NOVARTIS

Global Clinical Development - General Medicine

AMG 334

Clinical Trial Protocol CAMG334A2301 / NCT03096834

A 12-week double-blind, randomized, multicenter study comparing the efficacy and safety of once monthly subcutaneous 140 mg AMG 334 against placebo in adult episodic migraine patients who have failed 2-4 prophylactic treatments (LIBERTY)

Document type:	Amended Protocol Version
EUDRACT number:	2016-002211-18
Version number:	v04 Clean
Clinical trial phase:	3b
Release date:	22-May-2020

Clinical Trial Protocol Template Version 3.1 (February 2016)

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List of abbreviations

ACE/ARB	Angiotensin-Converting Enzyme inhibitor/Angiotensin-Receptor Blocker
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
[redacted]	[redacted]
CFR	US Code of Federal Regulations
CGRP	Calcitonin Gene-related Peptide
CPO	Country Pharma Organization
CQA	Compliance Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CM	Chronic migraine
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia Suicide Severity Rating Scale (paper or electronic)
[redacted]	[redacted]
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTRD	Clinical Trial Results Database
DAR	Drug Accountability Record
DBTE	Double-Blind Treatment Epoch
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EM	Episodic migraine
EMA	European Medicines Agency
EoT	End of Trial
EQ	EuroQuol
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GEE	Generalized estimation equations
[redacted]	[redacted]
IB	Investigator Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICHD	International Classification of Headache Disorders
ID	Identification
IEC	Independent Ethics Committee
IN	Investigator Notification
IPW	Inverse probability weighting
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD/IUS	Intrauterine Device/System
LFT	Liver function test
LOCF	Last observation carried forward
LPLV	Last Patient Last Visit
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MI	Multiple imputation
MMD	Monthly Migraine Days
MNAR	Missing not at random
MPFID	Migraine Physical Function Impact Diary
NSAID	Non-steroidal anti-inflammatory drug
OC/RDC	Oracle Clinical/Remote Data Capture
OLAS	Open-Label Analysis Set
OLTE	Open-Label Treatment Epoch
PK/PD	Pharmacokinetic/Pharmacodynamic
PP	Per Protocol
PRO	Patient-reported Outcome
PTA	Post-Trial Access
PTAS	Post-Trial Access Analysis Set
q.m.	once a month
QM	Quality Management
RR	Responder Rate
SAE	Serious Adverse Event (paper or electronic)
SAF	Safety Analysis Set
SAP	statistical analysis plan
s.c.	Subcutaneous
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Treatment Discontinuation
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization

WoC	Withdrawal of Consent
[redacted]	[redacted]

Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
Control drug	Drugs(s) 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 patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
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 patient 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

Amendment 4

Amendment rationale

The purpose of this amendment is to **provide Post-Trial Access (PTA)** for patients who have completed the 3 year Open-Label Treatment Epoch and demonstrated clinical benefit in the opinion of the Investigator, to ensure continued drug access until erenumab has received country-level launch and subsequent reimbursement decision or until December 2020 whichever comes first.

The PTA-Open-Label Treatment Epoch will evaluate further long-term safety and clinical benefit of erenumab. [redacted] The analysis plan has been updated.

The risk and benefits section has been updated with safety information as per the latest Investigator Brochure, version 11. In addition, details for potential trial conduct changes due to the COVID-19 pandemic have been incorporated in this protocol amendment.

A local amendment was completed (27-Jun-2018) to comply with Swedish Health Authority request to add clarity for publication of interim results. The changes are included in this global amendment.

Updates have been made to the relevant protocol sections.

Changes to the protocol

Protocol Summary

Updated to add details for revised study design and to list CGI scale in other assessments.

Section 1 Introduction

Added study 20120178 to additional safety section.

[redacted]

Section 3.1 Study design

Provided clarification for final CSR requirements and updated the text and Figure 3-1 to provide details for PTA-Open-Label Treatment Epoch.

Section 3.2 Rationale for study design

Added details for PTA-Open-Label Treatment Epoch.

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

Added details for PTA-Open-Label Treatment Epoch.

Section 3.5 Purpose and timing of interim analyses/design adaptations

The section has been updated to add the purpose and the possible outcome of the interim analyses during the open-label extension phase to comply with Swedish Health Authority request.

Section 3.6 Risks and benefits

Safety data updated to include information from IB 11.

Section 4 Population

Deleted recruitment numbers and outdated study retention numbers.

Section 5.1.1 Investigational and control drugs

Added details for PTA-Open-Label Treatment Epoch

Section 5.5.4 Instructions for prescribing and taking study treatment

Added details for PTA-Open-Label Treatment Epoch and a guidance section for COVID-19 related to delivery of study drug and self-administration of study drug for patients affected by the pandemic.

Section 5.6 Study completion and discontinuation

Added details for PTA-Open-Label Treatment Epoch including completion details and reasons for discontinuation of study drug during the PTA-Open-Label Treatment Epoch.

Section 6 Visit schedule and assessments

Included a guidance section for COVID-19 related to alternatives for conducting study visits with options to use phone calls, virtual visits etc. for patients affected by the pandemic. Added assessment Table 6-5 to include the assessments to be conducted during the PTA- Open-Label Treatment Epoch.

Section 6.4 Efficacy

Added guidance for COVID-19 that PRO scales may still be collected by using the eDiary for patients impacted due to the pandemic.

Section 6.5.4 Laboratory evaluations

Introduced guidance for COVID-19 to indicate that collection of laboratory samples may need to be modified for patients impacted due to the pandemic.

Section 6.5.6 Pregnancy and assessments of fertility

Introduced guidance for COVID-19 to indicate that urine pregnancy tests may be used at home instead of conducted in the clinic when serum or urine pregnancy tests were scheduled for patients impacted due to the pandemic.

Section 6.6 Other assessments

Added details for the clinical global impression scales.

Section 6.6.6 AMG 334 Antibody testing

Added guidance for COVID-19 that might limit the collection of anti-body samples for patients impacted due to the pandemic.

[redacted]

Section 7 Safety monitoring

Included guidance for COVID-19 indicating that regular phone or virtual calls would occur to monitor the safety of patients impacted due to the pandemic.

Section 7.6 Prospective suicidality assessment

Guidance for COVID-19 was added to indicate that eC-SSRS may still be administered by using the patient's e-diaries.

Section 9.1 Analysis sets

Details for PTA analysis set added.

Section 9.5.2 Safety variables

Added details for PTA-Open-Label Treatment Epoch.

[redacted]

Section 9.7 Interim analyses

Information already present in section 3.1 and section 3.5 has been repeated in this section on interim analyses to comply with Swedish Health Authority request.

Section 10.2 Informed consent procedures

Updated to add guidance for COVID-19 for patients that had self-administration of study drug and the requirements to sign an ICF to document the process.

Section 10.4 Publication of study protocol and results

Provided clarification for final CSR requirements.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 3 (March 2018)

The purpose of this amendment was to expand the duration of the Open-Label Treatment Epoch from 52 weeks (1 year) to 156 weeks (3 years), intended to collect further long-term safety and efficacy data on AMG 334 in episodic migraine patients who have previously failed 2 to 4 prophylactic migraine treatments. An additional endpoint was added for 30% reduction of

MMD and three additional analyses were added at Week 12 and after 1 and 2 years of the Open-Label Treatment Epoch.

[redacted]

Amendment 1 (December 2016)

The purpose of this amendment was to change the AMG 334 dose from 70 mg to 140 mg per administration, and to update the sample size based on new assumptions using 140 mg. The definitions of the formal end of trial (EoT) and final clinical study report (CSR) have been expanded upon, in addition to the clarification of various protocol sections based on feedback received from sites and regulatory authorities. Lastly, corrections of minor administrative and typographical errors identified after the initial protocol finalization have been incorporated.

Amendment 3

Amendment rationale

The purpose of this amendment is to expand the duration of the Open-Label Treatment Epoch from 52 weeks (1 year) to 156 weeks (3 years), intended to collect further long-term safety and efficacy data on AMG 334 in episodic migraine patients who have previously failed 2 to 4 prophylactic migraine treatments. Given that the enrolled patients have a particular unmet need as they have failed multiple treatments, it is assumed that many will need to be treated for a longer period of time. After the first year in the Open-Label Treatment Epoch, the patients can continue in the study under a reduced schedule of assessments, to minimize patient burden [redacted]

In addition, new endpoints have been added for the Open-Label Treatment Epoch, given that a 30% reduction of monthly migraine days is potentially a clinically meaningful reduction for these difficult to treat patients and as acute migraine-specific medication days is one of the important secondary endpoints.

There will be three additional analyses for the Open-Label Treatment Epoch, before the final analysis i.e. after all patients completed the initial 12 weeks of the Open-Label Treatment Epoch (weeks 12-24), as well as after 1 year and 2 years in the Open-label Treatment Epoch.

Moreover, corrections of minor administrative and typographical errors identified after the amendment 2 protocol finalization have been incorporated.

The first patient was screened on March 20, 2017 and the trial completed enrollment on July 6, 2017: 246 patients have been randomized in 59 sites. 242 patients completed the Double-Blind Treatment Epoch, out of which 240 patients continued in the Open-Label Extension Epoch. At the time of Protocol Amendment 3 finalization, 212 patients were ongoing in the Open-Label Extension Epoch.

Updates have been made to the relevant protocol sections.

Changes to the protocol

Section 1.1 Background

The section has been updated to include additional data from recently completed studies.

Section 2.1 Objectives and related endpoints

Endpoints related to the Open-Label Treatment Epoch have been updated. [redacted]

Section 3.1 Study Design

The section regarding the Open-Label Treatment Epoch has been updated.

Section 3.2 Rationale for Study Design

The section regarding the Open-Label Treatment Epoch has been updated.

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

The duration of the Open-Label Treatment Epoch has been updated.

Section 3.5 Purpose and timing of interim analyses/design adaptations

The additional interim analysis for the Open-Label Treatment Epoch have been added.

Section 3.6 Risks and Benefits

Updated as per latest available data.

Section 4 Population

The actual enrollment status has been included.

Section 5.1.1 Investigational and control drugs

The potential use of 140 mg/mL prefilled syringes for the Open-Label Treatment Epoch has been added.

Section 5.5.4 Instructions for prescribing and taking study treatment

The duration of the Open-Label Treatment Epoch has been updated.

Section 5.6. Study completion and discontinuation

Information related to the Open-Label Treatment Epoch has been updated.

Table 6-2 Assessment Schedule: Open-Label Treatment through week 64

Updated assessment schedule for V299 (now V213/week 64)

Table 6-3 Assessment Schedule: Open-Label Treatment from week 65 to week 116

Added assessment schedule for the additional first year of the Open-Label Treatment Epoch.

Table 6-4 Assessment Schedule: Open-Label Treatment after week 116

Added assessment schedule for the additional second year of the Open-Label Treatment Epoch.

Section 8 Data review and database management

Section regarding the centralized Novartis CRA organization has been updated

Section 9 Data analysis

The data analysis schedule has been updated.

[redacted]

Section 9.7 Interim analyses

The interim analyses schedule has been updated.

Section 10.4 Publication of study protocol and result.

The publication schedule has been updated.

Changed the Table numbers (additional Tables 6-3 and 6-4) throughout the document.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2

Amendment rationale

[redacted]

The first patient was screened on March 20, 2017 and the trial completed enrollment on July 6, 2017: 246 patients have been randomized in 59 sites.

The changes proposed by this amendment will not change the primary objective, study population, or primary or secondary endpoints.

Updates have been made to the relevant protocol sections as outlined in the below section.

Changes to the protocol

Section 1.1 Background

The section regarding commonly used prophylactic drugs or drug classes has been updated.

Section 1.2 Purpose

This section has been reworded.

