observed in clinical trials were very high (~95% with active treatment after 3 months and ~90% after 6 months with only minimal discontinuations attributed to

adverse events). This feature is important, as discontinuation rates are high for current migraine prophylaxis treatments, with the main drivers of discontinuation being either lack of efficacy or tolerability issues (Blumenfeld et al 2013). As such, there is a high unmet need for a therapy that is well-tolerated, has sustained response rates and excellent compliance.

Overall, given the characteristics of AMG 334 and the large experience in clinical trials, the overall benefit-risk assessment is supportive.

4 Population

The study population will consist of male and female patients, ages 18 to 65, with a documented history of episodic migraine as outlined in the inclusion criteria.

The goal is to randomize approximately 880 patients in approximately 100 centers worldwide. Assuming a 40% screening failure rate, approximately 1467 patients will be screened.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Adults ≥ 18 to ≤ 65 years of age upon entry into screening
3. History of migraine (with or without aura) for ≥ 12 months prior to screening according to the IHS Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or patient self-report
4. Migraine frequency 4 to 14 migraine days per month on average across the 3 months prior to screening (refer to Section 6.4.1 for the definition of migraine day)
5. Headache (ie, migraine and non-migraine headache) frequency < 15 headache days per month on average across the 3 months prior to screening (refer to Section 6.6.1 for the definition of headache day)
6. Migraine frequency 4 to 14 migraine days during the baseline period based on the eDiary calculations
7. Headache frequency < 15 headache days during the baseline period based on the eDiary calculations
8. Demonstrated at least 80% compliance with the eDiary (for example, completing eDiary items for at least 23 out of 28 days during the baseline period)

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Older than 50 years of age at migraine onset
2. History of cluster headache or hemiplegic migraine headache
3. Unable to differentiate migraine from other headaches
4. No therapeutic response with > 2 of the following 7 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:
    - Category 1: Divalproex sodium, sodium valproate

[redacted]

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

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

The following scenarios do not constitute lack of therapeutic response:

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

5. Used a prohibited medication, device, or procedure within 2 months prior to the start of or during the baseline period, or during the DBTP (Refer to Section 5.5.8 for the list of these excluded treatments)
6. Received botulinum toxin in the head and/or neck region within 4 months prior to the start of the baseline period or during the baseline period
7. Taken the following for any indication in any month during the 2 months prior to the start of the baseline period:
   - Ergotamines or triptans on ≥ 10 days per month, or
   - Simple analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) on ≥ 15 days per month, or
   - Opioid- or butalbital-containing analgesics on ≥ 4 days per month
8. Anticipated to require any excluded medication, device, or procedure during the study (Refer to Section 5.5.8 for the lists of these medications, devices, and procedures). Traditional medications and/or procedures are allowed if used at a stable dose/frequency for at least three months prior to randomization, and during the study
9. Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain)
10. History of major psychiatric disorder (such as schizophrenia and bipolar disorder), or current evidence of depression based on a Beck Depression Inventory (BDI)-II total score > 19 at screening. Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period.
11. History of seizure disorder or other significant neurological conditions other than migraine. Note: A single childhood febrile seizure is not exclusionary.
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

[redacted]

13. Human immunodeficiency virus (HIV) infection by history
14. 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
15. Myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening
16. History or evidence of any other unstable or clinically significant medical condition, that in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
17. Subject has any clinically significant vital sign, laboratory, or electrocardiogram (ECG) abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation
18. Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
19. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates)
20. Pregnant or nursing (lactating) women
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

[redacted]

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

22. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
23. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
24. Previously randomized into an AMG 334 study
25. Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (eg, independent completion of electronic diary [eDiary] items) to the best of the subject's and investigator's knowledge. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the investigational product listed below

- AMG 334 70 mg/1 mL pre-filled syringe
- Matching placebo in 1 mL pre-filled syringe, identical in appearance

The matching placebo to AMG 334 pre-filled syringe will have the same appearance as the investigational drug. Each syringe will be packaged individually in double-blinded fashion for the double-blind treatment period. The study treatments will be labeled as AMG 334 70 mg/1mL/Placebo.

