NOVARTIS

Clinical Development – General Medicine

AMG 334 (erenumab)

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)

Statistical Analysis Plan (SAP)

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SAP History

- *Version 1.0- SAP version 15-Mar-2017, Effective 16-Mar-2017*
  - *Initial SAP*
- *Final Amendment1- Amended SAP version 12-Dec-2017, Effective 14-Dec-2017*
  - *SAP updated with Amended Protocol v.2.0 from 23 October 2017 and review process*
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  - *SAP updated with Amended of Protocol v.3.0 from 8 March 2018*
- **Document History – Changes compared to previous final version of SAP**

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
8 Mar-2018	*After to Database lock*	*Add in additional post-hoc analyses which will be shown in CSR*	*N/A*	*Title page*
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
		Updated based on protocol amendment 3	*Moved all information about statistical analyses during OLTE from current SAP to a separate SAP dedicated for open-label*	*All sections*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			extension period due to extended OLTE SAP	
12-Dec-2017	*Prior to Database lock*	*Creation of SAP Amendment1*	*N/A - some minor edits to make it more clear*	*Title page*
		[redacted]	[redacted]	[redacted]
		Updated for more clear for programming purpose	*Changed calculation of migraine duration*	*Section 2.1.1 General Definitions*
		[redacted]	[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		[redacted]	[redacted]	[redacted]
		Added to be more clear for programming purpose	*Added Randomized Analysis Set (RAS) definition;*	*Section 2.2 Analysis sets* *Section 4 Change to protocol specified analyses*
		Added for population of analysis	*Patient disposition, demographic and other baseline characteristics including previous migraine treatments is summarized and presented on the Randomized Analysis Set (not FAS);*	*Section 2.3 Patient disposition, demographics and other baseline characteristic*
		Updated for clarification purpose	*Updated formula for compliance;*	*Section 2.4.1 Study treatment / compliance*
		Added similar to sensitivity analysis of MMD because 50% Responder rate is based on MMD	*Sensitivity analyses for Primary endpoint based on multiple imputation with assumption of MAR and MNAR are added;*	*Section 2.5.3 Sensitivity analyses* *Appendix 5.4.1 Primary analysis*
		Updated for data presentation purpose	*Changed sorting rules: alphabetically by SOC and in descending order of frequency for PT.*	*Section 2.7.1 Adverse events*
		Updated for clarity	*Summary statistics will be presented. No presentation will be based on CTCAE grade.*	*Section 2.7.2 Laboratory data*
		Updated for data presentation purpose	*Presentation in Table will be only for abnormal values.*	*Section 2.7.4 Electrocardiogram (ECG)*
		[redacted]		

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		clarity	*categorical - MPFID, [redacted]: the stratified CMH analysis will be used, not Logistic.*	*Patient-reported outcome analyses*
		Updated for clarity	*Changed title of Section 2.7.6 to Antibody Formation - Immunogenicity (IG) analysis set; Added Sections 2.7.6.1and 2.7.6.2;*	*Section 2.7.6 Antibody Formation - Immunogenicity (IG) analysis set*
		Updated for clarity	*Section Other imputation was deleted.*	*Section 5.1.6.1 was deleted*
		Updated for clarity and document the AE grade which were manually determined	*Inserted rules for AE coding/grading. Removed CTCAE grade for laboratory toxicity.*	*Appendix 5.2 AEs coding/grading, Appendix 5.3 Laboratory parameter derivation*
		Updated for clarity	*Changed text description to be clear that any mistakenly randomized subjects are not going to be excluded from FAS, inserted some PDs to be consistent with last version of DM document.*	*Appendix 5.5 Rule of exclusion criteria of analysis sets*
		Added for clarity	*Added to Appendix under 5.4.3 the description of Multiple Imputation Sensitivity Analyses steps*	*Appendix 5.4.3 Multiple imputation sensetivity analyses steps*
		Updated for clarity	*Sensitivity analysis for MPFID will not be performed*	*Appendix E*

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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
[redacted]	[redacted]
BOCF	Baseline Observation Carried Forward
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBTE	Double-Blind Treatment Epoch
EA	Everyday Activities
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EoS	End of Study
[redacted]	[redacted]
FAS	Full Analysis Set
GEE	Generalized Estimating Equations
GLMM	Generalized Linear Mixed Model
GPS	Global Programming and Statistical Environment
[redacted]	[redacted]
IRT	Interactive Response Technology
IP	Investigational Product
IPD	Important Protocol Deviations
IPW	Inverse Probability Weighting
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Multiple Imputation
MIN	Minimum function
MNAR	Missing Not at Random
MPFID	Migraine Physical Function Impact Diary
NRI	Non-Responder Imputation
OLAS	Open-Label Analysis Set
OLTE	Open-Label Treatment Epoch

PI	Physical Impairment
[redacted]	[redacted]
PP	Per-Protocol analysis set
PRO	Patient-Reported Outcomes
PT	Preferred Term
qm	once a month
RAS	Randomized analysis set
SAE	Serious Adverse Event
SAF	SAFety analysis set
SAP	Statistical Analysis Plan
sc	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
SSAP	Supplemental Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
UN	Unstructured covariance matrix
US	United States
VAS	Visual Analog Scale
WHO	World Health Organization
[redacted]	[redacted]

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the amended **Protocol 3.0** for AMG 334 Study CAMG334A2301 dated **March 8, 2018**. The scope of this plan includes the primary, secondary, [redacted], which will be executed by the Biostatistics Department. [redacted] The analysis plan for open-label epoch will be provided in a separate Statistical Analysis Plan for the open-label treatment period.

1.1 Study design

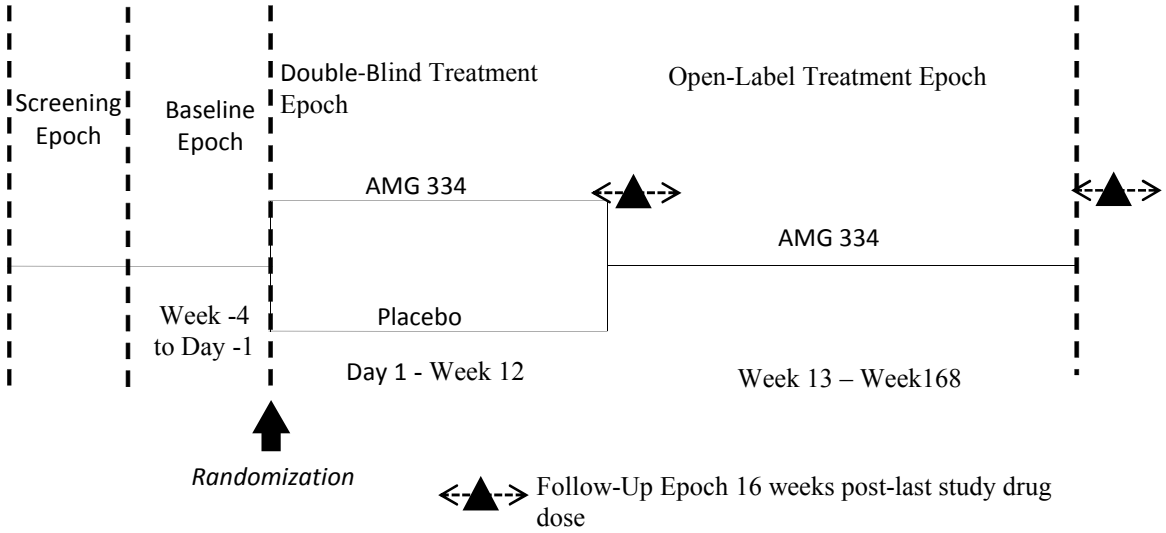
This study uses a single-cohort, 2-treatment arm, parallel-group randomized, double-blind, placebo-controlled design in adult patients with episodic migraine who have previously failed 2 to 4 prophylactic migraine treatments. The following epochs are included in the study design, with study visits at 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.
- **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.
- **Follow-Up Epoch (12 weeks) –** Unless patients continue onto commercial AMG 334 after completing the Double-Blind and/or Open-Label Epochs (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.

Randomization will be stratified by migraine frequency reported during the Baseline Epoch: 4-7 vs 8-14 migraines per month based on eDiary calculations.

The primary analysis will be triggered when the last patient completes the Double-Blind Treatment Epoch (DBTE). The database will be locked once when the last patient has completed the DBTE. Data of the DBTE will be summarized in a study report. A separate analysis will occur at the conclusion of the Open-Label Treatment Epoch.

Figure 1 **Study design**



Patients will receive either AMG 334 140 mg qm sc or matching placebo for 12 weeks in the Double-Blind Treatment Epoch, followed by a 3-year Open-Label Treatment Epoch of AMG 334 140 mg qm sc.