[redacted]

Table 6-2 Assessment Schedule: Open-Label Treatment

Updated assessment schedule for V199 as per Table 6-1 to properly reflect and ease the representation of the required assessments.

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do not affect the Informed Consent.

Amendment 1

Amendment rationale

The purpose of this amendment is to change the AMG 334 dose from 70 mg to 140 mg per administration, and to update the sample size based on new assumptions using 140 mg. The definitions of the formal end of trial (EoT) and final clinical study report (CSR) have been expanded upon, in addition to the clarification of various protocol sections based on feedback received from sites and regulatory authorities. Lastly, corrections of minor administrative and typographical errors identified after the initial protocol finalization have been incorporated.

The AMG 334 development program has focused on the exploration of two different doses in its phase 2 and 3 trials: 70mg and 140 mg, both administered once monthly. Results from the AMG 334 Phase 2b trial (Study 20120295), in chronic migraine (CM) patients, showed statistically significant and comparable results in both dose groups. In the subgroups of patients having failed either (a) at least one previous prophylactic treatment or (b) two or more prophylactic treatments, the observed treatment effect was numerically higher with 140 mg.

In the recently completed 20120296 episodic migraine (EM) trial that included both 70 mg and 140 mg AMG 334, the treatment effects observed with 140 mg showed consistently higher values that are considered clinically meaningful. In addition, similarly to the phase 2b CM trial, higher treatment effects were observed with 140 mg for subgroups of patients having failed either (a) at least one previous prophylactic treatment or (b) two or more prophylactic treatments. All of these subgroups, despite some having limited size, achieved nominal significance, suggesting that AMG 334 is highly effective in these specific patient populations.

The safety and tolerability profile of AMG 334 is similar to placebo and comparable across both 70 mg and 140 mg. The most commonly reported adverse events included injection site pain, infection of the upper respiratory tract and nausea. The only potentially dose-related adverse event observed to date is constipation, which has usually been mild and not clinically relevant.

Based on these results suggesting that patients who have failed two or more treatments could benefit from 140 mg AMG 334, the decision was made to change the dose from 70 mg to 140 mg in this study, which is enrolling patients who have failed 2-4 prophylactic migraine treatments. Updates to the background, dosing rationale and risk and benefits sections have been made to explain this change.

In support of the additional reasons for the protocol amendment, updates have been made to relevant protocol sections as outlined in the below section, Changes to the protocol.

The trial has not yet started enrolling patients, and given the substantial nature of this amendment (i.e., dose change), this amendment will require regulatory approval prior to any patient enrollment. Based on the phase 3 data outlined above, it is anticipated that the dose increase will have a positive impact for patients and the study objectives.

Changes to the protocol

The 70 mg study dose has been changed to 140 mg and, based on the half-life of the new dose, the duration between the last dose and the Follow-up visit has been changed from 12 to 16 weeks throughout the document.

Section 1.1 Background, Section 3.3 Rationale for dose, and Section 3.6 Risks and benefits

New data supporting the change from 70 mg to 140 mg has been added.

Table 2-1 Objectives and related endpoints and Section 9.5 Analysis of secondary variables

The secondary endpoints related to MPFID have been updated based on the results of the phase 3 trial data.

Section 3.1 Study design

Clarifications to the randomization stratification, primary analysis description have been made and a statement regarding End of Trial (EoT) has been added. Additionally, the timing of the Follow-up Visit has been corrected in Figure 3-1.

Section 4 Population

Sample size has been updated based on the treatment effect of the 140mg dose in the recently completed phase 3 study. Number of sites has been updated based on revised sample size.

Section 4.2 Exclusion criteria

Exclusion criterion #6: The text has been updated to reflect that the use of Botulinum toxin A within 4 months of baseline or baseline phase (not randomization) is excluded.

Exclusion criterion #8: Acupuncture has been removed as an excluded procedure, as it is considered “best supportive care” in some countries

Section 5.1 Study treatment

Updates to reflect the dose change have been made throughout this section.

Section 5.5.1 Patient numbering

The guidance to re-use the patient ID for re-screening patients has been changed to require that a new patient ID be used.

Section 5.5.4 Instructions for prescribing and taking study treatment

In addition to updates throughout the section related to the dose change, guidance regarding the time between dose administrations has been added.

Section 5.6.1 Study completion

The definition of End of Trial has been added.

Table 6-2 Assessment Schedule Open-Label Treatment

Removal of Chemistry/Hematology sample collection at Visit 201 (originally listed in error)

Section 6.2.1 Treatment failure confirmation

The process for checking the treatment failure inclusion criteria is updated.

Section 6.5.2 Vital signs

The type of equipment needed to obtain blood pressure has been clarified.

Section 6.5.5 Electrocardiogram (ECG)

The frequency of obtaining the ECG has been corrected to mirror Table 6-1.

Section 6.6.1 Patient reported outcomes (PROs)

Guidance regarding the documentation of site review of electronic PROs has been added.

Section 9.1 Analysis sets

The per protocol analysis description has been removed, as it is not used in this trial.

Section 9.4 Analysis of the primary variable(s)

Changes are made to further clarify the statistical model and sensitivity analyses.

Section 9.5 Analysis of the secondary variable(s)

The MPFID endpoints have been updated based on the results of the phase 3 trial data.

Section 9.8 Sample size calculation

This section has been updated to explain the rationale for the new sample size.

Changes to the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAMG334A2301
Title	A 12-week double-blind, randomized, multicenter study comparing the efficacy and safety of once monthly subcutaneous 140 mg AMG 334 against placebo in adult episodic migraine patients who have failed 2-4 prophylactic migraine treatments
Brief title	Study of efficacy and safety of AMG 334 in episodic migraine patients who failed 2-4 prophylactic migraine treatments
Sponsor and Clinical Phase	Novartis Phase 3b
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the safety and efficacy of AMG 334 compared to placebo in episodic migraine patients who have previously failed 2 to 4 prophylactic migraine treatments and therefore have a high unmet medical need. In the completed Phase 2/3 trials, patients with multiple treatment failures, particularly for lack of efficacy, are largely excluded and specific data for AMG 334 in these patients will only be available as subgroup analyses, without sufficient power for statistical evaluation. Data from this study, in addition to data from the Phase 2/3trial program, will provide important data for clinicians treating migraine patients as particularly for those patients, there are limited treatment options. In addition, these data will also be used to support national health technology assessments (HTAs).
Primary Objective	The primary objective of this study is to evaluate the effect of AMG 334 compared to placebo on the proportion of patients with at least 50% reduction from baseline in monthly migraine days
Secondary Objectives	• Objective 1: To evaluate the effect of AMG 334 compared to placebo on the change from baseline of monthly migraine days in the last month (Month 3) of the Double-Blind Treatment Epoch • Objective 2: To evaluate the effect of AMG 334 compared to placebo on the “impact on everyday activities” domain as measured by the MPFID • Objective 3: To evaluate the effect of AMG 334 compared to placebo on the “physical impairment” domain as measured by the MPFID • Objective 4: To evaluate the effect of AMG 334 compared to placebo on change from baseline in monthly acute migraine-specific medication treatment days in the last month (Month 3) of the Double-Blind Treatment Epoch • Objective 5: To evaluate the effect of AMG 334 compared to placebo on the proportion of patients with at least 75% reduction from baseline in monthly migraine days in the last month (Month 3) of the Double-Blind Treatment Epoch • Objective 6: To evaluate the effect of AMG 334 compared to placebo on the proportion of patients with a 100% reduction from baseline in monthly migraine days in the last month (Month 3) of the Double-Blind Treatment Epoch • Objective 7: To evaluate the safety, tolerability, and immunogenicity of AMG 334 during the entire study

Study design	This study has a 12-week 2-arm, double-blind, randomized, parallel-group design, followed by an optional 156-week Open-Label Treatment Epoch. Additional Open-Label Treatment Epoch has been added for patients in countries where erenumab has not yet been launched (see Section 3.1 for further details).
Population	The patient population will be comprised of 220 male and female episodic migraine patients between the ages of 18 and 65, inclusive.
Key Inclusion criteria	- Documented history of migraine (with or without aura) for ≥ 12 months prior to screening according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3) - 4 to 14 days per month of migraine symptoms (based on ICHD-3 criteria) on average across the 3 months prior to screening based on retrospective reporting - <15 days per month of headache symptoms (ie migraine and non-migraine) - Patients must have*: o Failed 2 to 4 prior migraine prophylaxis treatments out of the following: Propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen) o Failed one AND failed *or* not be suitable for a second of the following: ▪ Propranolol OR metoprolol ▪ Topiramate ▪ Flunarizine o Failed or not be suitable to valproate or divalproex
Key Exclusion criteria	- Older than 50 years of age at migraine onset - Unable to differentiate migraine from other headaches - History of cluster headache or hemiplegic migraine headache - Failed more than 4 prior migraine prophylaxis treatments out of the following: propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen) - Use of a prophylactic migraine medication within 5 half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase - Prior Botulinum toxin A treatment in the head/neck region (including cosmetic use or other licensed indications for Botox®) within 4 months prior to start of the baseline phase or during the baseline phase - Use of the following for any indication in the 1 month prior to the start of the baseline phase or during the baseline phase: o ergotamines or triptanes ≥10 days/month, or o simple analgesics (NSAIDs, acetaminophen, paracetamol) ≥15 days/month, or o opioid- or butalbital-containing analgesics ≥4 days/month
Study treatment	AMG 334 and placebo
Efficacy assessments	- Migraine days - Migraine Physical Function Impact Diary (MPFID)

	- Rescue medication
Key safety assessments	- Adverse event monitoring - Physical exams and vital signs - Monitoring of laboratory markers in blood - ECGs
Other assessments	[redacted]
Data analysis	The primary analyses will compare the 50% response rate, which is defined as the proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch, between AMG 334 vs placebo. A Cochran-Mantel-Haenszel (CMH) test stratified by the migraine frequency (4-7 and 8-14 monthly migraine days strata) will be used under a 2-sided significance level of 0.05 to evaluate the association between the 50% responder rate and the treatment. The p-value of the test and the estimated odds ratio between AMG 334 and placebo, as well as its 95% confidence interval, will also be reported. The secondary objectives that are continuous endpoints (e.g., change from baseline of monthly migraine days) will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The secondary objectives that are responder endpoints will be analyzed using the same method as for the primary endpoint.
Key words	Episodic migraine, treatment failure, monoclonal antibody, CGRP, Calcitonin Gene-related Peptide

1 Introduction

1.1 Background

Migraine is one of the most common neurological disorders 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.

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 the majority of the EU countries for CM use but not for EM.

Several prophylactic drugs or drug classes are commonly used and approved in the majority of EU countries, eg betablockers (mainly propranolol and metoprolol), topiramate, flunarizine or locally approved products. In a European harmonization procedure (EMA/CHMP 2017), amitriptyline has been approved across the European Union for the prophylaxis of migraine in adults. Other commonly used options include valproate, venlafaxine, certain ACE/ARB such as lisinopril and candesartan. Botulinum toxin (Botox®) is approved in the majority of the EU 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). The 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. Currently there are three Phase 2/3 trials

evaluating the safety and efficacy of AMG 334 compared to placebo in both EM and CM patient populations.

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.

Results from the AMG 334 Phase 2 study (Study 20120295) in patients with chronic migraine 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 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).

Results from two 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 2.88-day reduction from baseline in monthly migraine days compared with 1.84 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 3.23 and 3.67-day reductions from baseline, respectively compared with a 1.83 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 was reported in > six percent of patients treated with AMG 334; 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.

Additional safety data from the completed one-year extension studies (20120296 and 20130255) and the ongoing Open-Label Treatment Phase of 20120178 with 4+ years of exposure have confirmed the known safety and tolerability profile.