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial. Rescue medication is allowed as outlined in Section 5.5.6.

5.2 Treatment arms

Patients will be assigned to either AMG 334 140 mg or 70 mg, or placebo at the Randomization Visit (Visit 110), in a 2:3:3 ratio, stratified by prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure).

Study medication will be provided as follows:

[redacted]

- Placebo: Two pre-filled 1 mL syringes (PFS) containing placebo identical in appearance to AMG 334
- 70 mg: One PFS containing 70 mg/1 mL of AMG 334 and one PFS containing placebo identical in appearance to AMG 334
- 140 mg: Two PFS, each containing 70 mg/1 mL of AMG 334.

5.3 Treatment assignment and randomization

At Visit 110 (Day 1), all eligible patients/subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by prior prophylactic migraine treatment failure according to the planned randomization ratio within each stratum. The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Patients/subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study; (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

[redacted]

Unblinding will only occur in the case of patient emergencies (see Section 5.6) and at the conclusion of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

[redacted]

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the Case Record Form (CRF) book with a matching Subject Number in the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate screening period CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 3 treatment arms. Investigator staff will identify the 2 study drug packages to dispense to the patient by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the

[redacted]

completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Subcutaneous (sc) injections are to be administered in the clinic by qualified staff at drug dispensing visit. For purposes of study treatment dosing, "qm" refers to an every 4 weeks injection regimen. The study drug administration date should be in 4 week increments (+/- 5 days) from the first dose of study drug. Any dose administrations that may occur greater than +/- 5 days from the 4 week time point (eg, patient unavailability) should be discussed with the Sponsor prior to dosing. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen; the location of the injection sites should be documented in the source document.

Two injections will be administered by qualified study staff at each dosing visit during the 12-week double-blind treatment period (ie, at Day 1 and Weeks 4 and 8). Patients will be administered one of the following, depending on their randomization:

- 140 mg AMG 334: two 70 mg/mL syringes
- 70 mg AMG 334: one 70 mg AMG 334 syringe and one placebo syringe
- Placebo: two placebo syringes

The investigator must promote compliance administering the study treatment exactly as prescribed. The investigational product dose is fixed and will not be adjusted for individual patients during the study. There are no temporal restrictions for study drug administration (eg, proximity to meals, sleep or activity).

All kits of study treatment assigned will be recorded in the IRT. Novartis monitors will reconcile treatment assigned vs treatment administered and ensure that the information is congruent during their monitoring visits.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational or other treatment dose adjustments are not permitted. For patients/subjects who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of investigational drug are permitted in order to keep the patient on study drug. These changes must be recorded on the appropriate CRF.

5.5.6 Rescue medication

Patients can continue to use "best supportive care". This can include both pharmacologic interventions (ie, abortive treatments for acute attacks) and non-pharmacologic interventions (eg, biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine). Traditional medications (eg, herbal medicines) are allowed as determined by the investigator, as long as the regimen is not likely to interfere with headache assessments. Chronically administered "best supportive care" should be in a stable regimen for at least 2 months prior to baseline.

[redacted]

Site staff will pre-specify the name, dose strength, and route of administration of the patient's acute headache (rescue) medications in the patient's eDiary. If the patient takes an acute headache medication during aura or to treat a migraine or non-migraine headache, they will select one of the pre-specified medications (or "other" medication) and enter the date of administration, the number of times the medication was taken on that date and number of units taken. Use of rescue medication must be recorded in the eDiary. Relevant non-drug therapies as part of "best supportive care" use should also be recorded in appropriate CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