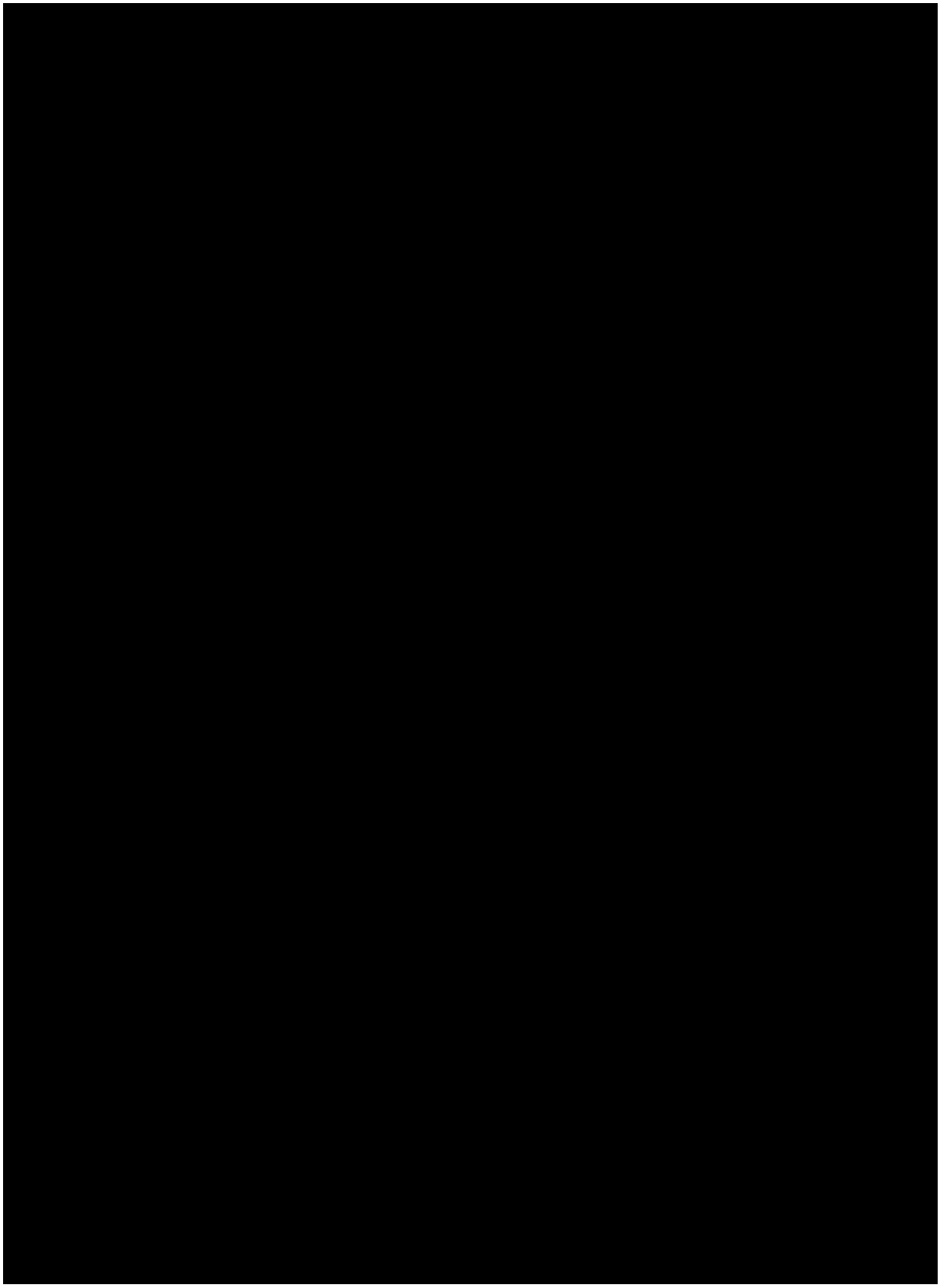
The primary objective is to evaluate the effect of 140 mg AMG 334 compared to placebo on the proportion of patients with at least 50% reduction from baseline in monthly migraine days in the last month (month 3) of the double-blind epoch.

No formal interim analyses or design adaptations are planned. The primary analysis will occur when the last patient completes the Double-Blind Treatment Epoch, prior to the end of both the Open-label Treatment and the Follow-Up Epochs. A study report will be prepared and finalized for the Double-Blind Treatment Epoch, and a second study report will be prepared incorporating previously locked data from the Double-Blind Treatment Epoch.

Table 1 Study Objectives and Endpoints

Objective	Endpoint
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 treatment epoch
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 treatment epoch

Objective	Endpoint
To evaluate the effect of 140 mg AMG 334 compared to placebo on the "impact on everyday activities" domain as measured by the Migraine Physical Function Impact Diary (MPFID)	Change from baseline to month 3 of the MPFID "impact on everyday activities" sub-domain score
To evaluate the effect of 140 mg AMG 334 compared to placebo on the "physical impairment" domain as measured by MPFID	Change from baseline to month 3 of the MPFID "physical impairment" sub-domain score
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-specific medication treatment days in the last month of the double-blind treatment epoch
To evaluate the effect of 140 mg AMG 334 compared to placebo on the proportion of patients with at least 75% reduction from baseline in monthly migraine days	The achievement of at least a 75% reduction from baseline in monthly migraine days in the last month of the double-blind treatment 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 a 100% reduction from baseline in monthly migraine days in the last month of the double-blind treatment epoch
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



1.1.1 Visit schedule and assessments

In Table 14 and **Error! Reference source not found.** there are listed all of the assessments and indicated 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.

1.1.2 Planned number of patients

The trial will involve the assessment of efficacy for one investigational treatment. The primary analysis will compare active investigational treatment arm to matching placebo. The goal is to randomize approximately 220 patients in approximately 65 centers worldwide. Assuming a 50% screening failure rate, approximately 440 patients will be screened (all details are in Section 3).

1.1.3 Randomization and stratification

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 during the Baseline Epoch (4-7 migraine days per month vs 8-14 migraine days per month).

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 package of study drug

to be dispensed to the patient. The randomization number will not be communicated to the caller.

2 Statistical methods

2.1 Data analysis general information

The first analysis will be conducted on all patient data when the Double-Blind Treatment Epoch of the trial ends. There will be a second set of analyses of all of the data, including the Follow-Up Epoch data, after the Open-label Treatment Epoch ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

For efficacy endpoints graphs will display results where it is appropriate.

Unless otherwise stated, summary tables/listings/figures will be presented for each treatment arm in the respective analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, the number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum will be presented. Summary tables will also be presented by visit wherever applicable.

In general and unless specified otherwise, all parameters of interest will also be listed by treatment and presented by country name/center#/patient_id/visit#.

Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, Cary, NC, USA.) version 9.3 or higher.

General information on treatment arm handling, decimal places and other output related information will be specified in tables, figures and listing (TFLs) shells accompanying to this analysis plan.

2.1.1 General definitions

Study drug

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

Two injections of AMG 334 70 mg (equaling 140 mg total dose) or placebo will be administered at each dosing visit. 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. The study treatments will be labelled as:

- AMG 334 70mg/1mL or Placebo for Double-Blind Treatment Epoch

Baseline

The baseline period for efficacy endpoints collected by the daily edairy (e.g., monthly migraine days, acute migraine-specific medication days, MPFID, etc.) is defined as the period

between week -4 visit (when eDiary device is dispensed to the patient for daily data capture) and the day prior to study day 1 (study day 1 is not included).
A baseline for PRO ([redacted] MPFID) and safety (including C-SSRS) values refers to the last evaluable measurement prior to the first administration of the study drug, irrespective of re-screening. In this case, baseline values will be the values obtained on the day of the randomization (Day 1, Visit 101), or on an earlier visit (scheduled or unscheduled) which is the closest to Visit 101, if Visit 101 is missing or the assessment was not done at baseline.

Change from Baseline in Monthly Efficacy Measurement

The change from baseline in monthly efficacy measurement is the monthly efficacy measurement in the monthly interval prior to the given time point minus the baseline monthly efficacy measurement. Please, refer to the monthly intervals for efficacy endpoints defined in Table 2. For example, change from baseline in monthly migraine days in the last month (month 3) of the double-blind epoch will be calculated based on the following:
(Monthly migraine days in the last month of the DBTE) – (monthly migraine days during the baseline phase)
If the baseline or post-baseline value is missing, then the change from baseline is set to be missing.

Percent Change from Baseline
The change from baseline divided by baseline and multiplied by 100:
(post-baseline – baseline) * 100 / baseline
50% (or 75%, 100%) response is defined as a decrease from baseline score value for at least 50% (or 75%, 100%).

Study day

Study Day 1 is defined as the first investigational product (IP) dose date. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Study Day is defined as the number of days from Study Day 1.
Before Study Day 1:
Study Day = (Date of Interest – Date of Study Day 1)
On or after Study Day 1:
Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is -1.

Last date of patient contact
The date of last patient contact will be selected as the minimum of the following non-missing dates:

1. 'Date of Discontinuation/study phase completion', either from the study completion page or
2. The treatment epoch completion page if calculated specifically for a study epoch.

Duration of Migraine

The duration of migraine in years (migraine with aura or migraine without aura, whichever is earlier) is calculated by the following formula: current age (in years) - age at migraine onset (in years).

Current age is calculated by the following formula, the date of informed consent – birth date (at least the year).

If the current age calculated as detailed above or the age at migraine onset is missing then duration of migraine will be missing.

Duration of exposure to AMG 334

For all calculations of exposure, dose date refers to receiving dose>0, but can include partial doses.

Duration of DB IP Exposure

If subject enters into the open-label treatment phase,
Duration = Minimum (Last DB Dose Date + 27, First OLTP Dose Date, EoS Date-1) – First DB Dose Date+1
Otherwise,
Minimum (Last DB Dose Date + 27, EoS Date) – First DB Dose Date+1

Duration of OL IP Exposure

Minimum (Last OLTE Dose Date + 27, EoS Date) – First OLTE Dose Date+1

Subject Incidence

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered that period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

Exposure-Adjusted Subject Incidence Rate

The exposure- adjusted subject incidence rate for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event in a given time period divided by total subject years at risk in that period. The time at risk for each subject will differ for each adverse event. For subjects with events, only the time until the first event contributes to the total subject years at risk. For subjects who do not experience the event, the time at risk will be calculated based on the safety analysis study window. This rate will be presented per 100 subject years. For subjects with multiple occurrences of the same event, the event will be only counted once per subject.

Time at risk

The time at risk matches the time generally considered for safety summaries except SAEs. In particular, it will be used in the analysis of adverse events to derive (exposure-adjusted) incidence rates.

Prior and concomitant medication

Prior medication will be defined as any non-study medication taken prior to the first dose of the randomized study medication, irrespective of whether the medication continued into the treatment period.

Any non-study medication administered at least once between the day of first dose of randomized study medication and end of the study will be a concomitant medication.

Analysis windows

In general, by-visit analyses, including evaluable scheduled and unscheduled data, will be conducted using analysis windows. Analysis windows will align with the scheduled visit day for each assessment and have its lower and upper bounds symmetrically between the analysis window midpoints (i.e. the scheduled visit day for the particular assessment).