In view of the adherence issues with current standard of care (SoC) therapies prompted by poor tolerability and/or lack of efficacy (Hepp et al 2014), one important question is to assess the safety and efficacy of AMG 334 in patients who have failed multiple therapies. In the Phase 2/3

trials, patients with more than two treatment failures in EM due to efficacy were excluded and more than three treatment failures in CM due to efficacy were excluded. To date, no prophylactic trial has been carried out to investigate the efficacy of AMG 334 specifically in patients who have previously failed multiple migraine prophylaxis therapies, which is an important clinical question and data from this study will complement the data from the Phase 2/3 studies.

1.2 Purpose

The purpose of this study is to determine the safety and efficacy of AMG 334 140 mg compared to placebo in episodic migraine patients who have previously failed 2 to 4 prophylactic migraine treatments. Data from this study, in addition to data from the Phase 2/3 trial program, will provide important data for clinicians treating migraine patients as particularly for those patients, there are limited treatment options. The design of this study was informed by initial health technology assessment (HTA) consultation. The data will also be used to support local and national HTA and reimbursement negotiations.

2 Study objectives and endpoints

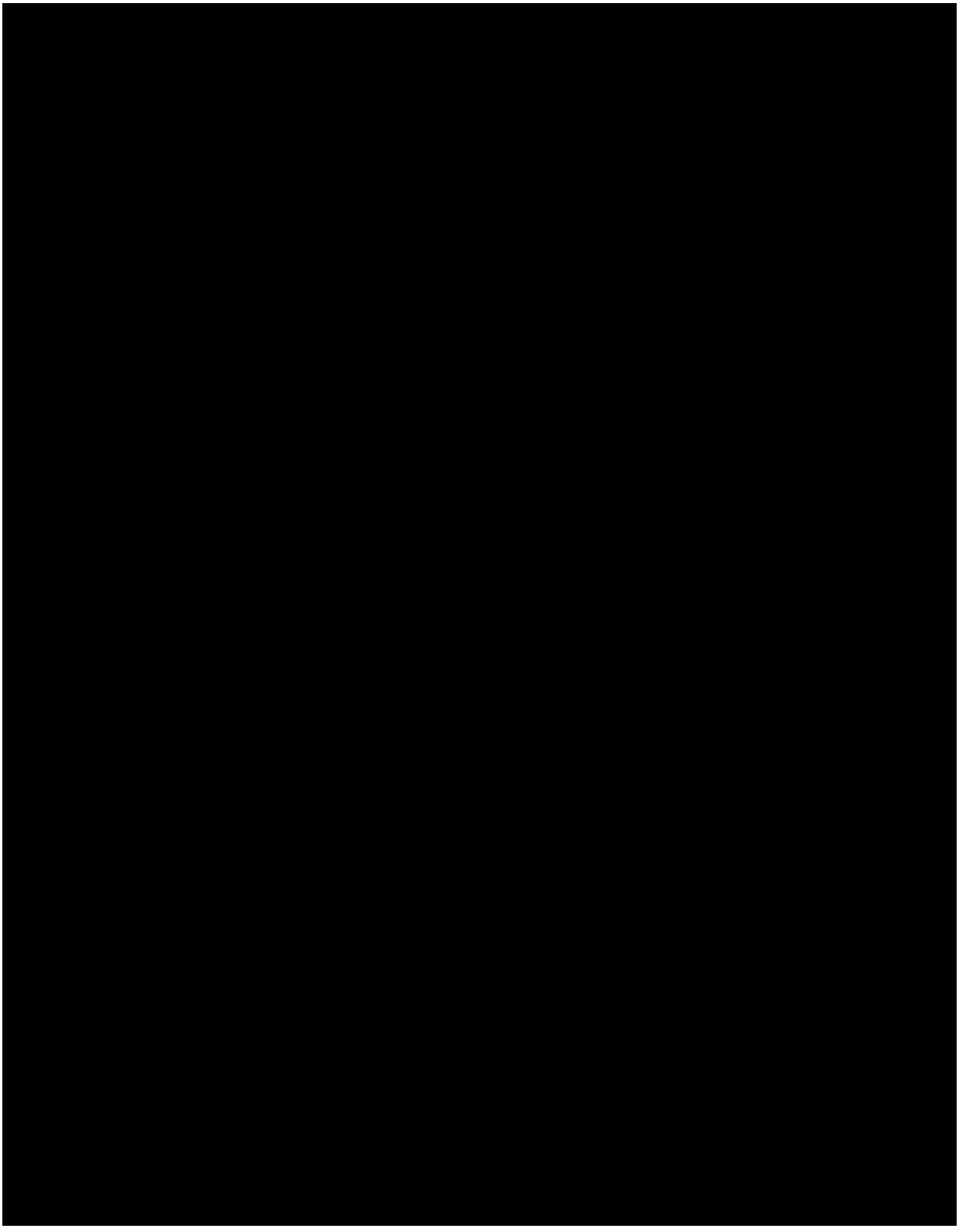
2.1 Objectives and related endpoints

Table 2-1 Objectives and Related Endpoints

Objective	Endpoint	Analysis
	Primary	
To evaluate the effect of 140 mg AMG 334 compared to placebo on the proportion of patients with at least 50% reduction from baseline in monthly migraine days	The achievement of at least a 50% reduction from baseline in monthly migraine days in the last month (month 3) of the double-blind epoch	Section 9.4
	Secondary	
To evaluate the effect of 140 mg AMG 334 compared to placebo on the change from baseline of monthly migraine days	Change from baseline in monthly migraine days in the last month of the double-blind epoch	Section 9.5
To evaluate the effect of 140 mg AMG 334 compared to placebo on the "impact on everyday activities" domain as measured by the MPFID	Change from baseline to month 3 of the MPFID "impact on everyday activities" sub-domain score	Section 9.5
To evaluate the effect of 140 mg AMG 334 compared to placebo on the "physical impairment" domain as measured by the Migraine Physical Function Impact Diary (MPFID)	Change from baseline to month 3 of the MPFID "physical impairment" sub-domain score	Section 9.5
To evaluate the effect of 140 mg AMG 334 compared to placebo on change from baseline in monthly acute migraine-specific medication treatment days	Change from baseline in acute monthly migraine medication treatment days in the last month of the double-blind epoch	Section 9.5
To evaluate the effect of 140 mg AMG 334 compared to placebo on the proportion of	The achievement of at least a 75% reduction from baseline in monthly	Section 9.5

Objective	Endpoint	Analysis
patients with at least 75% reduction from baseline in monthly migraine days	migraine days in the last month of the double-blind epoch	
To evaluate the effect of 140 mg AMG 334 compared to placebo on the proportion of patients with a 100% reduction from baseline in monthly migraine days	The achievement of at least a 100% reduction from baseline in monthly migraine days in the last month of the double-blind epoch.	Section 9.5
To evaluate the safety, tolerability, and immunogenicity of 140 mg AMG 334	Occurrence of cardiovascular events and evaluation of anti-drug antibodies in this patient population	Section 9.5

[redacted]



3 Investigational plan

3.1 Study design

This study uses a single-cohort, 2-treatment arm, parallel-group randomized, double-blind, placebo-controlled design in adult patients with episodic migraine who have previously failed 2 to 4 prophylactic migraine treatments. The following epochs are included in the study design, with study visits at 4 week intervals after completion of screening:

- **Screening Epoch (0-2 weeks) –** Required for all patients to assess initial eligibility.
- **Baseline Epoch (4 weeks) –** All patients successfully completing the Screening Epoch are invited to participate. Eligibility for randomization will be assessed based on migraine frequency and diary compliance during this epoch. Randomization will be stratified by migraine frequency reported during the Baseline Epoch: 4-7 vs 8-14 migraines per month based on eDiary calculations.
- **Double-Blind Treatment Epoch (12 weeks) –** All patients successfully completing the Baseline Epoch are invited to participate. Eligible patients will be randomized to one of two treatment arms. At the end of this epoch (Week 12), the final assessment to address the efficacy-related objectives will occur.
- **Open-Label Treatment Epoch (156 weeks) –** All patients completing the Double-Blind Treatment Epoch on study drug are invited to participate. Patients who discontinued study drug during the Double-Blind Treatment Epoch but remained in the study are **not** eligible for the Open-Label Treatment Epoch.
- **Follow-Up Epoch (12 weeks) –** Unless patients continue onto commercial AMG 334 after completing the Double-Blind and/or Open-Label Epoch (contingent upon marketing authorization and commercial availability in the participating country), a Follow-Up Visit 16 weeks after the last dose of AMG 334 will be required as part of routine safety monitoring.
- **PTA-Open-Label Treatment Epoch. (flexible duration – see below)** – Patients having demonstrated clinical benefit from erenumab based on Investigators opinion (e.g., using criteria of benefit through CGI) in countries without launch and subsequent reimbursement decision, are invited to participate. In order to ensure continued drug access patients will receive erenumab until country-level launch and subsequent reimbursement decision or until December 2020 whichever comes first. Patients who discontinued study drug during the Open-Label Treatment Epoch are **not** eligible for the PTA-Open-Label Treatment Epoch.
  Should a treatment gap exist between the two open-label treatment periods due to a delay of HA/EC approvals or other administrative/logistical reasons, the patients may enter the PTA-Open-Label Treatment Epoch at a later time. During this treatment gap the patient would remain in the study and is allowed to be treated with any medication as deemed appropriate by the Investigator to manage the patient's migraines. Upon HA/EC approval of the PTA-Open-Label Treatment Epoch, the patient will then be required to follow all protocol requirements for treatments allowed and for prohibited medications (Section 5.5.8).

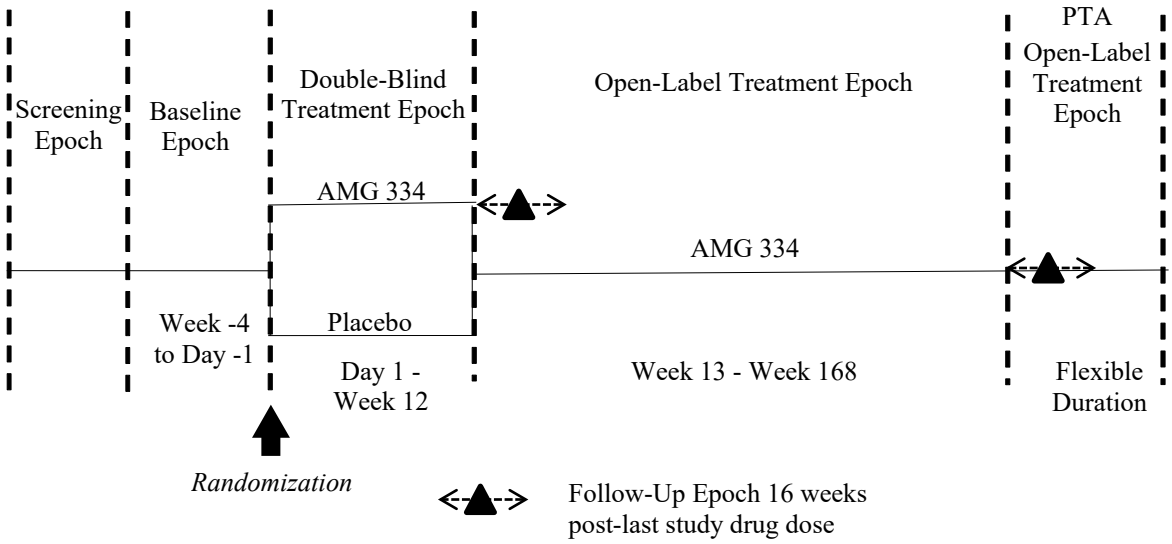
End of Trial will occur when the last patient completes last visit (LPLV).