1. The following medications used for any indication are excluded within 2 months prior to the start of the baseline period and throughout the study.
   - Divalproex sodium, sodium valproate, Topiramate, carbamazepine, gabapentin
   - Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol,propranolol, timolol)
   - Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
   - Venlafaxine, desvenlafaxine, duloxetine, milnacipran
   - Flunarizine, verapamil
   - Cyproheptadine
   - Pizotifen
   - Butterbur, feverfew, magnesium ($\geq$ 600 mg/day), riboflavin ($\geq$ 100 mg/day)
2. Botulinum toxin (in the head and/or neck region) is excluded within 4 months prior to the start of the baseline period and throughout the study.
3. Ergotamine-derivatives, steroids, and triptans used for migraine prophylaxis are excluded within 2 months prior to the start of the baseline period and throughout the study.
4. Devices and procedures used for migraine prophylaxis (eg greater occipital nerve block, invasive or non-invasive neuromodulation) are excluded within 2 months prior to the start of the baseline period and throughout the study. Use of other non-pharmacological treatments and traditional techniques such as acupuncture, traditional and herbal medicine, etc. is in general allowed if the dose/regimen is stable for 2 months prior to the start of the baseline phase and throughout the study.
5. Investigational medications, devices, and procedures, unless specifically allowed as per above, are excluded throughout the study.

[redacted]

Subjects with anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months prior to the start of the baseline period.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time. Patients may continue at the investigator's discretion after the blind has been broken.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. The study will be considered completed when the last patient completes their last visit planned in the protocol.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.5 and Section 7.6)

[redacted]

- Use of prohibited treatment as per recommendations in Section 5.6.2.
- Any situation in which study participation might result in a safety risk to the patient
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study, and should continue recording in the eDiary as per protocol. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unplanned treatment discontinuation visit" in Table 6-1 should be completed and recorded in the appropriate CRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate CRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events/Serious Adverse Events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.6.3 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (eg telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

[redacted]

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 Assessment Schedule

Period	Screening		Treatment					Follow-Up
Visit Name	Screening	Baseline	Treatment	Week 2[2]	Week 4	Week 8	End of Treatment	Follow-Up
Visit Numbers[1]	1	20	110	120	130	140	150 and TD/PSD	1999
Days	-42 to -28	-28 to -1	Day 1	14	28	56	84	168
Weeks	-6 to -4	-4 to -1	1	2	4	8	12	24
Informed consent	X							
[redacted]								
Medical history/current medical conditions	X	X						
Demography	X	X						
Safety Follow up Call				X				
Physical Examination	X	X	X		X			X
Vital signs and body measurements[3]	X	X	X		X	X	X	X
Electrocardiogram (ECG)	X		X		X		X	
Hematology	X		X		X		X	X
Clinical Chemistry	X		X		X		X	X
Pregnancy Test (serum)	X						X	
Pregnancy test (urine)		X	X		X	X		X
Urinalysis	X							
Urine Drug Screen	X							
Hepatitis screen[4]	X							
Anti-AMG 334 antibodies			X		X		X	X
[redacted]								
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X		X	X	X	X
Beck Depression Inventory-II (BDI-II)	X							
Randomization			X					
Study drug administration			X		X	X		
Clinical Outcome Assessment(s)		X[6]						

[redacted]

Period	Screening		Treatment					Follow-Up
Visit Name	Screening	Baseline	Treatment	Week 2[2]	Week 4	Week 8	End of Treatment	Follow-Up
Visit Numbers[1]	1	20	110	120	130	140	150 and TD/PSD	1999
Days	-42 to -28	-28 to -1	Day 1	14	28	56	84	168
Weeks	-6 to -4	-4 to -1	1	2	4	8	12	24
Healthcare Resource Questionnaire		X[7]						
Headache Impact Test (HIT-6)			X		X	X	X	
[redacted]								
Adverse Events[9]			X	X	X	X	X	X
Serious Adverse Events[10]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X
Study completion information							X	X