For efficacy parameters: In case of multiple assessments within a analysis window, the scheduled visit will be used regardless of the distance from the target day. Unscheduled visit will only be used when there is no measurement from the scheduled visit in the defined window. In that case the assessment value closest to the scheduled visit day will be used. In case of equal distances, the latest assessment value will be used. The exception is an assessment at early study withdrawal visits along with another assessment within a window. In such cases the early-withdrawal assessment will be used.

For safety parameters: in case of competing assessments within a analysis window, the last one closest to the scheduled visit day will be used.

Listings will include all assessments, sorted by scheduled visit and time of assessment, flagging unscheduled visits. The listings will include analysis windows and corresponding flags to indicate the assessment's inclusion in analysis.

Further details regarding analysis windows for specific domains are included in Tables below.

Monthly Interval for Efficacy Endpoints

Monthly efficacy measurements will be calculated based on the subject's monthly investigational product(IP) dosing schedule defined below using eDiary data collected from beginning of the baseline phase (week -4 visit) up to open label treatment period.

Table 2 Study Intervals for Efficacy Endpoints

Study Phase	**Assessment Timepoint**	**Interval Based on Dose Dates**	
		Start date	**End date**
Baseline Epoch	Baseline	From eDiary device assignment date (or Week -4 visit)	Day prior to study day 1
Double-Blind Treatment Epoch	Week 4	Study Day 1	• Week 4 dose date-1 • Study day 28 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4) Note: if day 1 dose is the last IP dose subject received, the rest of monthly rates during DBTE will be calculated based on consecutive 28-day interval beginning on study day 29 (ie, 29-56 for week 8, 57-84 for week 12)
	Week 8	• Week 4 dose date Study day 29 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4)	• Week 8 dose date-1 Study day 56 if Week 8 dose is not received (either missed or IP discontinued prior to Week 8)
	Week 12	• Week 8 dose date Study day 57 if Week 8 dose is not received (either missed or IP discontinued prior to Week 8)	• Week 12 IP dose date-1 • If Week 12 dose is not received (either missed or IP discontinued prior to Week 12) o MIN (Study day 84, EOS) if Week 8 dose is not received o MIN (Week 8 dose date + 27, EOS) if week 8 dose is

			received

Study Visit

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to a study visit.

The next study day window will be utilized to define study visit for lab, vital signs, C-SSRS and some PROs collected during office visits [redacted] before dose is administered [redacted]

Table 3 Study Visit Windows

Study visit	Target Day	Study Day for vital signs, C-SSRS (for lab [redacted] include only Day1,Week 12, 24, 64)	Study Day [redacted]
Baseline	Please refer to Section 2.1.1		
Day 1	1	1	1
Week 4	29	16-43	16-43
Week 8	57	44-71	44-71
Week 12	85	1.72 to (week 12 OLTE dose date) for subjects who receive OLTE dose at week 12 2.72-99 for subjects who did not receive OLTE dose at week 12	1.72 to (week 12 OLTE dose date) for subjects who receive OLTE dose at week 12 2.72-99 for subjects who did not receive OLTE dose at week 12

For safety analyses which are summarized by study phase, analysis windows will be set up based on study phase:

Table 4 Study Phases for Safety analysis

Study Phase	Start Time Point	End Time Point
Double-blind Treatment Epoch	Study Day 1 (after the 1st DB IP Dose)	• First OLTE Dose Date - 1 for subjects receive OLTE IP dose; • MIN(EoS Date, last IP dose date + 84 days) for subjects did not receive any OLTE IP dose

Note: all anti-AMG 334 antibody data during all epochs will be included in immunogenicity analysis.

2.1.2 Definition of terms included in study endpoints

Efficacy endpoints

eDiary Day

A day in which a subject uses the eDiary.

Migraine Day

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 (IHS, 2013) 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.

Monthly Migraine Days

Number of migraine days between each monthly IP dose that are normalized in a 28-day interval. Monthly migraine days at baseline are the number of migraine days in the baseline period that are normalized in a 28-day interval. Days without eDiary data in each normalized monthly interval will be prorated. All details of calculation are in Section 5.1.2 (The same proration method will be applied for other efficacy endpoints thereafter).

Achievement of at least a 50% reduction from baseline in monthly migraine days in the last month of the double-blind treatment epoch

Calculated based on the following: if (monthly migraine days in the last month of the DBTE - baseline monthly migraine days)*100/baseline monthly migraine days is less than or equal to - 50%

[redacted]

Headache Day

A headache day is any calendar day in which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache). A qualified headache is defined as**:**

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

Monthly Headache Days

Number of headache days between each monthly IP dose. Monthly headache days at baseline are the number of headache days in baseline period. Days without eDiary data in each monthly interval are handled by proration according to Section 5.1.2.

Monthly Acute Headache Medication Treatment Days

Number of days on which acute headache medications are used as recorded in eDiary between each monthly IP dose. Monthly acute headache medication treatment days at baseline are the number of acute headache medication treatment days in the baseline period. Days without eDiary data are handled by proration according to Section 5.1.2.

[redacted]

Monthly Acute Migraine-Specific Medication Treatment Days

Number of days on which acute migraine-specific medications are used as recorded in eDiary between each monthly IP dose. Migraine-Specific medications include two categories of medications: triptan-based migraine medications and ergotamine-based migraine medications. Monthly migraine-specific medication use at baseline is the number of migraine-specific medication treatment days in the baseline period. Days without eDiary data are handled by proration according to Section 5.1.2.

Change from baseline in monthly acute migraine-specific medication treatment days in the last month of the double-blind treatment epoch

Calculated based on the following: (monthly acute migraine-specific medication treatment days in the last month of the DBTE) – (baseline monthly acute migraine-specific medication treatment days)

Response

At least 50% (or 75%, 100%) reduction from baseline in monthly migraine days.

[redacted]

Migraine Physical Function Impact Diary (MPFID)

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. Subjects 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. The recall period is the past 24 hours. Please refer to Section 2.10 and Appendix E.1 for details.
Subjects will complete the MPFID every day using the eDiary during DBTE.
Monthly average MPFID score is defined as the sum of observed MPFID scores divided by the total number of observed MPFID scores between each monthly IP dose. Monthly average MPFID score at baseline is the average MPFID score in the baseline period.

Change from baseline in monthly average physical impairment scores as measured by the MPFID in the last month of the double-blind treatment epoch
Calculated based on the following: (monthly average physical impairment scores as measured by the MPFID in the last month of the DBTE) – (baseline monthly average physical impairment scores as measured by the MPFID)

Change from baseline in monthly average impact on everyday activities scores as measured by the MPFID in the last month of the double-blind treatment epoch

Calculated based on the following: (monthly average impact on everyday activities scores as measured by the MPFID in the last month of the DBTE) – (baseline monthly average impact on everyday activities scores as measured by the MPFID)

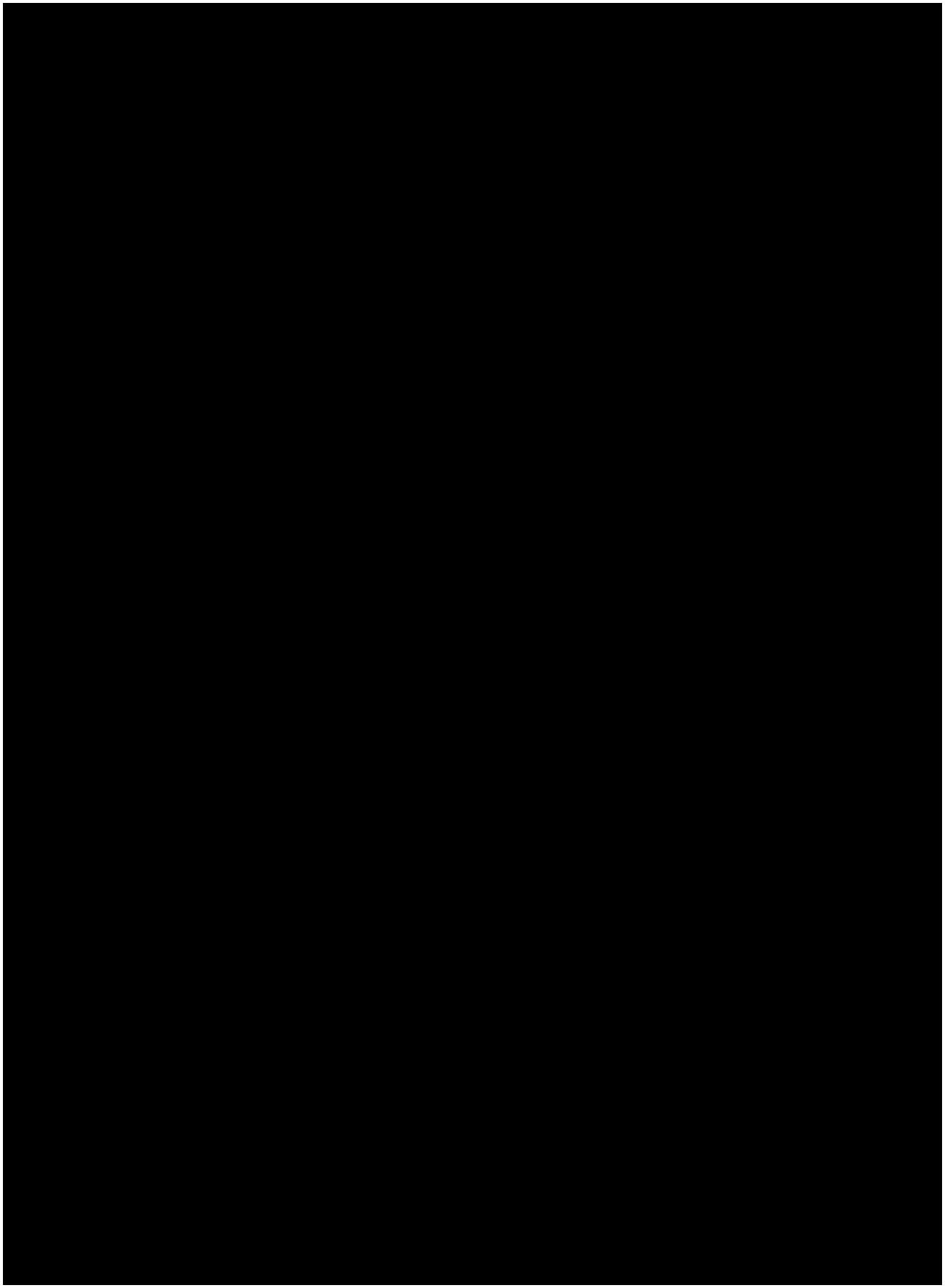
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



Safety Endpoints

Treatment-Emergent Adverse Event (TEAE)

Adverse Events (AEs) recorded on the Adverse Events eCRF page that occurs on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events eCRF and up to and including 112 days after the end of IP (16 weeks after the last dose of IP).