The primary analysis will occur when the last patient completes the Double-Blind Epoch, prior to the end of both the Open-label Treatment and the Follow-Up Epochs. An initial study report will be prepared and finalized for all data from the Double-Blind Epoch.

Analyses will also occur once all patients completed the initial 12 weeks of the Open-Label Treatment Epoch (weeks 12-24), as well as once all patients completed 1 year and 2 years in the Open-Label Treatment Epoch. Only a selected set of efficacy analyses will be conducted for the 12-24 weeks analysis, whereas the 1 and 2 years analyses will be complete.

A final study report will be prepared, incorporating data from the Open-Label Treatment Epoch including the Follow-Up Epoch, and the PTA-Open-Label Treatment Epoch after all patients have completed their respective last visit (LPLV).

Figure 3-1 Study design



3.2 Rationale for study design

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

The study design was 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. A parallel-group, placebo-controlled design is a standard way of assessing efficacy and safety of new migraine prophylactic agents. A 3- month study duration is in general considered sufficient in duration.

The specifics of prior treatment failure requirements were designed based on feedback from clinical experts, a payer advisory board and consultations with national HTA bodies.

The length of the initial 52 weeks open-label extension was in line with the recommendations from various national and European guidelines that in general recommend the use of migraine prophylactic agents for up to one year after which a re-assessment of the further need should be

considered (Steiner et al 2007). Given that the enrolled patients have a particular unmet need as they have failed multiple treatments, it is assumed that many of them will need to be treated for a longer period of time. The confirmed good safety and tolerability profile of AMG 344 does not suggest increased risks for patients with longer exposure out to 64 weeks (Ashina et al 2017). Therefore, in order to collect additional long-term safety and efficacy data in this patient population the duration of the Open-Label Treatment Epoch has been extended from 52 weeks (1 year) to 156 weeks (3 years) plus additional data in a subset of patients in the PTA-Open-Label Treatment Epoch (anticipated up to an additional 6 months of data).

The Open-Label Treatment Epoch is a mechanism to provide PTA to erenumab until country-level launch and subsequent reimbursement decision (see Section 3.1 for further details), for patients who completed the 3 years open-label treatment period on study drug and who have demonstrated clinical benefit to erenumab as per investigators opinion.

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. 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 3a trials for EM.

Results from the CM Phase 2b trial (Study 20120295) showed statistically significant and comparable results in both dose groups. However, in the subgroups of patients having failed (due to lack of efficacy or poor tolerability) either (a) at least one previous prophylactic treatment or (b) two or more prophylactic treatments, the observed treatment effect was numerically higher with 140 mg.

In the recently completed 20120296 trial 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. In addition, similarly to CM as above, in study 20120296 higher treatment effects were particularly observed with 140 mg for the subgroups of patients having failed either (a) at least one previous prophylactic treatment or (b) two or more prophylactic treatments. All of these subgroups despite some of them having limited size, achieved nominal significance ($p<0.05$), suggesting that AMG 334 is highly effective in these particular patient populations.

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. Additional safety data from one year extension

studies (20130255) or active treatment phases (20120296) have not shown any new safety findings.

Based on these results, which suggest that those patients who have failed two or more treatments in particular could benefit from 140 mg AMG 334, the 140 mg dose was chosen for this trial.

Patients will receive either AMG 334 140 mg q.m. s.c. or matching placebo for 12 weeks in the Double-Blind Treatment Epoch, followed by 156 weeks of Open-Label Treatment of AMG 334 140 mg q.m. s.c., followed by PTA-Open-Label Treatment of AMG 334 140 mg q.m. s.c. for patients in countries without launch of erenumab (as specified in Section 3.1).

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 at the time of the original protocol design are propranolol, metoprolol, topiramate and flunarizine. In some countries, additional choices exist that are only approved and/or available on a national level (e.g., oxetorone in France, or pizotifen or methysergide in a few European countries). Other drugs, while not formally approved, are considered acceptable alternatives and are recommended within national or European treatment guidelines. Examples with evidence for migraine headache prophylaxis include other drug classes such as antidepressants (mainly venlafaxine and amitriptyline, which was approved for migraine prophylaxis on 23 February 2017 across the European Union), ACE/ARBs (mainly candesartan and lisinopril) and valproate/divalproex. Valproate has shown robust evidence as a migraine prophylactic agent in several placebo-controlled trials and is approved for migraine prophylaxis in the US but not in Europe. Despite that fact, valproate is commonly recommended as a potential migraine prophylactic agent in various treatment guidelines, including the European Headache Foundation (Steiner et al 2007), European Federation of Neurological Societies (EFNS guidelines 2009) and the majority of national European treatment guidelines. In Germany, the use of valproate although technically off-label, is endorsed for reimbursement in patients having failed established treatment options (GBA 2010). 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. Additionally, no specific studies have been carried out with any of the currently used prophylactics in patients who have failed multiple prophylactic migraine treatments, therefore no specific evidence for a particular therapy in this population has been identified. 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 lack of consensus on treatment choice in a patient population that has failed various treatments, 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

No formal interim analyses or design adaptations are planned during the Double-Blind Treatment Epoch.

During the Open-Label Treatment Epoch, interim analyses will be conducted after all patients completed the initial 12 weeks of the Open-Label Treatment Epoch (weeks 12 – 24), as well as once all patients completed 1 year (week 64) and 2 years (week 116) in the Open-Label Treatment Epoch. Only a selected set of efficacy analysis will be conducted for the 12-24 weeks analysis, whereas the 1 and 2 years analyses will be complete.

The results of these three interim analyses, summarizing long-term safety and efficacy data in this study population, will be submitted for publication.

It is anticipated that the outcome of these interim analyses will not lead to any changes that affect the conduct of the present study.

3.6 Risks and benefits

AMG 334 is being developed as for migraine prophylaxis in a large clinical development program including more than 4800 patients. Key risks and benefits are briefly summarized below. For further information, please refer to the most recent Investigator Brochure.

There were no significant findings in the toxicology studies with AMG 334 that would predict a risk to human patients. There were no significant effects on electrocardiogram (ECG) parameters, blood pressure (BP) or respiration rate in the single dose cardiovascular study in cynomolgus monkeys.

As of May 2019, approximately 4817 patients have received at least 1 dose of AMG 334, accounting for approximately 4418 patient-years. To date, no important risk has been identified for AMG 334.

A theoretical cardiovascular safety risk with CGRP pathway blockade is lack of compensatory vasodilation, particularly in the context of the coronary circulation during ischemic-related conditions although there has been no clinical evidence suggesting that selective blockade of the CGRP pathway during ischemia worsens myocardial ischemia to date. Patients in clinical trials will continue to be monitored for cardiovascular effects, and patients with pre-existing cardiovascular disease will be excluded from participation.

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 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.

Adverse reactions reported in the Feb 2020 (Edition 11) release of the Investigator Brochure were injection site reactions, constipation, muscle spasm and pruritus (all with common frequency, ≥ 1/100 to < 1/10) based on the pooled safety data from the blinded study phase of the Phase 2/3 studies. In post-marketing experience, serious hypersensitivity reactions, including rash, angioedema and anaphylactoid reactions, have been reported with Aimovig. These reactions may occur within minutes, although some may occur more than one week after treatment. Constipation with serious complications has also been reported in post-marketing setting. In a majority of these cases, the onset was reported after the first dose of Aimovig; however, patients have also experienced these events later on in the treatment.

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 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.

AMG 334 140 mg demonstrated a favorable benefit-risk profile for the prevention of migraine in adults in pivotal studies (CM Study 20120295 [including the open-label extension Study 20130255] and EM Study 20120296). 140 mg was also used into the long-term extension of study 20120178.

The key benefits of AMG 334 for prevention of migraine in adults consist of results that include reduction in frequency of MMDs, reduction in acute medication use, reduction in the impact of migraine on physical functioning (as measured by the MPFID PRO), as well as improvements in a range of other PROs, favorable tolerability (over the standard of care), low treatment discontinuation rates, convenience (once-monthly [QM] self-administered injections), and rapid onset of effect.

Overall, the safety profile of AMG 334 has been favorable. A limited number of adverse drug reactions have been identified at low frequencies (< 5%), most of which were mild or moderate in severity and generally did not lead to study discontinuation.

AMG 334 140 mg addresses an unmet need as an effective, safe, and tolerable preventive treatment of migraine. The key benefits of AMG 334 outweigh the risks in this population.

4 Population

The study population will consist of male and female patients, ages 18-65, with a documented history of episodic migraine (4 to 14 baseline migraine days), who have failed 2-4 previous migraine prophylactic treatments for lack of efficacy or tolerability. The physician decision that patients are not deemed suitable for specific prophylactic therapies due to other medical reasons will also be taken into account. See inclusion criteria 6-8 for detailed definitions.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria. For inclusion purposes, one month equals one calendar month.

During the Screening Epoch:

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. Documented history of migraine (with or without aura) for ≥12 months prior to screening according to the International Classification of Headache Disorders-12rd Edition (ICHD-3)
4. 4 to 14 days per month (in at least two separate attacks) of migraine symptoms (based on ICHD-3 criteria) on average across the 3 months prior to screening based on retrospective reporting
5. <15 days per month of headache symptoms (ie migraine and non-migraine)

Patients must have*:

6. Failed 2 to 4 prior migraine prophylaxis treatments out of the following:
   - Propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen)
7. Failed one AND failed *or* not be suitable for a second of the following:
   - Propranolol OR metoprolol
   - Topiramate
   - Flunarizine
8. Failed *or* not be suitable for valproate or divalproex

* The following definitions are applicable for inclusion criteria 6-8:

- Efficacy failure is defined as “no meaningful reduction in headache frequency after administration of the respective medication for an adequate period of time (at least 2-3 months are recommended by the European Headache Federation treatment guidelines) at generally accepted therapeutic dose(s) based on the investigator’s assessment within the last 5 years prior to screening.”
- Tolerability failure is defined as “documented discontinuation due to adverse events of the respective medication at any previous time.”
- “Not suitable” for the purpose of this study is defined as “patient is not considered to be suitable for the treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding

documents, or other medically relevant reasons" as confirmed by the treating physician.

During the Baseline Epoch:

9. Migraine frequency of 4 to 14 migraine days during the Baseline Epoch, confirmed by the eDiary
10. ≥80% eDiary compliance during the Baseline Epoch

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. Calendar months are used for exclusion purposes.

1. Older than 50 years of age at migraine onset
2. Unable to differentiate migraine from other headaches
3. History of cluster headache or hemiplegic migraine headache
4. Failed more than 4 prior migraine prophylaxis treatments out of the following:
   - Propranolol/metoprolol, topiramate, flunarizine, valproate/divalproex, amitriptyline, venlafaxine, lisinopril, candesartan, locally approved products (e.g. oxeterone or pizotifen)
5. Use of a prophylactic migraine medication within 5 half-lives, or a device or procedure within one month prior to the start of the baseline phase or during the baseline phase
6. Prior Botulinum toxin A treatment in the head/neck region (including cosmetic use or other licensed indications for Botox®) within 4 months prior to the start of the baseline epoch or during the baseline epoch
7. Use of the following for any indication in the 1 month prior to the start of the baseline phase or during the baseline phase:
   - Ergotamines or triptanes ≥10 days/month, or
   - Simple analgesics (NSAIDs, acetaminophen, paracetamol) ≥15 days/month, or
   - Opioid- or butalbital-containing analgesics ≥4 days/month
8. Anticipated to require any excluded medication (see Section 5.5.8, Table 5-1) or device (e.g., occipital nerve stimulators, transcranial magnetic stimulation) during the study
9. Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain)
10. History or current evidence of major psychiatric disorder (such as schizophrenia, bipolar disorder or type B personality disorder that might interfere with the ability to properly report clinical outcomes)
11. Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report
12. Current evidence of depression based on a BDI-II total score of > 19 at screening. Patients 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 one medication per disorder. Patients must have been on a stable dose within the 3 months prior to the start of the baseline phase

13. History of seizure disorder or other significant neurological conditions other than migraine
14. 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
15. Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
16. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
17. 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
18. Hepatic disease by history or total bilirubin ≥2×ULN or ALT or AST ≥3xULN as assessed by central laboratory at initial screening
19. Pregnant or nursing (lactating) women
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 110 days after stopping of study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., 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 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), eg hormone vaginal ring or transdermal hormone contraception
    - 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

    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 (e.g. 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.

21. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
22. History of hypersensitivity to the study drug or its excipients.
23. Any prior exposure to investigational products targeting the CGRP pathway, including previous AMG 334 studies
24. Unlikely to be able to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (e.g., independent completion of electronic diary items) to the best of the patient's and investigator's knowledge

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 1mL 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 epoch and in the open-label fashion for open-label treatment epoch and PTA-Open-Label Treatment Epoch. The study treatments will be labeled as:

- AMG 334 70mg/1mL / Placebo for Double-Blind Treatment Epoch
- AMG 334 70mg/1mL for Open-Label Treatment Epochs. If and when 140 mg/mL pre-filled syringes become available during the Open-Label Treatment Epoch, the 140 mg dose may be administered by a single 140 mg/mL s.c. injection.

5.1.2 Additional treatment

No additional treatment beyond investigational product and control drug is included in this trial.

5.2 Treatment arms

Patients will be assigned to either AMG 334 140 mg or placebo at the Randomization Visit (Visit 101), in a 1:1 ratio, stratified by monthly migraine headache frequency (4-7 migraine days per month during the Baseline Epoch vs 8-14 migraine days per month during the Baseline Epoch).

5.3 Treatment assignment and randomization

At Visit 101 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the two 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 packages of study drug to be dispensed to the patient. Randomization will be stratified by monthly migraine headache frequency (4-7

migraine days per month during the Baseline Epoch vs 8-14 migraine days per month during the Baseline Epoch). 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 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 stratified by migraine frequency. 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).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and Novartis personnel and their delegates will remain blinded to the identity of the treatment from the time of randomization until the conclusion of the Double-Blind Treatment Epoch and primary analysis, 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 with the exception of the randomization office, (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.

Unblinding will only occur in the case of patient emergencies (see Section 5.6). Randomization information will be available to the investigator when the study report for the Double-Blind Epoch has been finalized.

There is no blinding in the Open-Label Treatment Epochs.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). 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.

Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Disposition CRF, in addition to the completion of select pages of the eCRF as outlined in Section 6.1.

Investigators may re-screen a patient (Screening Epoch only) if there is reasonable certainty that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Some examples of re-screening reasons are listed below. If needed, questions regarding re-screen eligibility may be discussed with Novartis.

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

A patient may can fail the Screening Epoch one time; should this occur, the site should re-consent the patient and assign a new patient identification number. A repeat of the Baseline Epoch is not allowed. Once randomized, the patient identification number must remain constant throughout the entire clinical study.

5.5.2 Dispensing the study drug

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

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

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.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will provide all study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor for review. Used and unused study treatment should be disposed of in accordance with local requirements.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Subcutaneous (s.c.) injections are to be given for each investigational product administration. For purposes of study treatment dosing, "q.m." 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 (e.g., 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.

Double-Blind Treatment Epoch:

Two injections of AMG 334 70 mg (equaling 140 mg total dose) or placebo will be administered by qualified study staff at each dosing visit during the 12-week double-blind treatment epoch (i.e., at Day 1 and Weeks 4 and 8).

Open-label Treatment Epoch and PTA-Open-Label Treatment Epoch:

Two injections of open-label AMG 334 70 mg (equaling 140 mg total dose) will be administered by qualified study staff at each dosing visit during the 156-week open-label treatment epoch (ie, at Weeks 12, 16, 20, 24, etc.) and during the PTA-Open-Label Treatment Epoch (ie, at Weeks 168, 172, 176, 180 etc.). If and when 140 mg/mL pre-filled syringes become available during the Open-Label Treatment Epoch, the 140 mg dose may be administered by a single 140 mg/mL s.c. injection.

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 (e.g., 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.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, delivery of study drug directly to a patient's home is generally permitted in the event the Investigator has decided that an on-site visit by the patient is no longer appropriate or possible, and that it is in the interest of the patient's health to administer (e.g., self-injection or study staff administration at patients'

home) the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis (see Section 10.2 for required training process). The dispatch of study drug from the site to the patient's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1 month supply. In this case, regular phone calls or virtual contacts (at the time of every scheduled visit, or more frequently if needed) will occur between the site and the patient for instructional purposes, safety monitoring, and discussion of the patient's health status until the patients can again visit the site.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational dose adjustments are not permitted. Interruptions are allowed as specified in Section 7.3. Additionally, investigator-initiated interruptions will be considered on a case-by-case basis.

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 (e.g., biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine).

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 the eCRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after enrolling 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 concomitant medications/ significant non-drug therapies eCRF.

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 treatments

Use of the treatments displayed in Table 5-1 is NOT allowed as designated due to the potential confounding of efficacy assessments unless in the context of a different pre-existing condition in stable doses for at least 3 months prior to baseline.

Table 5-1 Prohibited Treatments

Treatment	Prohibition period
All oral beta blockers Topiramate Flunarizine Valproate/Divalproex Antidepressants (amitriptyline, venlafaxine, desvenlafaxine) ACE/ARB (lisinopril, candesartan) Serotonin antagonistic agents (oxetorone, pizotifen, methysergide)	Within 5 half-lives of the start of the baseline epoch and throughout the study when used for migraine prophylaxis
Botulinum toxin (in the head and/or neck region)	Within 4 months of the start of the baseline epoch and throughout the study
Devices or invasive interventions (eg, nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation)	Within 1 month of the start of the baseline epoch and throughout the study

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. If the IRT system is not available for technical reasons, the IRT help desk can facilitate emergency code break requests. 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 e-mail 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 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 patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time. If a code break occurs, the patient may continue in the Double-Blind Treatment Epoch (DBTE) and Open-Label Treatment Epoch (OLTE) at the investigator's discretion.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the Double-Blind Treatment Epoch when the patient has completed Visit 199 in the protocol. A patient will be considered to have completed the Open-Label Treatment Epoch when the patient has completed Visit 299 in the protocol. A patient will be considered to have completed the PTA-Open-Label Treatment Epoch when the patient has completed Visit 499 in the protocol.

Patients can stay in the Open-Label Treatment Epoch for 156 weeks (3 years), or until the study is early terminated by the sponsor. Patients may stay in the PTA-Open-Label Treatment Epoch as specified in Section 3.1.

The study will be considered complete (End of Trial) when the last patient completes their last visit (i.e., LPLV) in the study.

The patient's completion status will be recorded on the appropriate Study Phase Completion eCRF pages.

For all patients not continuing on AMG 334, either in the Open-Label Treatment Epoch or commercially, outside the study (if locally available), a safety follow-up visit (visit 301) should be conducted 16 weeks after the last AMG 334A dose administration. The information to be collected at this follow up visit is outlined in Table 6-1,and Table 6-4.

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 6.5.6 and Section 7.5)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study treatment might result in a safety risk to the patient
- Unsatisfactory therapeutic effect
- Patient's condition no longer requires study treatment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

In addition, study treatment should be discontinued under the following circumstances during the PTA- Open-Label Treatment Epoch:

- Upon country-level launch (as specified in Section 3.1)

- Patient is no longer clinically benefitting from treatment in the opinion of the investigator

If discontinuation of study treatment occurs in the Double-Blind Treatment Epoch, the patient should NOT be considered withdrawn from the study, and should continue recording in the eDiary as per protocol. If permanent discontinuation of study treatment occurs during the Open-Label Treatment Epoch or during the PTA-Open-Label Treatment Epoch, the patient should be discontinued from the study.

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 (week 12 if during the DBTE, week 168 if during the OLTE, or visit 499 if during the PTA-Open-Label Treatment Epoch) will be performed. At this final visit, the adverse event and concomitant medications should be reconciled on the eCRF. Patients will return for a follow-up visit approximately 16 weeks after their last dose of study medication, and perform the study procedures outlined in Table 6-1 or Table 6-4 or Table 6-5, depending upon the duration of study participation at the time of discontinuation. After study treatment discontinuation from the Double-Blind Treatment Epoch, the patient, if willing, should continue to follow the visit schedule until Week 12 is reached. At a minimum, 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 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 (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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 the assessment table below.

5.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. 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 for example slow enrollment or an unreasonably low number of patients continuing). In the event that the study is terminated early, the IRBs/IECs will be informed. Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn 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.

6 Visit schedule and assessments

Table 6-1, Table 6-2, Table 6-3 Table 6-4 and Table 6-5 list all of the assessments and indicate with an "X" when the visits are performed.

Patients 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.

If the **COVID-19 pandemic** limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the patient's home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the patient to visit the site again (see Section 6.4 efficacy, Section 6.5.4 Laboratory evaluations, Section 6.5.6 Pregnancy and assessments of fertility, Section 6.6.6 AMG 334 Antibody testing, [redacted] Section 7 Safety monitoring and Section 7.6 Prospective suicidality assessment for further COVID-19 guidance related to sample collection).

Table 6-1 Assessment Schedule: Double-Blind Treatment

Epoch	Screen	Baseline[3]	Double-Blind Treatment[1,4]				Follow-Up[2]	Notes
Visit	**1**	**2**	**101**	**102**	**103**	**199**	**301**	Follow up visit is 16 weeks after last dose of IMP (V103 / Wk 8), which is 12 weeks after last DBT visit (V199 / Wk 12).
Week	**-6**	**-4**	**Day 1**	**4**	**8**	**12/PSD/TD**	**24/FU**	
Obtain Informed Consent	X							
Randomization			X					
Demography	X							
Medical & Medication History	X							Including prior prophylactic migraine medication
Treatment Failure Confirmation	X							
Complete Physical Exam	S					S	S	
Brief Physical Exam		S	S	S	S			
Height	X							
Weight	X		X			X	X	
Vital Signs[5]	X	X	X	X	X	X	X	
Chemistry/Hematology	X		X			X	X	
Serum Pregnancy	X					X		
Urine Pregnancy		X	X	X	X		X	
ECG	X		X	X		X		
Anti-AMG Antibodies			X			X	X	
[redacted]								
eDiary Dispensing		S						
eDiary Return			S	S	S	S		Pt brings to each visit for use at site
Clinical Outcomes (eDiary)		Daily (Migraine days, [redacted] duration, severity, rescue medication)						

Epoch	Screen	Baseline[3]	Double-Blind Treatment[1,4]				Follow-Up[2]	Notes
Visit	**1**	**2**	**101**	**102**	**103**	**199**	**301**	Follow up visit is 16 weeks after last dose of IMP (V103 / Wk 8), which is 12 weeks after last DBT visit (V199 / Wk 12).
Week	**-6**	**-4**	**Day 1**	**4**	**8**	**12/PSD/TD**	**24/FU**	
[redacted]								
MPFID (eDiary)		Daily						
[redacted]								
C-SSRS	X	X	X	X	X	X	X	Should also be performed at unscheduled visits.
[redacted]								
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events[7]			X	X	X	X	X	
Serious Adverse Events[7]	X	X	X	X	X	X	X	
Study Drug Administration[8]			X	X	X			
Contact IRT[9]	X	X	X	X	X	X		
Screening Phase Completion Form	X							
Baseline Phase Completion Form		X						
Double Blind Phase Completion form						X		
Follow-Up Phase Completion Form							X	

1 – All study visit target dates are to be calculated from the Day 1 visit date, and all study procedures for a given visit should be completed in the same day.