[1] Visit structure given for internal programming purpose only
[2] Telephone visit.
[3] Height collected at screen visit only. Weight collected at screen, baseline, and End of Treatment Visit. Blood pressure, pulse and body temperature collected at every visit.
[4] Hepatitis testing consists of Hepatitis B Core Antibody (HepBcAb), Hepatitis B Surface antigen (HepBsAg),and Hepatitis C virus antibody. If the result for HepBcAb is positive and HepBsAg is negative, additional testing for Hepatitis B virus DNA by Polymerase Chain Reaction (PCR) is necessary. If both are positive, no additional testing is necessary.
[redacted]
[6] Patients will record headache and headache medication information daily, using the provided eDiary platform.
[7] To be completed by the patient after each headache.
[8] Completed daily via the eDiary.
[9] Adverse Events will be collected from the randomization (Visit 110) through the end of the Follow-Up Period (16 weeks after the last dose of study drug). Events occurring between screen and the first dose of investigational product should be captured as medical history, if warranted.
[10] SAEs will be collected after signing of the informed consent through the end of the Follow-Up Period (16 weeks after the last dose of study drug).

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next period will have the appropriate CRFs for the screening period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients include: date of birth, age, sex, race, ethnicity, source of patient referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded.

Prior headache characteristics and previous headache medication history will be collected as part of baseline characteristics.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Study medication is administered by the investigator or designated study staff at each visit. This information should be captured in the source document and the CRF at each visit. All study treatment administered must be recorded in the Drug Accountability Log. Site staff will review eDiary compliance with the patient at each visit.

6.4 Efficacy

Efficacy assessments will include:

- Migraine days

The timing and frequency of these assessments are outlined in Table 6-1. Patients will record the efficacy information using the provided eDiary platform. To aid in compliance, it is recommended that the information be completed at the same time every day that is convenient for the patient. Retroactive completion will be allowed one day prior to the time of completion. Any entries > 2 days old will not be allowed and will be considered missing data.

6.4.1 Appropriateness of efficacy assessments

- The definition of migraine day (Section 6.4.2) is consistent with the diagnostic criteria of migraine and probable migraine according to the International Classification of Headache Disorder (ICHD-3). The monthly migraine days will be calculated using migraine day data collected from the eDiary. Migraine days are commonly used as a primary endpoint in pivotal trials as acknowledged both in the IHS guidelines for controlled trials of drugs in migraine (Tfelt-Hansen et al 2012).

  As the mean change in monthly migraine day (MMD) however describes a population-based measure and given the natural variability in migraine trials often is associated with small effect sizes, clinically an important complementary information is the proportion of

[redacted]

patients that achieve a certain clinical benefit, which is usually described with achieving at least a 50% reduction of migraine days compared to the individual baseline ("50% responder rate"). In pivotal trials, 50% (or higher) responder rates are usually included as secondary or key secondary outcomes. The HIT-6 has been selected as a secondary outcome because it is the most commonly used PRO in clinical practice. Reduction in acute monthly migraine-specific medication is an important secondary outcome, as many patients with longer-term and very frequent use of rescue medication can potentially develop medication-overuse headache as a complication. [redacted]

6.4.2 Migraine days

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

1.≥ 2 of the following pain features:

- Unilateral
- Throbbing
- Moderate to severe
- Exacerbated with exercise/physical activity

2.≥ 1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

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

To further characterize a migraine day, the following information will be collected:

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

6.5 Safety

Safety assessments will include:

- Laboratory evaluations

[redacted]

- Physical examination
- Vital signs
- Height/Weight
- Pregnancy testing (females of childbearing potential
- Electrocardiogram (ECG)

The timing and frequency of these assessments are outlined in Table 6-1.

6.5.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.1.1 Hematology

The following parameters will be measured at the frequency outlined in Table 6-1: red blood cells (RBCs), nucleated RBCs, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, reticulocytes, platelets, white blood cells (WBCs), WBC differential. The differential will measure: bands/stabs, neutrophils, eosinophils, basophils, lymphocytes, monocytes, myeloblasts, promyelocytes, myelocytes, metamyelocytes, and atypical lymphocytes.

6.5.1.2 Chemistry

The following parameters will be measured at the frequency outlined in Table 6-1: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, BUN/urea, bilirubin (direct and total), alkaline phosphatase, ALT (SGPT), AST (SGOT), total cholesterol, HDL, LDL, triglycerides, CPK, and eGFR.