Serious Adverse Event (SAE)

SAEs determined by the flag indicating if the adverse event is serious on the Adverse Events eCRF page will include those that occur after signing of the informed consent and up to and including end of study.

Serious Treatment-Emergent Adverse Event

A serious treatment-emergent adverse event is an SAE considered to be treatment-emergent.

Treatment-Related Adverse Event

A treatment-related AE is defined as a treatment-emergent adverse event that is considered by investigators to have reasonable possibility that it may have been caused by IP as determined

by the flag indicating that there is a reasonable possibility that the AE is related to investigational product on the Adverse Events eCRF page.

Serious Treatment-Related Adverse Event
A serious treatment-related adverse event is an SAE considered to be treatment-related.

Treatment-Emergent Adverse Event of Special Interest
A treatment-emergent adverse event of special interest (EOI) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Predefined search strategies such as standardized MedDRA queries (SMQ) or Novartis defined queries may be applied to EOIs. The EOI search list is a living document and will be updated in response to the emerging safety profile of AMG 334.

Columbia-Suicide Severity Rating Scale (C-SSRS)

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.
Two versions depending on the type of visits will be used in this study: Life-time and Since Last Visit. The C-SSRS consists of a maximum of 20 items to evaluate suicidal behavior and suicidal ideation.

2.1.3 Study Dates

Informed Consent Date
The date on which subject signs the informed consent form.
eDiary Device Assignment Date
The date on which an eDiary device is assigned to a subject for the first time after completion of initial screening at week -4 visit.
Randomization (Enrollment) Date in DBTE
Randomization (Enrollment) Date in DBTE is the date on which a subject is assigned to one of the treatments through IRT in DBTE.
First IP Dose Date
First IP Dose Date is the date on which a subject is administered the first dose of investigational product following randomization, which may be the same day or after the randomization date. For subjects who are randomized but not dosed with double-blind IP after randomization, First IP Dose Date is considered missing.
Last IP Dose Date
Last IP Dose Date for each subject is defined as the latest date IP is administered.
End of IP Admin Date
End of IP Admin for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF page.
Subject-level End of Study (EoS) Date

End of study (EoS) date for each subject is defined as the last date on which the subject participated in the study.

Primary Completion Date

The Primary Completion Date is the date Double-Blind Treatment Study Completion Form for the last subject who completes DBTE.

Study Completion Date

The Study Completion Date is the EoS date of the last subject in the study.

2.1.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- inadvertent breaking of the blind before formal unblinding
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated.

2.1.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

2.1.6 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, appropriate transformations or the non-parametric alternatives will be used, such as Van Elteren statistic (Van Elteren 1960).

2.2 Analysis sets

The **Randomized Analysis Set** (RAS) will consist of all participants who received a randomization number, regardless of receiving study medication.

The **Full Analysis Set** (FAS) will consist of all participants who started study medication and have completed at least one post-baseline monthly migraine day measurement in the doubleblind treatment epoch. In FAS, subjects will be analyzed according to randomized treatment, regardless of the actual treatment received. Analyses for efficacy endpoints and patient reported outcomes (PROs) will utilize this analysis set.

The **SAFety analysis set** (SAF) will consist of all randomized subjects who received at least one dose of investigational product and will be analyzed based on actual treatment received. Analyses for safety endpoints and summary of IP administration will utilize this analysis set.
Rule of exclusion criteria of analysis sets is presented in Appendix 5.5.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be summarized on RAS. The number and proportion of patients, who complete the study, are ongoing in the study or discontinue the study prematurely along with the primary reason for discontinuation will be presented. Listings will also be provided for primary reason for early discontinuation.
The number of patients in each analysis set described above will also be presented. Reason for screen failure will be summarized for all screened participants.
A listing will present all patients randomized, but not treated.

Randomized
Subjects are considered randomized if they have been assigned a randomization number.
Completing the DBTE
Subjects are defined as completing the DBTE if they complete the week 12 assessment, or if they miss the week 12 assessment, but continue to enter the OLTE. It will be derived from the Double-Blind Treatment Study Completion Form with “Completed” as the reason for ending study epoch.
Completing the Study
Subjects are defined as completing study if they complete the whole 64 weeks of study evaluation**.**
Exposed to Investigational Product
Subjects are defined as being exposed to IP if they receive at least one dose of IP.
Completing the Double-Blind Investigational Product
Subjects are defined as completing double-blind IP if they complete the week 8 IP dose or temporally withhold IP at week 8 and continue to receive IP during OLTE.
Completing Open-label Investigational Product
Subjects are defined as completing open-label IP if they complete the week 60 IP dose.

2.3.2 Background and demographic characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized using descriptive statistics by randomized treatment group and overall study population using the RAS.
At baseline, following demographic and baseline characteristics will be summarized:
• Sex
• Ethnicity
• Race

- Age
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m^2)
- Acute headache medication (migraine-specific/non migraine-specific) during baseline phase
- Summary of prior migraine prophylactic treatment and reasons for discontinuation [redacted]
- Age at onset of migraine (years)
- Disease duration of migraine
- Monthly migraine days during baseline phase [redacted]
- Monthly headache days during baseline phase
- Monthly acute medication use in days during baseline phase

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each treatment group and for all participants (total). The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants (total).

2.3.3 Medical History

Relevant medical history/current medical conditions present before signing the Informed consent #1 will be recorded on the 'Medical History' CRF page. Only listings will be presented.

Medical history possibly contributing to liver dysfunction will be record separately on the 'Medical History Possibly Contributing to Liver Dysfunction' CRF page and presented separately in frequency tables by SOC and PT and in listings.

Any condition entered will be coded using the latest version Medical Dictionary for Regulatory Activities (MedDRA) prior to database lock and summarized by primary system organ class (SOC) and preferred term (PT) for each treatment arm for RAS.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Subcutaneous (sc) injections are to be given for each investigational product administration. For purposes of study treatment dosing, "qm" refers to an every 4 weeks injection regimen.

Double-Blind Treatment Epoch:

AMG 334 140 mg or placebo will be administered by qualified study staff at the each dosing visit during the 12-week double-blind treatment epoch (ie, at Day 1 and Weeks 4 and 8).

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.

Compliance:
Compliance to eDairy at each month is calculated as:
1.(Number of observed eDairy days at baseline or between IP doses/ 28)*100% if Number of actual days in Baseline epoch or between IP doses interval<=28 or
2.(Number of observed eDairy days at baseline or between IP doses/ Number of actual days in Baseline epoch or between IP doses interval)*100% if Number of actual days in Baseline epoch or between IP doses interval>28.

2.4.2 Rescue medication

Patients can continue to use "best supportive care". This can include both pharmacologic interventions (ie, abortive treatments for acute attacks) and non-pharmacologic interventions (eg, biofeedback, psychotherapy, acupuncture or other locally accepted and endorsed interventions for migraine).
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.

2.4.3 Prior, concomitant and post therapies

The number and percentage of participants receiving rescue medications, prior best supportive care non-drug therapies and concomitant medication will be summarized by primary SOC, PT (according to the latest World Health Organization drug dictionary (WHO-DD) at the time of database lock, including Anatomical Therapeutic Chemical (ATC) classification code) and treatment arm.

The number and percentage of participants taking any prohibited or restricted treatment will also be summarized for SAF.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

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.

The primary analysis will contrast active investigational drug versus placebo in the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The following hypothesis refers to alternative hypothesis. For tests of superiority, null hypothesis presuppose no difference between the treatment groups with respect to the parameter of interest.

Primary hypothesis

- The active treatment arm group is superior to placebo with regard to 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;

$$H_1: \theta_1 > 1$$

where θ_1 is the odds ratio of active over corresponding placebo.
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. Patients with missing monthly migraine days' data at month 3 of the double-blind treatment epoch will be imputed as non-responders.

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 significance level of 0.025, one-sided (0.05, two-sided) to evaluate the association between the 50% responder rate and the treatment. The estimated common odds ratio, 95% confidence intervals and two-sided p-values will be reported.

Additionally, the estimated common relative risk and risk difference with their asymptotic (Wald) confidence limits will be provided.

2.5.3 Sensitivity analyses

In order to assess the robustness of the analysis for primary endpoint during the double-blind treatment epoch, next analyses will be done:

1. Without any imputation for missing data, a generalized linear mixed model (GLMM) which account for temporal variability will be used.
2. Logistic regression analysis will be used to get odds ratio of AMG 334 vs placebo in the 50% response rate after the missing data are imputed as non-response.
3. Stratified CMH test will be repeated based on multiple imputation with assumption of MAR and MNAR.

In all cases, the odds ratio of treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided.
All details of models descriptions are in Section 5.4.1.
To address the impact of missing data on primary efficacy analysis, the amount of missing data, the distribution of missing data among treatment groups, and the reasons for missing data will be examined. If substantial amount of missing data is observed or if imbalance occurs amongst the treatment groups, additional sensitivity analyses, including those based on alternative missing data assumptions, will be performed as deemed appropriate and necessary.