2 – The Follow-Up Visit is required for all patients who either discontinue study drug early or complete the study in either the Double-Blind or Open-Label Treatment Epochs and do not continue commercial drug (if locally available).

3 – Enrollment into the Baseline Epoch can occur only if the patient successfully completes all requirements for the Screening Epoch.

Epoch	Screen	Baseline[3]	Double-Blind Treatment[1,4]				Follow-Up[2]	Notes
Visit	**1**	**2**	**101**	**102**	**103**	**199**	**301**	Follow up visit is 16 weeks after last dose of IMP (V103 / Wk 8), which is 12 weeks after last DBT visit (V199 / Wk 12).
Week	**-6**	**-4**	**Day 1**	**4**	**8**	**12/PSD/TD**	**24/FU**	

4 – Entry (ie, randomization) into the Double-Blind Treatment Epoch using the IRT System must occur only after the successful completion of all Baseline Epoch requirements and prior to the first dose of study drug (randomization and administration of the first dose must occur on Day 1).

5 – Includes blood pressure, pulse and temperature.

[redacted]

7 - SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch end of study (16 weeks after the last dose of study drug). Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (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.

8 – Study drug is administered by study staff, during the applicable study visits. Two pre-filled syringes will be administered at every visit.

9 - Sites will access the Interactive Response Technology (IRT) System to enter the patient into the initial screening phase, to randomize an eligible patient into the double-blind treatment phase, and to register study early termination. Patient data will be collected in the IRT System including, but not limited to, reason for screen fail (if applicable). The IRT system will automatically assign study drug when a patient is randomized.

[redacted]

TD = Study treatment discontinuation; PSD = Premature patient discontinuation; X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

Table 6-2 Assessment Schedule: Open-Label Treatment– Weeks 13-64 (1st year in Open-Label extension)

Epoch	Open-Label Treatment[1,2,3]													
Visit	**199**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**
Week	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**
Open-label Treatment Phase Entry	X													
Complete Physical Exam	S													S
Brief Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S	
Weight	X			X										X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry/Hematology	X			X										X
Serum Pregnancy	X													X
Urine Pregnancy		X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X	X												X
Anti-AMG Antibodies	X			X										X
[redacted]														
eDiary Dispensing[5]	S	S	S				S			S			S	
eDiary Return[5]	S	S	S	S				S			S			S
Clinical Outcomes (eDiary)[6]	Daily						X			X			X	
[redacted]														
MPFID[6,9] (eDiary)	Daily						X			X			X	
[redacted]														

Epoch	Open-Label Treatment[1,2,3]													
Visit	**199**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**
Week	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**
[redacted]														
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 – All study visit target dates are to be calculated from the Day 1 visit date, and all study procedures for a given visit should be completed in the same day.

2 – The Follow-Up Visit is required for all patients who either discontinue study drug early or complete the study and do not continue commercial drug (if locally available) in either the Double-Blind or Open-Label Treatment Epochs.

3 – Entry into the Open-Label Treatment Epoch can occur only if the patient successfully completes all requirements for the Double-Blind Treatment Epoch.

4 – Includes blood pressure, pulse and temperature.

5 – eDiaries will be used for the first 12 weeks of the Open-Label Treatment Epoch and again at periodic intervals as identified in the assessment schedule.

6 - Daily collection during the respective 4 week periods

7 - HRQ collection after migraines during the respective 4 week periods

[redacted]

10 - SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch end of study (16 weeks after the last dose of study drug). Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (16 weeks after the last dose of study drug).

11 – Two pre-filled syringes will be administered by study staff, during the applicable study visits, q.m., s.c..

12 - Sites will access the Interactive Response Technology (IRT) System to enter the patient into the open-label treatment phase and to register study early termination.

X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

Table 6-3 Assessment Schedule: Open-Label Treatment – Weeks 65-116 (2nd Year in Open-Label extension)

Epoch	**Open-Label Treatment[1, 2]**												
Visit	**214**	**215**	**216**	**217**	**218**	**219**	**220**	**221**	**222**	**223**	**224**	**225**	**226**
Week	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**
Year in OLTE													**2**
Complete Physical Exam													S
Brief Physical Exam	S	S	S	S	S	S	S	S	S	S	S	S	
Weight													X
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry/Hematology													X
Serum Pregnancy													
Urine Pregnancy	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG													X
Anti-AMG Antibodies							X						X
[redacted]													
eDiary Dispensing[4]		S			S			S			S		
eDiary Return[4]			S			S			S			S	
Clinical Outcomes[5] (eDiary)		X			X			X			X		
MPFID[5,6] (eDiary)		X			X			X			X		
[redacted]													
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT[10]	X	X	X	X	X	X	X	X	X	X	X	X	X

Epoch	Open-Label Treatment[1, 2]												
Visit	**214**	**215**	**216**	**217**	**218**	**219**	**220**	**221**	**222**	**223**	**224**	**225**	**226**
Week	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**
Year in OLTE													**2**

1 – All study visit target dates are to be calculated from the Day 1 visit date, and all study procedures for a given visit should be completed in the same day.

2 – The Follow-Up Visit is required for all patients who either discontinue study drug early or complete the study and do not continue commercial drug (if locally available) in either the Double-Blind or Open-Label Treatment Epochs. Follow up visit is 16 weeks after last dose of IMP (V238 / Week164), which is 12 weeks after last OLTE visit (V299 / Week 168).

3 – Includes blood pressure, pulse and temperature.

4 – eDiaries will be used for the first 12 weeks of the Open-Label Treatment Epoch and thereafter at periodic intervals as identified in the assessment schedule.

5 – Daily collection during the respective 4 week periods

[redacted]

8 - SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch end of study (16 weeks after the last dose of study drug). Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (16 weeks after the last dose of study drug).

9 – Two pre-filled syringes will be administered by study staff, during the applicable study visits, q.m., s.c.. If and when 140 mg/mL pre-filled syringes become available during the Open-Label Treatment Epoch, the 140 mg dose may be administered by a single 140 mg/mL s.c. injection.

10 - Sites will access the Interactive Response Technology (IRT) System to enter the patient into the open-label treatment phase and to register study early termination.

X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

Table 6-4 Assessment Schedule: Open-Label Treatment – Weeks 117-168 (3rd year in Open-Label extension)

Epoch	Open-Label Treatment[1, 2]													FU[2]
Visit	**227**	**228**	**229**	**230**	**231**	**232**	**233**	**234**	**235**	**236**	**237**	**238**	**299/PSD**	**301**
Week	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**	**164**	**168**	**180**
Year in OLTE													**3**	
Complete Physical Exam													S	S
Brief Physical Exam	S	S	S	S	S	S	S	S	S	S	S	S		
Weight													X	X
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry/Hematology													X	X
Serum Pregnancy													X	
Urine Pregnancy	X	X	X	X	X	X	X	X	X	X	X	X		X
ECG													X	
Anti-AMG Antibodies							X						X	X
eDiary Dispensing[4]	S			S			S			S		S		
eDiary Return[4]		S			S			S			S		S	
Clinical Outcomes[5] (eDiary)	X			X			X			X		X		
MPFID[5,6] (eDiary)	X			X			X			X		X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration[9]	X	X	X	X	X	X	X	X	X	X	X	X		
Contact IRT[10]	X	X	X	X	X	X	X	X	X	X	X	X		

Epoch	Open-Label Treatment[1, 2]													FU[2]
Visit	**227**	**228**	**229**	**230**	**231**	**232**	**233**	**234**	**235**	**236**	**237**	**238**	**299/PSD**	**301**
Week	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**	**164**	**168**	**180**
Year in OLTE													**3**	
Open-Label Phase Completion													X	
Follow-Up Phase Completion														X

1 – All study visit target dates are to be calculated from the Day 1 visit date, and all study procedures for a given visit should be completed in the same day.

2 – The Follow-Up Visit is required for all patients who either discontinue study drug early or complete the study and do not continue commercial drug (if locally available) in either the Double-Blind or Open-Label Treatment Epochs. Follow up visit is 16 weeks after last dose of IMP (V238 / Week164), which is 12 weeks after last OLTE visit (V299 / Week 168).

3 – Includes blood pressure, pulse and temperature.

4 – eDiaries will be used for the first 12 weeks of the Open-Label Treatment Epoch and thereafter at periodic intervals as identified in the assessment schedule.

5 – Daily collection during the respective 4 week periods

[redacted]

8 - SAEs will be collected after signing of the informed consent through the end of the Follow-Up Epoch end of study (16 weeks after the last dose of study drug). Non-serious AEs will be collected after randomization (Visit 101) through the end of the Follow-Up Epoch (16 weeks after the last dose of study drug).

9 – Two pre-filled syringes will be administered by study staff, during the applicable study visits, q.m., s.c.. If and when 140 mg/mL pre-filled syringes become available during the Open-Label Treatment Epoch, the 140 mg dose may be administered by a single 140 mg/mL s.c. injection.

10 - Sites will access the Interactive Response Technology (IRT) System to enter the patient into the open-label treatment phase and to register study early termination.

PSD = Premature patient discontinuation; X = Assessment to be recorded in the source documents and the clinical data base; S = Assessment to be recorded as source documentation only.

Table 6-5 Assessment Schedule – PTA-Open-Label Treatment

Epoch		PTA Open-Label Treatment						
		Initial 3 month cycle			Repeat 3-Month cycle until end of PTA			
Visit	299	401	402	403	404	405	406	499[2] / End PTA
Weeks	168	172	176	180	184	188	192	
Study drug administration	X	X	X	X	X	X	X	
Contact IRT	X	X	X	X	X	X	X	
Adverse Events/ Serious Adverse Events	X	X	X	X	X	X	X	X
Concomitant medications / therapies	X	X	X	X	X	X	X	X
Clinical Global Impression - Severity	X							
Clinical Global Impression - Improvement		X	X	X	X	X	X	X
Clinical Global Impression – Efficacy Index		X	X	X	X	X	X	X
Pregnancy test (urine)[1]				X			X	X
PTA-Open-Label Treatment Epoch Completion								X

X Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Results of pregnancy tests will be documented in source documents.

[2] Once PTA ends in a country the patient should come to the clinic for a final End of Treatment visit (occurs 4 weeks after previous dose)

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the Double-Blind Treatment Epoch will have the Screening Phase Disposition and the Baseline Phase Completion eCRF (as applicable), 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, including information on the suitability for migraine prophylactics will be collected as part of baseline characteristics.

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

6.2.1 Treatment failure confirmation

Confirmation of eligibility related to treatment failure inclusion criteria will be confirmed via the eDiary prior to entry into the Baseline Epoch.

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 eCRF at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Site staff will review eDiary compliance with the patient at each visit, when applicable.

6.4 Efficacy

Efficacy assessments will include:

- Migraine days
- Migraine Physical Function Impact Diary (MPFID)

The timing and frequency of these assessments are outlined in Table 6-1 , Table 6-2, Table 6-3 and Table 6-4. 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.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, efficacy information including PRO scales may still be collected by using the provided eDiary.

6.4.1 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)

6.4.2 Migraine Physical Function Impact Diary (MPFID)

Patients will complete the MPFID every day using the eDiary at time points outlined in Table 6-1 , Table 6-2, Table 6-3 and Table 6-4. The recall period is the past 24 hours.

The Migraine Physical Function Impact Diary (MPFID) is a self-administered 13-item instrument measuring physical functioning. It has two domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and one stand-alone global question which provides an assessment of overall impact on everyday activities. Patients respond to items using

a 5-point scale, with difficulty items ranging from “Without any difficulty” to “Unable to do” and frequency items ranging from “None of the time” to “All of the time.”