6.5.1.3 Urinalysis

The following parameters will be measured at the frequency outlined in Table 6-1: specific gravity, pH, blood, protein, glucose, bilirubin, WBC, RBC, epithelial cells, bacteria, casts, and crystals.

6.5.1.4 Hepatitis testing

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

The following laboratory testing will be performed to determine Hepatitis B and C status:

- Hepatitis B Surface Antigen (HepBsAg) and total Hepatitis B Core Antibody (HepBcAb)
  - If results are HepBcAb positive and HepBsAg positive, no additional testing is necessary
  - If results are HepBcAb positive and HepBsAg negative, additional testing for Hepatitis B virus DNA by Polymerase Chain Reaction (PCR) is necessary

[redacted]

- Hepatitis C virus antibody
  - If results are Hepatitis C virus antibody positive, additional testing for Hepatitis C virus RNA by PCR is necessary

6.5.1.5 Urine drug screening

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

6.5.2 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A brief physical exam, as per local practice, will include the examination of general appearance and will be at all visits starting from Visit 20/Screening, except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to randomization must be included in the appropriate section of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded in the appropriate section of the CRF.

6.5.3 Vital signs

Vital signs include BP, pulse and temperature measurements. Pulse, systolic and diastolic blood pressure will be measured three times when the patient has been sitting for approximately five minutes. The repeat sitting measurements should be made at approximately 1 - 2 minute intervals and the mean of the three measurements will be used for analysis purposes. If an automated blood pressure device is used, it should be calibrated according to the manufacturer's guidelines. The method to take temperature should be consistent throughout the study.

6.5.4 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

6.5.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum pregnancy tests will be performed at the beginning and end of the study, with urine pregnancy tests performed at the remaining visits. The specific schedule is outlined in Table 6-1.

[redacted]

6.5.6 Electrocardiogram (ECG)

All ECGs must be recorded as outlined in the central ECG reading manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) as reported by the central reader should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, printed on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, patient initials, subject number, date and time, and filed in the study site source documents. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding and forwarded to the central ECG laboratory for assessment. Clinically significant ECG findings at randomization (pre-dose) must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs as appropriate.

6.6 Other assessments

- Clinical outcomes assessments
- Patient reported outcomes
- Resource utilization
- [redacted]
- AMG 334 antibody testing

6.6.1 Clinical Outcome Assessments (COAs)

Clinical outcomes assessments (COAs) will be collected by subjects using a handheld electronic diary (eDiary) at various frequencies.

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

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

The eDiary will categorize headache events as migraine days or headache days based on the definitions below:

[redacted]

- Headache Day: Any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:
  - a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
  - a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
  - a headache of any duration for which acute headache treatment is administered.
- Migraine Day: See Section 6.4.2 for details.

6.6.2 Patient Reported Outcomes (PROs)

The eDiary will collect the following patient-reported outcomes:

- HIT-6, monthly
- [redacted]
- Beck Depression Inventory, screen
- [redacted]

The site study staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day during the baseline period and double-blind treatment period and to bring the eDiary to every study visit. At the Day 1 study visit, the investigator will use the subject's eDiary to review all data entered during the baseline period and confirm the relevant inclusion and exclusion criteria. Please refer to the eDiary manual for additional details.

6.6.2.1 Headache Impact Test (HIT-6)

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

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

No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items. Patients will complete this at the frequency outlined in Table 6-1. The questionnaire takes approximately 5 minutes to complete.

[redacted]

[redacted]

6.6.2.4 Beck Depression Inventory (BDI)-II

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

Patients will complete the BDI-II at the time point outlined in Table 6-1. The recall period is the preceding two weeks, including the day of completion. The questionnaire takes approximately 10 minutes to complete.

[redacted]

[redacted]

[redacted]

6.6.3 Resource utilization

Healthcare resource utilization question will be incorporated into daily eDiary to capture use of healthcare resources due to migraine attack (eg, general practitioner, specialist, emergency room visit, hospital visit).

[redacted]

[redacted]

[redacted]

6.6.7 AMG 334 Antibody testing

Blood samples for antibody testing are to be collected for the measurement of anti-AMG 334 binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity, and presence of immune complexes. Additional blood samples may be obtained for further evaluation of anti-AMG 334 antibodies during the study.