2.6 Analysis of secondary efficacy objectives

2.6.1 Secondary endpoints

The secondary endpoints during double-blind treatment epoch are:

- Change from baseline in monthly migraine days in the last month (month 3) of the double-blind treatment epoch
- Change from baseline in "impact on everyday activities" domain as measured by the MPFID in the last month (month 3) of the double-blind treatment epoch
- Change from baseline in "physical impairment" domain as measured by the MPFID in the last month (month 3) of the double-blind treatment epoch
- Change from baseline in acute monthly migraine-specific treatment days in the last month (month 3) of the double-blind treatment epoch
- The achievement of at least a 75% reduction from baseline in monthly migraine days in the last month (month 3) of the double-blind treatment epoch
- The achievement of a 100% reduction from baseline in monthly migraine days in the last month (month 3) of the double-blind treatment epoch

2.6.2 Statistical methods of analyses

Analysis of secondary efficacy endpoints will utilize the FAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

For efficacy analysis at week 12, the continuous change from baseline efficacy endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

The dichotomous secondary efficacy endpoints derived from corresponding continuous endpoints will be analyzed using the stratified Cochran-Mantel-Haenszel (CMH) test after the missing data are imputed as non-response.

In all cases, estimates (difference/or odds ratio) of treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided. Additionally, the estimated common relative risk and risk difference with their asymptotic (Wald) confidence limits will be provided for the dichotomous secondary efficacy variables.

2.6.3 Sensitivity analyses

The following sensitivity analyses will be provided:

Analaysis of continuous efficacy variables will be repeated using an analysis of covariance (ANCOVA) model including treatment group and stratification factor as fixed effects in the model with baseline value as covariate. Missing data at Week 12 will be imputed using its baseline value (BOCF). 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 (the models descriptions are in Section 5.4.2).
Analaysis of dichotomous efficacy endpoints which are derived from corresponding continuous endpoints will be repeated using the GLMM and logistic regression as in Section 2.5.3. In all cases, estimates (difference/or odds ratio) of treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided.

Detailed primary and secondary efficacy analysis methods, sensitivity analyses, and covariates included in the models are summarized in the table below.

Table 5 Summary of Efficacy Endpoints and Analysis Methods during DBTE

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Primary: The achievement of at least a 50% reduction from baseline in monthly migraine days in the last month (4 weeks of the 12-week) of the double-blind epoch	*Analysis Method I:* 1. Summary statistics by visit using observed data 2. A stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as non-response 3. Additional analysis to estimate relative risk and risk difference.	*Analysis Method II*: Without any imputation for missing data, adjusted odds ratios from a generalized linear mixed model that includes treatment group, baseline migraine days, stratification factor, scheduled visit, and the interaction of treatment and scheduled visit using observed data with unstructured (UN) covariance matrix structure, and using responder rate calculated using mean monthly migraine days *Analysis method III*, NRI: analyze using a logistic regression model that includes treatment and stratification factor as fixed effects and baseline migraine

		days as covariate *Analysis Method I:* A stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed with assumption of MAR and MNAR
Secondary: Change from baseline in monthly migraine days in the last month of the double-blind epoch	*Analysis method IV:* 1. Summary statistics by visit using observed data 2. Least squares mean at each timepoint calculated based on a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit using observed data. Unstructured covariance matrix structure will be used. 3. Test treatment difference using a contrast from the model above.	*Analysis method V:* ANCOVA Analysis for missing data are imputed as baseline (BOCF) *Analysis method VI:* MI with assumption of MAR and MNAR (control-based pattern imputation and treatment effect adjusted imputation)
Change from baseline in monthly physical impairment scores as measured by MPFID in the last month of the double-blind epoch	*Analysis method IV.*	
Change from baseline in monthly impact on everyday activities as measured by MPFID in the last month of the double-blind epoch	*Analysis method IV.*	
Change from baseline in monthly acute migraine-specific medication treatment days in the last month of the double-blind epoch	*Analysis method IV.*	
The achievement of at least a 75% reduction from baseline in monthly migraine days in	*Analysis Method I.*	

the last month of the double-blind epoch		
The achievement of a 100% reduction from baseline in monthly migraine days in the last month of the double-blind epoch	*Analysis Method I.*	

2.6.4 Subgroup analyses

The primary and secondary efficacy endpoints will be analyzed at week 12 for the following subgroups that defined by categorical variables at baseline:

- Monthly migraine days per stratification factor (4-7 vs 8-14)
- Age (< median vs ≥ median)
- Sex (Male vs Female)
- [redacted]

The effect of other explanatory variables, maybe investigated with respect to the primary and secondary efficacy analyses if, upon clinical review, differences between treatment groups are deemed clinically meaningful.

The subgroup analysis will be assessed for the primary and secondary efficacy endpoints using primary analysis method and presented at Week 12. For continious variables the interaction p-value will be defined from modified primary model with additional terms of subgroup and subgroup by treatment group interaction as two additional effects. However, for subgroup of dichotomous variables, the interaction p-value will come from Logistic regression that includes treatment group, stratification factor, subgroup factor and treatment by subgroup factor interaction as fixed effect with baseline value as covariate.

If the value of the group variable cannot be determined, the subject will be excluded from the corresponding subgroup analysis. For each subgroup analysis, if, in any treatment group, the number of subjects is less than 10 for a subgroup, then the summary for that subgroup will be displayed but will not be included in tests for subgroup-by-treatment interaction when the test is based on categorical subgroups (when the test is based on a continuous variable, the subject data will be included).

The adjusted mean changes from baseline, SE's, and 95% CIs for each subgroup and the nominal p-value for subgroup by treatment interaction will be calculated.

[redacted]

2.7 Safety analyses

For safety endpoints, all randomized subjects who received at least one dose of investigational product (ie, utilizing the SAF for DBTE will be analyzed based on the randomized treatment unless a subject has received the incorrect dose the entire period of interest (phase or study).

No statistical testing comparing treatment groups will be performed in the safety analyses.

2.7.1 Adverse events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or later will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT). All adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (see details in Section 5.2). All adverse event tables will be summarized by treatment group.
AE tables by SOC and PT (and grade), will be sorted alphabetically by SOC and then descending order of frequency based on the AMG 334 140 mg dose by PT within each SOC. AE tables by preferred term only will be sorted in descending order of frequency based on the AMG 334 140 mg dose, then the placebo dose and then alphabetically.
Overall subject incidence of AEs will be summarized for all treatment-emergent AEs (TEAEs), serious AEs, AEs leading to withdrawal of IP, and fatal AEs for the DBTP.
Subject incidence of all TEAEs, serious AEs, AEs leading to withdrawal of IP, serious AEs leading to withdrawal of IP, fatal AEs will be tabulated by SOC and PT for the DBTE.
In addition, subject incidence of all treatment-emergent AEs and serious AEs will be tabulated by SOC, PT and CTCAE grade for the DBTE.
Subject incidence and exposure-adjusted subject incidence of all TEAEs and serious AEs will be tabulated by PT in descending order of frequency for the DBTE.
Treatment-related treatment-emergent AEs will be summarized for DBTE by SOC, PT and CTCAE grade.

2.7.2 Laboratory data

Summary statistics will be presented for absolute as well as change from baseline of laboratory haematology, blood chemistry results over time by treatment and laboratory test category.

Summary of change from baseline for absolute neutrophil count (ANC), alanine transaminase (ALT) and aspartate aminotransferase (AST) will also be provided for entire study.
Additional liver test summary table will provide the number and percentage of subjects by following categories:

- AST and ALT (> 3x ULN; > 5x ULN; > 10x ULN; > 20x ULN respectively)
- ALT/AST > 3x ULN and Total Bili > 2x ULN and ALP ≤ 2x ULN
- ALT/AST > 3x ULN and Total Bili > 2x ULN and ALP > 2x ULN

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

No statistical testing will be performed on C-SSRS. The number and percentage of subjects reporting any suicidal ideation and any suicidal behavior will be summarized descriptively by treatment group for DBTE. Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group for DBTE.

2.7.4 Electrocardiogram (ECG)

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Subject incidence of abnormal ECG diagnosis will be summarized by treatment group separately for the DBTE. However, since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, these data are not expected to be useful for meta-analysis with data from other trials.

2.7.5 Vital signs

The analyses of vital signs (systolic/diastolic blood pressure, pulse rate, and weight) will include summary statistics of change from baseline over time separately for DBTE by treatment group.
Summaries will be provided at each time-point for subjects meeting the following defined categories:

- Change from baseline: ≥ 15 mmHg in diastolic blood pressure and/or ≥ 20 mmHg in systolic blood pressure and analyzed for systolic blood pressure (< 90 mmHg, > 180 mmHg) and diastolic blood pressure (<50 mmHg, > 105 mmHg)
- Change from baseline in heart rate of ≥ 15 bpm (ie, an increase of at least 15 bpm) or heart rate > 120 bpm
- Change from baseline in heart rate of ≤ -15 bpm (ie, a decrease of at least 15 bpm) or heart rate < 50 bpm

2.7.6 Antibody Formation - Immunogenicity (IG) analysis set

The number and percentage of patients who are positive for anti-AMG334 antibodies at baseline (Visit 101, Day 1, pre-dose) and who develop anti-AMG 334 antibodies (binding and, if positive, neutralizing) will be tabulated by treatment group for randomized subjects during DBTE. The list of subjects with positive at any time will be provided. In addition, the number and percentage of subjects who develop anti-AMG 334 antibodies at any time post-dose (Visit 199,203, 299, 301) will be tabulated by DBTE treatment group for the entire study.

The Immunogenicity prevalence set includes all patients in the Full analysis set with a determinant baseline IG sample **or** at least one determinant post-baseline IG sample.
The Immunogenicity incidence set includes all subjects in the Immunogenicity prevalence set with a determinant baseline IG sample **and** at least one determinant post-baseline IG sample.

2.7.6.1 Sample anti-drug antibody (ADA) status

Each ADA sample is assessed in a two tiered ADA testing approach. All ADA samples are analyzed in the initial screening assay (first tier). Samples testing positive in the screening assay are then subjected to a confirmatory assay to demonstrate that ADA are specific for AMG334 (second tier). Samples identified as positive in the confirmatory assay are considered ADA positive and are further characterized in the neutralization assay to indicate the presence of neutralizing antibodies (NAb).