These are assigned scores from 1 to 5, with 5 representing the greatest burden. For each domain, the scores will be calculated as the sum of the item responses and the sum will be rescaled to a 0 - 100 scale, with higher scores representing greater impact of migraine (ie, higher burden). There will be a score for each of the two domains and a third score for the stand-alone item. Patients with a reduction of 5 or more points in either of the two domains will be evaluated as responders.

6.4.3 Appropriateness of efficacy assessments

The definition of migraine day (Section 6.4.1) 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 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 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. Given that this trial is not considered a pivotal trial but rather should provide clinical guidance, the 50% RR was considered more relevant as therefore been chosen as the primary endpoint. The change in physical impairment and impact on everyday activities as assessed by the MPFID was selected because they are highly clinically relevant and provide complementary information to the primary endpoint in the evaluation of AMG 334 as a migraine prophylactic agent.

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]

6.5 Safety

Safety assessments will include:

- Adverse events (Section 7.1)
- Physical examination
- Vital signs
- Height/Weight

- Laboratory evaluations
- Pregnancy testing (females of childbearing potential)
- ECG
- Columbia Suicide Severity Rating Scale (C-SSRS) (Section 7.6)

The timing and frequency of these assessments are outlined in Table 6-1 , Table 6-2, Table 6-3 Table 6-4 and Table 6-5.

6.5.1 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 2, 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 Medical History part of the eCRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.

6.5.2 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.

6.5.3 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.

6.5.4 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.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, or if visits by site staff to a patient's home are not feasible, the collection of samples may be modified by Novartis and will be communicated to the Investigator (e.g., local lab collection of samples).

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Bilirubin (total, direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT), and GGT will be measured.

6.5.5 Electrocardiogram (ECG)

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, patient 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 medical history/Current medical conditions/AE eCRFs as appropriate.

6.5.6 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 , Table 6-2, Table 6-3 , Table 6-4 and Table 6-5.

During COVID-19 pandemic, if a patient cannot visit the site to have pregnancy tests conducted the patient may complete a urine pregnancy test at home and report the result to the site. It is important that patients are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the patient so that the Site is informed of the pregnancy test results.

6.5.7 Appropriateness of safety measurements

The safety assessments have been selected based upon the safety profile of the drug as reported in the Investigator Brochure, are standard for this patient population and drug class.

6.6 Other assessments

[redacted]

- Anti-AMG antibody collection

[redacted]

The timing and frequency of these assessments are outlined in Table 6-1, Table 6-2, Table 6-3 and Table 6-4 and Table 6-5.

6.6.1 Patient Reported Outcomes (PROs)

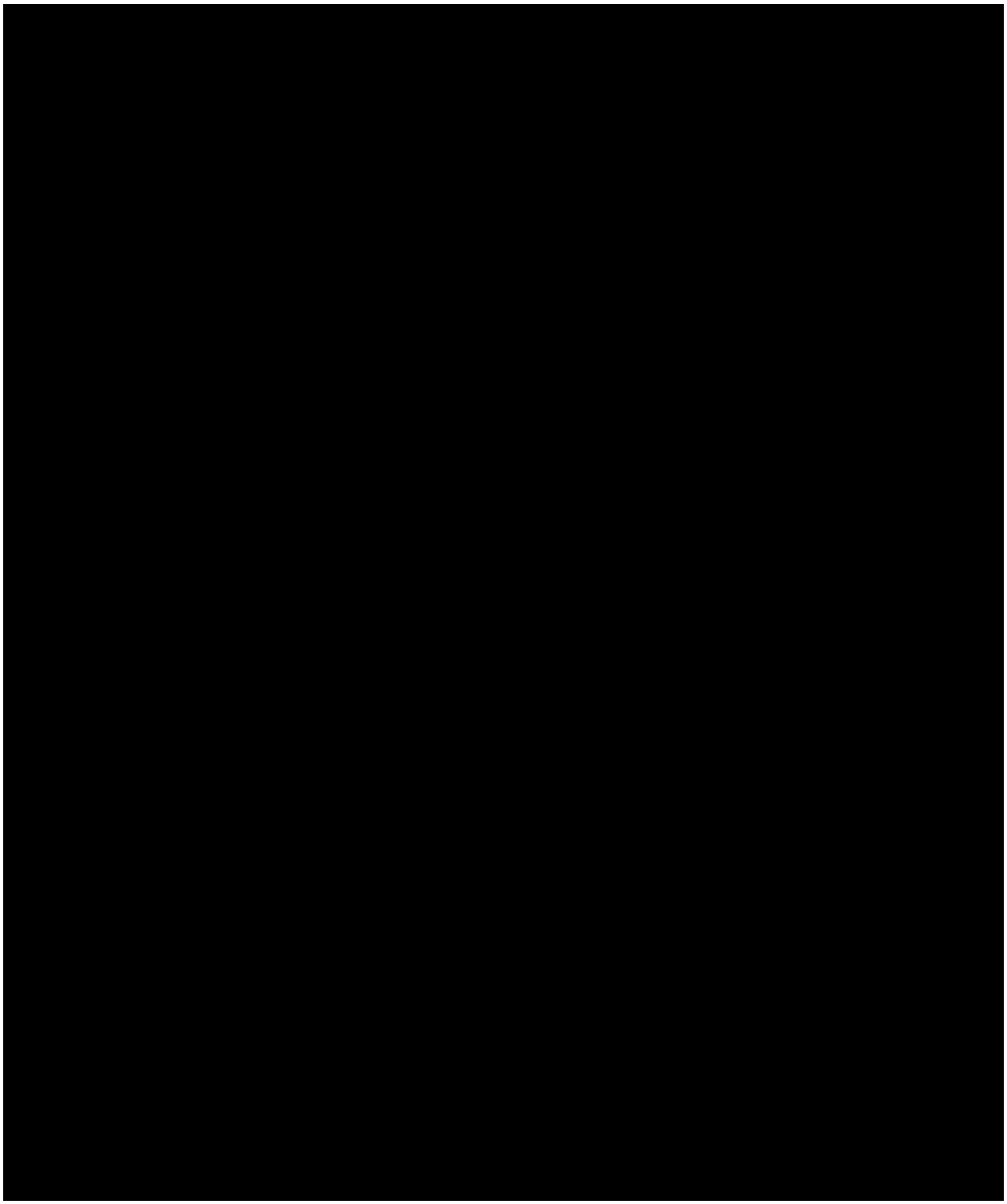
Patients will complete all Patient Reported Outcome (PRO) questionnaires using the provided eDiary platform. For those questionnaires that are completed in-clinic, during visits, completion should occur before any other assessments are performed.

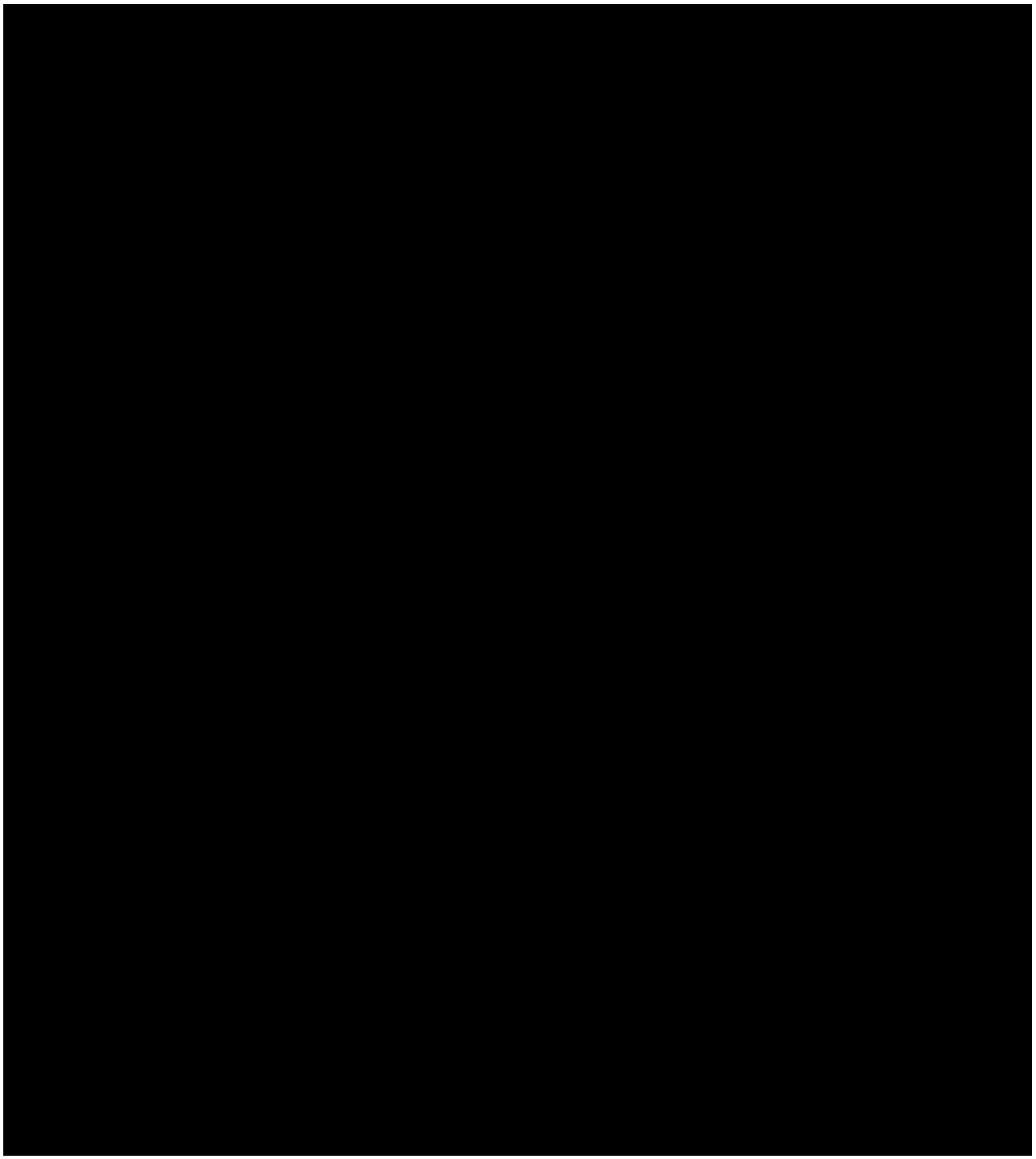
All questionnaires will be completed in the language most familiar to the respondent, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation.

Patients should be given sufficient space and time to complete all study PROs. If patients experience any difficulties with submission after they complete the PROs, the study staff should assist them with submitting their PRO responses. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this should be documented in study source records.

Site staff will review eDiary compliance with the patient at each applicable visit. Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs), and the review should be documented in the patient's source document accordingly. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

[redacted]





6.6.4 Pharmacokinetics

Not applicable.

[redacted]

6.6.6 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.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, or if visits by site staff to a patient's home are not feasible, the collection of samples may be modified by Novartis and will be communicated to the Investigator.

[redacted]

7 Safety monitoring

During the **COVID-19 pandemic** that limits or prevents on-site study visits, regular phone or virtual calls will occur (at the time of every scheduled visit or more frequently if needed) for safety monitoring and discussion of the patient's health status until the patient can again visit the site.

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient from randomization (Visit 101) until the end of study visit. Any events occurring during the Screening and Baseline Epochs should be documented as medical history. 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.

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity 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 (no/yes)
- 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 [investigational] treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational 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, eg, 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.

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, e.g. 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.

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 completion of the Follow-Up Epoch must be reported

to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the completion of the Follow-Up Epoch should only be reported to Novartis 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 study treatment, 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.