Sites will not be notified of positive neutralizing antibody results to the investigational product for a patient prior to that patient's final scheduled study visit. The patients with a positive neutralizing antibody response will continue to be dosed during the course of study.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (eg, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

[redacted]

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the [severity grade/Common Toxicity Criteria (CTC) AE grade]
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding AMG 334 treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (eg further observation only)
- AMG 334treatment dosage increased/reduced
- AMG 334 treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, eg defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured in the CRF; SAEs also require individual expedited reporting to Novartis Chief Medical Office and Patient Safety (CMO&PS) as per Section 7.2.2.

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

[redacted]

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring should be entered into the appropriate CRFs. Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the appropriate CRFs.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (eg, disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on the appropriate CRFs.

7.4 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

[redacted]

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration CRF (Yes/No)	Document in AE CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.5 Prospective suicidality assessment

The C-SSRS is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS must be administered at each visit, including unscheduled visits.

A validated version of the C-SSRS will be used to capture self-reported C-SSRS data via a web-based interactive response system (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS patient interview, evaluating each patient's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the investigator will receive a detailed eC-SSRS Findings Report via e-mail or fax. If the system assesses the patient as having positive suicidal signs, the investigator will be immediately notified by either fax, email and/or via telephone.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the patient must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the patient is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a patient answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior must be reviewed by the Safety Management Team.

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. There will be a follow-up of the newborn assessed at approximately 12 months after birth.

The pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy

[redacted]

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After

database lock or when a site is closed, the investigator will receive copies of the patient data for archiving at the investigational site.

The Principal Investigator is responsible for assuring that the data entered by the site personnel into CRF is complete, accurate, and that entry and updates are performed in a timely manner.

8.3 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Diary data will be entered into an electronic diary by the patient OR Patients/subjects will fill in their PRO data in a site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

[redacted]

[redacted]

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The primary analysis will be conducted on all subject data after LPLV (the last Follow-Up Visit) has occurred. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The All Randomized Set (ARS) includes all subjects who were randomized in the study. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Tabulations of demographic and baseline characteristics, disposition, and important protocol deviations (IPD) will utilize this analysis set.

The Full analysis set (FAS), which is a subset of ARS, will consist of all participants who started study medication and have completed at least one post-baseline efficacy measurement during the DBTP. In FAS, subjects will be analyzed according to randomized treatment, regardless of the actual treatment received.

The Safety analysis set (SAF) will consist of all randomized subjects who received at least one dose of investigational product and will be analyzed based on actual treatment received.

9.2 Patient demographics and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each treatment group and for all participants (total). The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants (total). In addition, all relevant medical history will be summarized following the same strategy.

9.3 Treatments

A data listing and a summary of the investigational drug (AMG 334 or placebo) injections administered will be provided. In addition, the number and percentage of participants receiving rescue medications, concomitant medications, and significant non-drug therapy will be summarized by preferred term (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment arm, and be listed.

[redacted]

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary efficacy variable is the change from baseline in monthly migraine days in the last month (Month 3) of the DBTP.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy endpoint variable will be analyzed using a generalized linear mixed model based on observed monthly data during the DBTP and pairwise comparisons (AMG 334 140mg vs. placebo, and AMG 334 70mg vs. placebo) will be conducted.

The model will include treatment, scheduled visit, treatment by visit interaction, and the stratification variable and baseline values as covariates. If applicable, unstructured covariance structure is assumed. Least squares means (LSMs) for each treatment group and its associated 95% confidence intervals, difference of LSMs compared to placebo group and the associated 95% confidence interval of the differences, as well as the nominal two-sided p-values, will be tabulated by visit and treatment.

A hierarchical gate-keeping procedure and the Hochberg method will be used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints. See further details in Section 9.5.