The following properties of each sample will be provided in the source data:

- Positivity in confirmatory assay according to pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Presence of NAb: yes or no

Sample ADA status will only be listed. It is determined based on the following definitions:

- ADA-negative sample: Determinant sample where ADA screening or confirmatory assay is negative.
- ADA-positive NAb sample: Determinant sample where NAb ADA assay is positive.
- ADA-positive sample: Determinant sample where ADA confirmatory assay is positive.

  The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample:
  - treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline.
  - treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with ADA-positive sample at baseline.

2.7.6.2 Patient ADA status

The following overall summaries will be provided using the Immunogenicity incidence set:

- Treatment-boosted ADA-positive: number and percent of patients with at least one treatment-boosted ADA-positive sample. The denominator is the number of patients with an ADA-positive sample at baseline.
- Treatment-induced ADA-positive: number and percent of patients with at least one treatment-induced ADA-positive sample. The denominator is the number of patients with an ADA-negative sample at baseline.
- ADA-negative: number and percent of patients with no treatment-induced or treatment-boosted ADA-positive sample.

- ADA incidence (i.e. % ADA-positive): number and percent of patients with at least one treatment-induced or treatment-boosted ADA-positive sample.

The following summaries, both overall and by timepoint (including baseline), will be provided using the Immunogenicity prevalence set. For summaries by timepoint, the denominator is the number of patients at that timepoint with determinant samples:

- ADA prevalence: number and percent of patients with at least one ADA-positive sample.
- NAb ADA prevalence: number and percent of patients with at least one ADA-positive NAb sample.

A listing will be provided by subject with supporting information (i.e. ADA sample status at each timepoint (including positive samples) and patient ADA status

2.7.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group and by phases. The number and percentage of subjects with dose change, reason for dose change and duration of exposure to investigational product in days will be summarized by treatment group.

2.7.8 Summary Concomitant Medication Use

The number and proportion of subjects receiving headache-related medications will be summarized by acute medication category for each treatment group.

[redacted]

2.10 Patient-reported outcome analyses

PRO scales were included to gather information about "impact on everyday activities" and "physical impairment" (MPFID), [redacted]

All variables assessing change from baseline will be calculated by subtracting the baseline score from the visit score. The baseline score will be the score recorded on Day 1 (Section 2.1.1). Change from baseline in total score (or subscale if applicable) of MPFID, [redacted], will be analyzed similarly as the secondary analysis of continuous endpoints described in the Section 2.6.2 (Analysis method IV).

[redacted]

[redacted]

In all cases, estimates (difference/or odds ratio) of treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided.

Descriptive statistics/frequency tabulations will be presented for each visit for PRO scales.

[redacted]

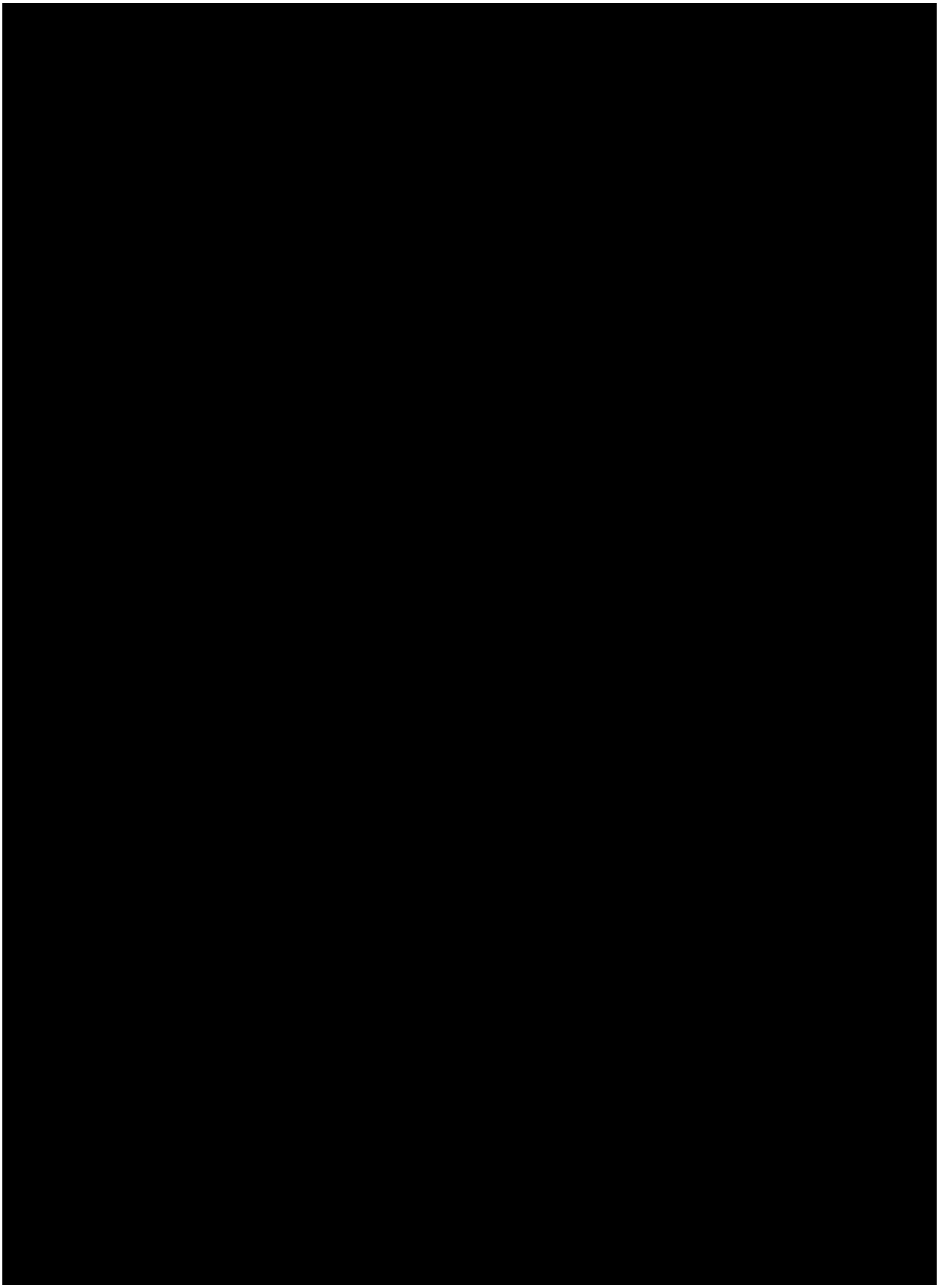
[redacted]

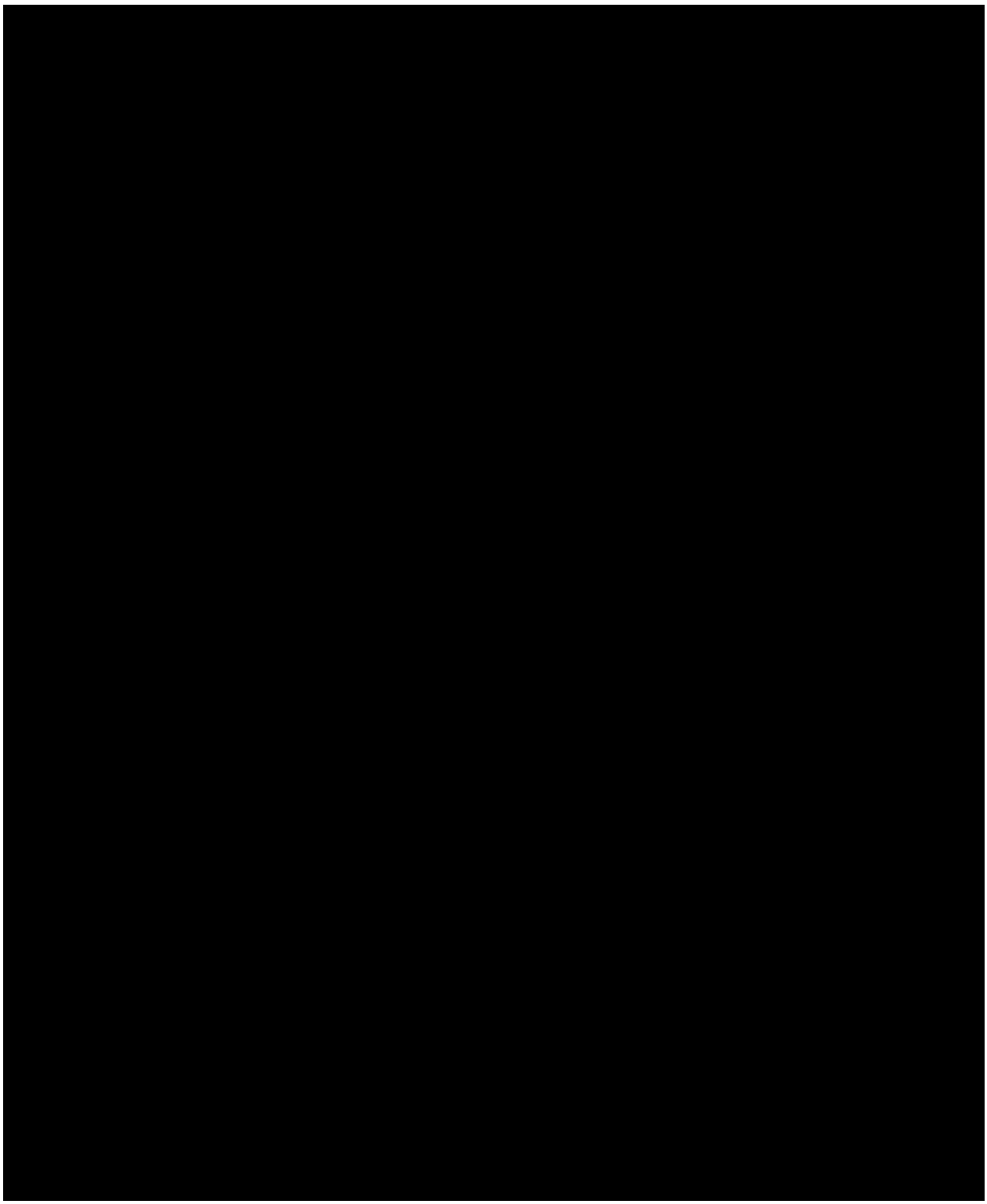
2.10.5 Migraine Physical Function Impact Diary (MPFID)

For each domain, the scores will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 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.