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):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

Please refer to Table 13-1-Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1-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 13-2-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 Liver eCRF pages.

- 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 (e.g., 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 appropriate eCRF pages, including the liver event overview eCRF pages.

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 (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 dose administration record (DAR) eCRF 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.

Table 7-1 Guidance for Capturing the Study Treatment Errors Including Misuse/Abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	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 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.

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

7.6 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (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 in a web-based interactive response system (eC-SSRS) via the patient's eDiary or via the web link. 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, e-mail 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 or early project teams.

During the **COVID-19 pandemic** that limits or prevents on-site study visits, the eC-SSRS may still be collected via the patient's eDiary or via the web link.

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 CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (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 entries on the eCRFs, 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. Data will be remotely monitored to identify trends, patterns and risk factors by a centralized Novartis Clinical Research Associate (CRA) organization.

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 eCRFs 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 eCRF entries. 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 will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. 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 eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct 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 (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

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 database will be sent electronically to Novartis (or a designated CRO).

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]

8.4 Data Monitoring Committee

Based on the existing safety profile of AMG 334, a data monitoring committee is not necessary for this phase 3b study.

8.5 Adjudication Committee

Not required.

9 Data analysis

The first analysis will be conducted on all patient data when the Double-Blind Treatment Epoch of the trial ends.

There will be three additional analyses during the Open-Label Treatment Epoch, before the final analysis.) i.e. after all patients completed the initial 12 weeks of the OLTE (weeks 12-24), as well as after 1 year and 2 years in the OLTE. Only a selected set of efficacy analyses will be conducted for the 12-24 weeks analysis, whereas the 1 and 2 years analyses will be complete.

There will be a final analysis of all the data, including the Follow-Up Epoch data, after the Open-label Treatment Epoch and PTA-Open-Label Treatment Epoch end.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The Full analysis set (FAS) will consist of all patients who started study medication and have completed at least one post-baseline monthly migraine day measurement in the double-blind treatment epoch. In FAS, patients will be analyzed according to randomized treatment, regardless of the actual treatment received.

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

The open-label analysis set (OLAS) will consist of all patients receiving at least one dose of AMG 334 in the open-label treatment epoch. This analysis set will be used when summarizing data collected during the Open-Label Treatment Epoch.

The PTA analysis set (PTAS) will consist of a subset of OLAS patients receiving at least one dose of AMG 334 in the PTA-Open-Label Treatment Epoch.

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 patients (total). The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients (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 patients 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.

9.4 Analysis of the primary variable(s)

The primary endpoint is the achievement of at least a 50% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch.

9.4.1 Variable(s)

The primary variable, 50% responder rate, is the proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analyses will compare the 50% response rate, which is defined as the proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch, between AMG 334 vs placebo.

A Cochran-Mantel-Haenszel (CMH) test stratified by the migraine frequency (4-7 and 8-14 monthly migraine days strata) will be used under a 2-sided significance level of 0.05 to evaluate the association between the 50% responder rate and the treatment. The p-value of the test, and the estimated odds ratio between AMG 334 and placebo, as well as its 95% confidence interval, will also be reported. Patients with missing monthly migraine day data at month 3 of the double-blind treatment epoch will be imputed as non-responders.

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. 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

For sensitivity analysis purposes, two models will be used: (1) a logistic regression model with missing monthly migraine days measurement for month 3 imputed as non-responder and (2) a generalized linear mixed model (GLMM) with no imputation on missing monthly migraine days.

In addition, 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 for the Double-Blind Treatment Epoch.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary variables are:

During the Double-Blind Treatment Epoch:

- Change from baseline in monthly migraine days in the last month (month 3) of the double-blind treatment epoch
- Change from baseline to month 3 of the MPFID “impact on everyday activities” domain score
- Change from baseline to month 3 of the MPFID “physical impairment” domain score
- Change from baseline in acute monthly migraine-specific treatment days in the last month (month 3) of the double-blind treatment epoch
- 75% responder rate: Proportion of patients who achieve at least a 75% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch.
- 100% responder rate: Proportion of patients who achieve at least a 100% reduction from baseline in monthly migraine days in the last month (month 3) of the Double-Blind Treatment Epoch.

The above continuous endpoints (ie, change from baseline) will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The responder endpoints will be analyzed using the same method as for the primary endpoint.

9.5.2 Safety variables

Safety variables are:

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

As safety analyses, patient incidence of treatment-emergent adverse events will be tabulated by system organ class and preferred term by treatment group for the Double-Blind Treatment Epoch.

Change from baseline for clinical laboratory values and vital signs will be summarized by visit and by treatment group for the double-blind treatment epoch.

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

For the Open-Label Treatment Epoch, follow-up time adjusted patient incidence rate of treatment-emergent adverse events will be tabulated overall and by randomized treatment group. Measurements of safety laboratory and vital signs will be summarized over time and laboratory shift tables will be provided.

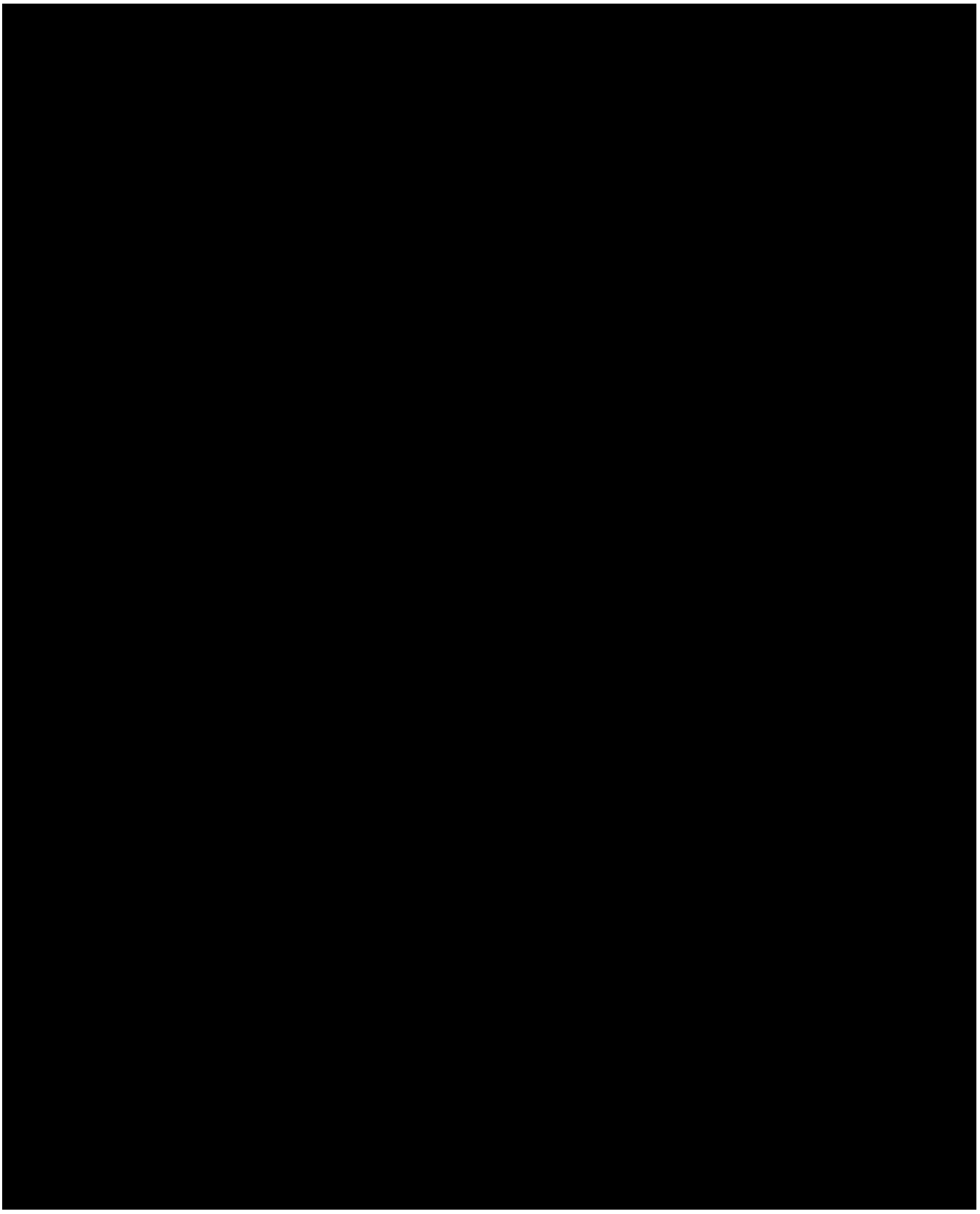
Safety analyses will be performed for the Double-Blind Treatment Epoch, as well as for the combined Open-Label Treatment Epoch and PTA-Open-Label Treatment Epoch.

[redacted]

9.5.4 PK/PD

Not applicable.

[redacted]



9.7 Interim analyses

No interim analysis will be performed during the Double-Blind Treatment Epoch.

During the Open-Label Extension period, interim analyses, summarizing long-term safety and efficacy data in this study population, will be conducted according to the schedule stated in Section 3.5, and summary statistics will be produced for the endpoints listed in Section 9.6.

Only a selected set of efficacy analyses will be conducted for the 12-24 weeks analysis, whereas the 1 and 2 years analyses will be complete.

9.8 Sample Size Calculation

The treatment effect of AMG 334 140mg (compared to placebo) observed in study 296 at month 3 for overall episodic migraine patients (Full Population), patients with one or more treatment

failures (1+TF), and patients with two or more treatment failures (2+TF) are described in Table 9-1.

Table 9-1 Observed Treatment Effect at Month 3 in Study 296 (140mg vs. placebo)

	Placebo Response	AMG 334 Response	Treatment Effect Odds Ratio	Treatment Effect Rate Difference
Full Population	26.3%	48.5%	2.64	22%
1+ TF	18.3%	45.5%	3.73	27%
2+ TF	14.8%	47.4%	5.19	33%

Assuming a treatment effect similar to the effect observed in a previous study with AMG 334 in episodic migraine, the following sample size considerations apply.

Under 2-sided 0.05 alpha level, with 90% power, it takes 220 patients (110 per treatment group) to detect about an absolute 20% improvement on the response rate of 50% reduction on migraine days assuming 18% response rate in placebo group (equivalent of 2.8 in terms of odds ratio.

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 may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide a proposed informed consent form to investigators 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.

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.

[redacted]

During the **COVID-19 pandemic** the Investigator should discuss the home-delivery of study drug, and should provide detailed step by step instructions for the proper method for self administration of study drug including: 1) the correct handling, 2) self-administration procedure, and 3) storage of study drug. This training may be done in person or videoconference or by telephone if patient visits to site are not possible. This training process needs to be documented in the patient chart with the patient's verbal/e-mail/ or chat function agreement. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial patient and person obtaining informed consent, etc). Written informed consent must be obtained once protocol amendment 4 is approved at the site.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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.

An initial study report will be prepared and finalized for all data from the Double-Blind Epoch. A second and final study report will be prepared, incorporating data from the Open-Label Treatment Epoch including the Follow-Up Epoch and the PTA-Open-Label Treatment after all patients have completed their respective last visit (LPLV).

In addition, upon completion of each of the interim analyses (weeks 12-24 of the Open-Label Treatment Epoch, 1 year and 2 years of the Open-Label Treatment Epoch) and upon finalization of the initial and final study reports 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 (CQA), 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.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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 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.

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13 Appendices

Appendix 1: Clinically notable laboratory values

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

Notable 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 μmol/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

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

Table 13-1 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) • 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 13-2 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 study drug	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• 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 (e.g., 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 • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
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.