9.4.3 Handling of missing values/censoring/discontinuations

The method of handling missing data for efficacy endpoints will be described for each set of endpoints. For the primary analysis, missing data will not be imputed, but various sensitivity analyses under missing at random and missing not at random assumptions will be performed. Missing data will not be imputed for safety endpoints. Details of the missing data handling will be specified in the statistical analysis plan (SAP).

9.4.4 Sensitivity analyses

Multiple imputation (MI) techniques applying missing at random (MAR) and missing not at random (MNAR) approaches will be used to assess the impact of missing values on the interpretation of the results during the DBTP. In addition, the baseline observations carried forward (BOCF) method will also be used.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables (all during the DBTP) are:

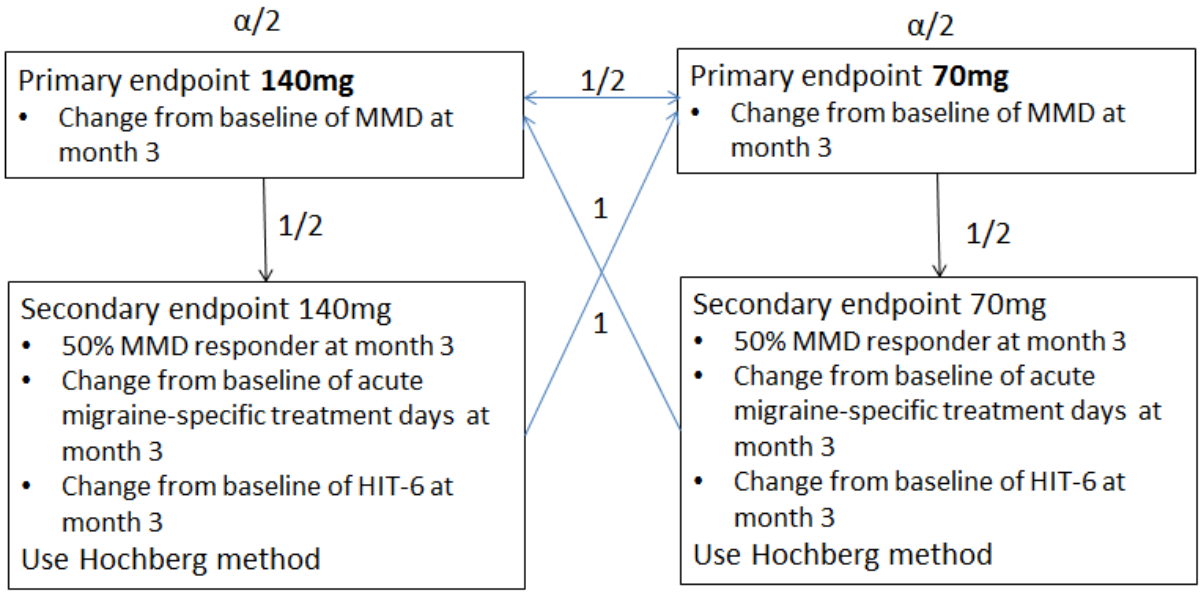
- Proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month of DBTP (Month 3).
- Change from baseline in monthly acute migraine-specific treatment days in Month 3 of the DBTP
- Change from baseline in headache impact scores as measured by the HIT-6 in Month 3 of the DBTP

[redacted]

The above continuous endpoints (ie, change from baseline) will be analyzed using a linear mixed effects model similar to the primary endpoint. The dichotomous endpoints will be analyzed by Cochran-Mantel-Haenszel (CMH) test with patients who are missing monthly migraine day data at Month 3 of the DBTP imputed as non-responders. Nominal 95% confidence intervals and p-values will be reported.

A hierarchical gate-keeping procedure and the Hochberg method will be used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints. The primary endpoint, the change from baseline in monthly migraine days to the last 4 weeks of the 12-week double-blind treatment period, will be initially tested at a 2-sided significance level of 0.025 for each of the AMG 334 treatment group (140 mg and 70 mg) compared to the placebo group, respectively. If the primary endpoint and all secondary endpoints are statistically significant for an AMG 334 treatment group, the corresponding significance level will be carried over to the primary endpoint for the other AMG 334 treatment group, and the primary endpoint will be re-compared to the placebo group at a 2-sided significance level of 0.05 (full alpha). If the primary endpoint of one dose group is statistically significant but not all the secondary endpoints, only half of the initial alpha of the dose (0.0125) can be transferred to the primary endpoint of the other dose. The testing sequence can be found in the figure below.