[redacted]

No sensitivity analysis will be conducted for PROs.





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

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

• Incidence of headache (ie, migraine with or without aura or non-migraine headache)
• Time of onset of headache
• Time of resolution of headache
• Pain severity per headache
• Symptoms (eg, nausea, vomiting, photophobia, phonophobia)
• Presence of aura
• Use of acute medication during aura or to treat headache

Site study staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's eligibility to enter the baseline phase). The site study staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit. Prior to randomization, the investigator will use the subject's eDiary to review all data entered during the baseline phase and confirm the relevant inclusion and exclusion criteria as noted in Section 5.5.

A subject will interact with his/her eDiary each day during the baseline, double-blind treatment and open-label treatment epochs.

The subject's eDiary will also be used for the completion of the following patient-reported outcomes (PROs) measures:

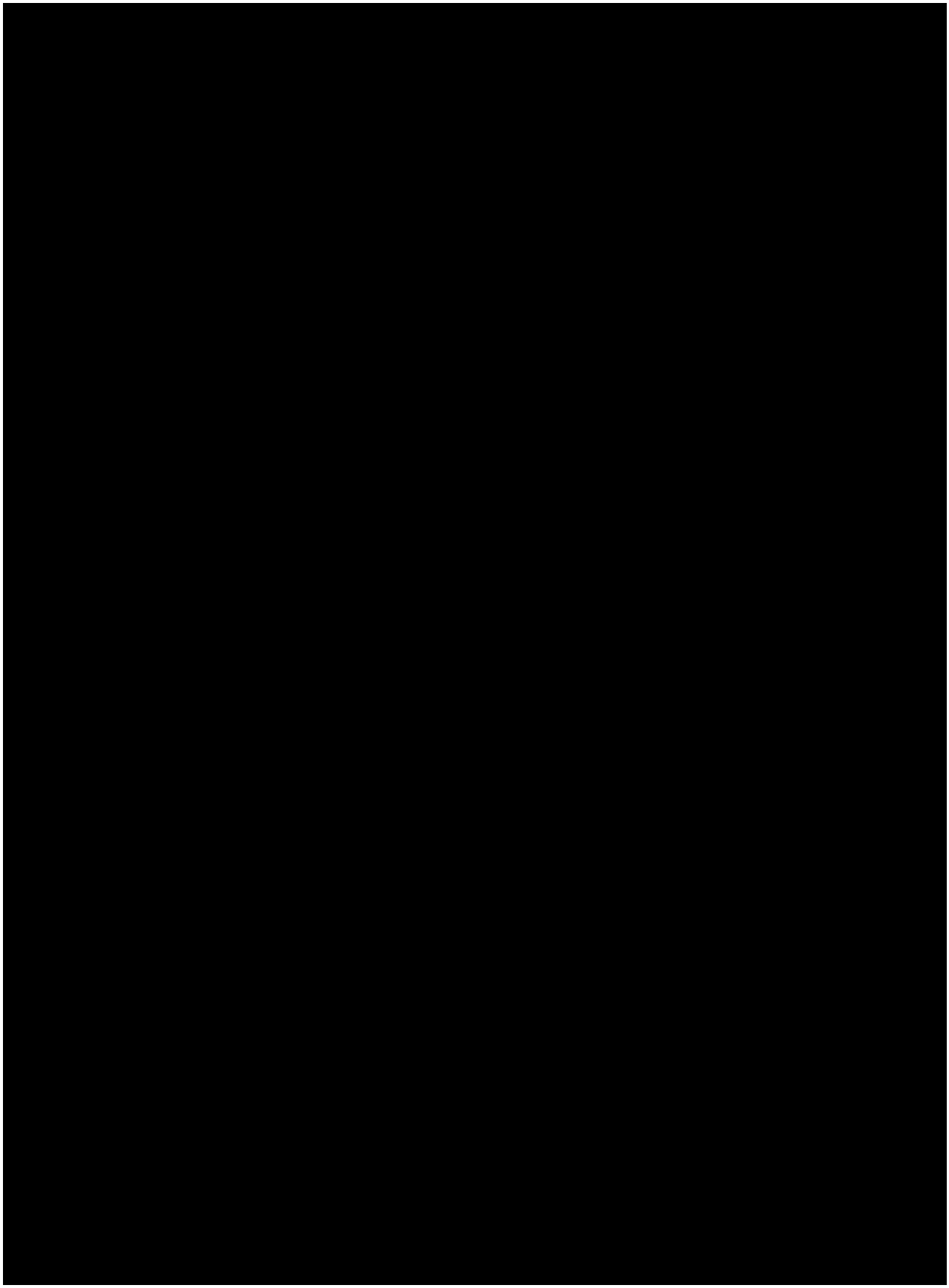
- Migraine Physical Function Impact Diary (MPFID)

[redacted]

Assessment schedule and frequency of all PROs are in Appendix D.

Refer to the eDiary manual for details.

[redacted]



[redacted]

2.14 Interim analysis

Not applicable.

3 Sample size calculation

Assuming a treatment effect similar to the effect observed in a previous study 296 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).
The power calculation is derived through nQuery 7.0.

4 Change to protocol specified analyses

1. The per-protocol (PP) analysis set, last observation carried forward (LOCF) method, inverse probability weighted (IPW) method using generalized estimate equation (GEE) to handle missing data will not be used as not informative for sensitivity purpose.

2. To evaluate the effect of AMG 334 compared to placebo the following additional endpoints were inserted:

- [redacted]
- [redacted]
- [redacted]

4. Randomized Analysis Set (RAS) was defined to use for medical history, patient disposition, demographics and baseline characteristics.
5. [redacted]

5 Appendix

5.1 Imputation rules

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, most of the efficacy endpoint will be collected via eDiary and subjects could miss entering several days of data in each 28-consecutive day interval. The general procedures outlined below describe what will be done when a data point is missing.

5.1.1 Study drug

Date of first study drug administration (Day 1)

Day 1 is defined as the first day of administration of randomized study drug (AMG334 or matching placebo). All other days will be labeled relative to Day 1. If subject will not be dosed at Day 1, the Study Day 1 is defined as day of randomization.

Date of last study drug administration

The date of last dose of randomized study drug is simply the day of the last dose.

5.1.2 eDiary data

The eDiary includes the following clinical outcome assessments:
• Incidence of headache (ie, migraine with or without aura or non-migraine headache)
• Time of onset of headache
• Time of resolution of headache
• Pain severity per headache
• Symptoms (eg, nausea, vomiting, photophobia, phonophobia)
• Presence of aura
• Use of acute medication during aura or to treat headache
As well as, patient-reported outcomes (PROs) measures of MPFID, [redacted]
Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following method:
1. For monthly intervals with ≥ 14 days of eDiary days (including retrospective eDiary days) in each interval**:**

a) Monthly frequency measurements (including migraine days, headache days, [redacted] acute medication use, acute migraine specific medication use etc.) will be prorated to 28-day equivalents**.** Prorated result does not need to be rounded.

b) [redacted] impact on everyday activities scores as measured by MPFID will calculated as the average of observed scores

2. For monthly intervals with < 14 days of eDiary use (including retrospective eDiary days), all monthly measurement will be set as missing and will be handled as described in Section 5.1.6.

Table 8 Rules for handling missing and incomplete eDiary data

Monthly Endpoint	Condition	Proration Method (does not need to be rounded)
Monthly frequency measurements (including migraine days, headache days, [redacted] hours of migraine headaches, acute headache medication treatment days, acute migraine-specific medication treatment days)	If diary days in entire baseline or interval post baseline >=14 (including retrospective eDiary days), then do proration; Else monthly measurement is set to missing [diary days is a day with all headache related questions completed retrospectively or not]	Number of observed migraine days * 28/ Number of information days in interval [information day is a diary day or headache day]
[redacted]	If days with observed daily domain score in interval >=14 then calculate the average; Else missing	Arithmetic mean of the observed daily domain score over the monthly interval
[redacted]	[redacted]	[redacted]

Missing PROs scheduled to be collected at office visit at certain assessment will not be imputed.
Missing safety endpoints will not be imputed. Missing day portion of AE start time will be imputed based on next Section 5.1.3.
Missing anti-AMG 334 antibody data will not be imputed.

5.1.3 AE and Concomitant medication date imputation

Missing or incomplete dates will be listed as it is in any listings.

Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to Study Day 1 if an adverse event starts the same year and month as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month	01Jan	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month/Year	No imputation	

5.1.4 Prior therapies date imputation

For prior medications with a stop date prior to the treatment phase (not possible to be at or after first drug administration), the start date will be imputed as the earliest possible start date and the stop date as the latest possible stop date:

For a missing/incomplete start date the minimum of the following will be imputed:

- The maximum of the earliest possible start date and the imputed birth date;
- The latest possible start date;
- The latest possible stop date.

For a missing/incomplete stop date the maximum of the following will be imputed:

- The minimum of the latest possible stop date and the date of first drug administration -1;
- The earliest possible stop date;
- The earliest possible start date.

Here, the earliest (latest) possible date is defined as:

- The date itself if it is complete;
- The date of the first (last) day of the month, if month and year are available but day is missing;
- The date of the first (last) day of the year, if year is available but day and month are missing;

- A very early (late) date, e.g., 01JAN1000 00:00hrs (01JAN3000 23:59hrs), if the date is completely missing.

5.1.5 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

All subjects included in the full analysis set will have baseline monthly rate or monthly average of migraine and non-migraine headaches related measurements after applying proration rule defined in Section 5.1.2 since only subject with ≥ 80% compliance of eDiary use during baseline will be eligible for randomization.