Figure 9-1 Hierarchical Testing Procedure



9.5.2 Safety variables

Safety variables are:

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

[redacted]

As safety analyses, patient incidence of treatment-emergent adverse events will be tabulated by system organ class and preferred term by treatment group. Change from baseline for clinical laboratory values and vital signs will be summarized by visit and by treatment group.

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

All safety analyses will be performed for the Double-Blind Treatment Period and Safety Follow-up Period separately.

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

[redacted]

9.7 Interim analyses

To account for potential larger than expected variability during the DBTP of the trial, a blinded interim assessment is planned after about 50% of subjects finish their DBTP or early withdraw. Only the standard deviation of the primary variable, change from baseline in monthly migraine days in month 3, based on pooled (blinded) data from all subjects who had the opportunity to complete the week 12 assessment in the trial, will be estimated. The sample size will be increased appropriately, up to an additional 200 subjects, only if the standard deviation is larger than 5.

The type I error of the primary analysis will be maintained, as the treatment assignment will remain blinded and there is no intention to stop the study early due to efficacy.

[redacted]

9.8 Sample size calculation

A treatment difference of -1.79 days for change from baseline in monthly migraine days in Month 3 between AMG 334 140mg and placebo was observed in study 20120296 (STRIVE). A treatment difference of -1.16 days for change from baseline in monthly migraine days in Month 3 between AMG 334 70mg and placebo was observed based on pooled analysis on the combined data from studies 20120296, 20120297, and 20120178.

Assuming a treatment effect similar to the effect observed in previous studies with AMG 334 in episodic migraine, the treatment difference in terms of change from baseline on monthly migraine days during week 9-12 (primary variable) for erenumab 140mg vs. placebo and 70mg vs. placebo is assumed at -1.5 days and -1.1 days, respectively. The common standard deviation of the primary variable is assumed at 4. Given a 2:3:3 randomization ratio among erenumab 140mg, 70mg, and placebo, a total of 880 subjects (including 10% drop out rate) would enable both doses to achieve higher than 90% power under overall 0.05 full alpha level to detect the designed treatment difference. In addition, the sample size will also ensure the trial to have adequate power to detect treatment difference under initial 2-sided 0.025 alpha level assigned to each dose (equally split between the erenumab two doses).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (eg all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the patient.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

[redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

The study includes an optional DNA component which requires a separate signature if the patient agrees to participate If optional DNA collection for the study is approved by the site IRB/IEC board. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these DNA assessments will in no way affect the patient's ability to participate in the main research study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, documented informed consent form, consent form updates, subject recruitment procedures (eg, advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

[redacted]

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

[redacted]

12 References

References are available upon request.

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Only selected lab parameters which have potential to be sensitive to AMG 334 exposure are listed.

Table 13-1 Clinically notable laboratory values

Laboratory Variable	Gender (M/F/Both)	Standard Units	SI Units
LIVER FUNCTION AND RELATED VARIABLES			
SGOT (AST)	F	>93 U/L	>93 U/L
SGOT (AST)	M	>111 U/L	>111 U/L
SGPT (ALT)	F	>90 U/L	>90 U/L
SGPT (ALT)	M	>123 U/L	>123 U/L
Total bilirubin	Both	>3.6 mg/dL	>63 mmol/L
Alkaline Phosphatase	F	>832 U/L	>832 U/L
Alkaline Phosphatase	M	>1032 U/L	>1032 U/L
HEMATOLOGY VARIABLES			
Neutrophils	Both	<1.5x 10^3/uL	<1.5x10^9/L

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term)

[redacted]

- ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

- Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

	study drug • Establish causality • Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (eg, reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

	• Hospitalize the patient • Establish causality • Complete liver CRF	
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]