5.1.6 Missing Post-baseline Evaluation in Double-Blind Treatment Epoch

Primary analysis of continuous efficacy endpoints during the 12-week randomized DBTE will be conducted using the generalized linear mixed model on observed data without imputation.
In the sensitivity analysis on primary and secondary efficacy endpoints during the 12-week DBTE, missing continuous efficacy endpoints will be handled using baseline observation carried forward (BOCF) method, and multiple imputation (MI) with assumption of missing at random (MAR) and missing not at random (MNAR) (with control-based pattern imputation and treatment effect adjusted imputation), respectively.
In BOCF method, post-baseline missing continuous efficacy endpoints during double-blind treatment phase will be imputed using the baseline observed value. For example, if subject has all of the post-baseline values as missing, then all of the post-baseline values will be imputed using the observed baseline value.
In non-responder imputation (NRI) method, post-baseline missing dichotomous secondary efficacy endpoint (responder [Yes/No] based on ≥50% reduction from baseline in monthly migraine days) during double-blind treatment phase will be imputed as non-responder at each corresponding time point.
If the proportion of missing data in primary endpoint is high (eg, > 20% for primary analysis at week 12), further analysis will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (eg, due to measurement or sample processing error)

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Adverse event severity is graded based on NCI Common Toxicity Criteria version 4 or higher, which is available at the following: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

The CTCAE displays Grades 1 through 4 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 - Moderate; minimal, local or noninvasive intervention indicated;

Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling;

Grade 4 - Life-threatening consequences; urgent intervention indicated.

The mapping to Grade 3 and 4 will be done manually, in a case by case basis.

For those cases, the list of patients with severe (Yes) or serious AEs (Yes) with relevant information about hospitalization, its outcome and relation to treatment will be presented to study clinical team – discussion co-lead by Clinical Development Medical Director (CDMD) and Brand Safety Leader (BSL) - to define if the event may be mapped to grade 3 or grade 4. The decision about Grade 3 or 4 will be documented and saved as excel file in GPS CAMG334A2301 study folder and documented in CREDI.

5.3 Laboratory parameters derivations

CTCAE grading for the laboratory toxicity will not be derived.

5.4 Statistical models

5.4.1 Primary analysis

Primary Hypothesis

The null hypothesis stating that the odds ratio between the two treatment arms less than or equal to 1 will be tested against the one-sided alternative.

$$H_0: \theta_1 \leq 1 \text{ vs } H_1: \theta_1 > 1$$

where θ_1 is the odds ratio of active over corresponding placebo.

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 AMG334 140 mg vs placebo.

Test statistic

After the missing data are imputed as non-response 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 significance level of 0.025, one-sided (0.05, two-sided) to evaluate the association between the 50% responder rate and the treatment. The estimated common odds ratio, 95% confidence intervals and two-sided p-values will be reported.

Additionally, the estimated common relative risk and risk difference with their asymptotic (Wald) confidence limits will be provided. They will be got using SAS, PROC FREQ with options CMH, RELRISK, RISKDIFF under TABLE statement.

Sensitivity analysis for primary endpoint

(1) Without any imputation for missing data, adjusted odds ratios from a generalized linear mixed model that includes treatment group, baseline migraine days, stratification factor, scheduled visit, and the interaction of treatment and scheduled visit using observed data with type of unstructured covariance matrix (UN). Restricted maximum likelihood estimation will be used.

(2) Logistic regression analysis will be used to test the superiority of AMG334 arm in the 50% response rate after the missing data are imputed as non-response. Baseline migraine days will be used as a covariate along with treatment and stratification factor as fixed effects in the model.

(3) Stratified CMH test will be used to support the superiority of AMG334 arm in the 50% response rate after the missing data are imputed based on MAR and MNAR assumptions.

The odds ratio of treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided.

5.4.2 Analysis methods

Generalized Linear Mixed Model

Generalized mixed effects repeated measure model fits data with correlations or nonconstant variability and where the response is not necessarily normally distributed, which is also known as generalized linear mixed models (GLMM). The correlations can arise from repeated observation of the same sampling units, shared random effects in an experimental design, spatial (temporal) proximity, multivariate observations, and so on.

GLMMs, like linear mixed models, assume normal (Gaussian) random effects. Conditional on these random effects, data can have any distribution in the exponential family. The exponential family comprises many of the elementary discrete and continuous distributions. The binary, binomial, Poisson, and negative binomial distributions, for example, are discrete members of this family. The normal, beta, gamma, and chi-square distributions are representatives of the continuous distributions in this family.

Suppose Y represents the (nx1) vector of observed data and γ is a (rx1) vector of random effects. GLMM Models assume that

$$E(Y|\gamma)=g^{-1}(X\beta+Z\gamma)$$

where is g a differentiable monotonic link function and 1/g is its inverse. The matrix X is an (nxp) matrix of rank k, and Z is an (nxr) design matrix for the random effects. The random effects are assumed to be normally distributed with mean 0 and variance matrix G.

The GLMM contains a linear mixed model inside the inverse link function. This model component is referred to as the linear predictor,

$$\eta=(X\beta+Z\gamma)$$

The variance of the observations, conditional on the random effects, is

$$\mathrm{Var}[Y|\gamma]=A^{1/2}RA^{1/2}$$

The matrix A is a diagonal matrix and contains the variance functions of the model. The variance function expresses the variance of a response as a function of the mean.

The GLIMMIX procedure distinguishes two types of random effects. Depending on whether the parameters of the covariance structure for random components in your model are contained in G or in R, the procedure distinguishes between “G-side” and “R-side” random effects. The associated covariance structures of G and R are similarly termed the G-side and

R-side covariance structure, respectively. R-side effects are also called “residual” effects. Simply put, if a random effect is an element of , it is a G-side effect and you are modeling the G-side covariance structure; otherwise, you are modeling the R-side covariance structure of the model. Models without G-side effects are also known as marginal (or population-averaged) models. Models fit with the GLIMMIX procedure can have none, one, or more of each type of effect.
For a model containing random effects, the GLIMMIX procedure, by default, estimates the parameters by applying pseudo-likelihood techniques as in Wolfinger and O’Connell 1993 and Breslow and Clayton 1993. You can also fit generalized linear mixed models by maximum likelihood where the marginal distribution is numerically approximated by the Laplace method (METHOD=LAPLACE) or by adaptive Gaussian quadrature (METHOD=QUAD).
Once the parameters have been estimated, you can perform statistical inferences for the fixed effects and covariance parameters of the model. Tests of hypotheses for the fixed effects are based on Wald type tests and the estimated variance-covariance matrix.

Multiple Imputation (MI) and MCMC Method
The multiple imputation assume that the missing data are missing at random (MAR), that is, the probability that an observation is missing may depend on the observed values but not the missing values. It also assumes that the parameters q of the data model and the parameters f of the missing data indicators are distinct. That is, knowing the values of q does not provide any additional information about f, and vice versa. If both MAR and the distinctness assumptions are satisfied, the missing data mechanism is said to be ignorable. The MI procedure provides three methods for imputing missing values and the method of choice depends on the type of missing data pattern. For monotone missing data patterns, either a parametric regression method that assumes multivariate normality or a nonparametric method that uses propensity scores is appropriate. For an arbitrary missing data pattern, a Markov chain Monte Carlo (MCMC) method that assumes multivariate normality can be used.
In MCMC, one constructs a Markov chain long enough for the distribution of the elements to stabilize to a common, stationary distribution. By repeatedly simulating steps of the chain, it simulates draws from the distribution of interest.
In Bayesian inference, information about unknown parameters is expressed in the form of a posterior distribution. MCMC has been applied as a method for exploring posterior distributions in Bayesian inference. That is, through MCMC, one can simulate the entire joint distribution of the unknown quantities and obtain simulation-based estimates of posterior parameters that are of interest.
Assuming that the data are from a multivariate normal distribution, data augmentation is applied to Bayesian inference with missing data by repeating a series of imputation and posterior steps. These two steps are iterated long enough for the results to be reliable for a multiply imputed data set (Schafer 1997). The goal is to have the iterations converge to their stationary distribution and then to simulate an approximately independent draw of the missing values.
Sample SAS code for MI using MCMC method will be provided as instruction to TFLs.
Further, as a sensitivity analysis, the pattern-mixture model approach is used to model the distribution of a response as the mixture of a distribution of the observed responses and a

distribution of the missing responses, for which the missing values can be imputed under a plausible scenario for which the missing data are missing not at random. The control-based pattern imputation, in which, the set of observations from control group are used to derive the imputation model.

Van Elteren Test for Continuous Response Variable with Strata

When assumption of normality in analysis of covariance model is violated, then a Van Elteren's test for stratified continuous data can be used. Van Elteren's test is a nonparametric test that compares treatments in the presence of blocking. The test is an extension of Wilcoxon's rank-sum test (Van Elteren 1960).

Van Elteren proposed to combine stratum-specific Wilcoxon rank-sum statistics with weights inversely proportional to stratum size.

Suppose that the data obtained for the subjects in two treatment groups are split into J strata. Then, the stratified Wilcoxon test statistic is

$$W^* = \frac{\sum_{j=1}^{J} a_j (T_j - E(T_j))}{\sqrt{\sum_{j=1}^{J} a_j^2 Var(T_j)}}$$

where j=1,..,J denote the strata, $(T_j - E(T_j))$ and $\sqrt{Var(T_j)}$ are the numerator and denominator respectively of the Wilcoxon statistic for the data in strata j and a_j is the weight applied to each strata. The test statistic can be rewritten in the form

$$W^* = \frac{\sum_{j=1}^{J} a_j \sqrt{\frac{n_{0j} n_{1j}}{n_{0j} + n_{1j}}} \left(\frac{1}{n_{0j}} \sum_{k=1}^{n_{oj}} R_{0jk} - \frac{1}{n_{1j}} \sum_{k=1}^{n_{1j}} R_{1jk} \right)}{\sqrt{\sum_{j=1}^{J} a_j^2 \frac{1}{n_{0j} + n_{1j} - 1} \sum_{i=0}^{1} \sum_{k=1}^{n_{ij}} (R_{ijk} - \bar{R}_{\bullet j \bullet})^2}}$$

where R_{ijk} is the rank of the observation X_{ijk} within strata j, i=0,1 denotes the treatment group, j=1,.., J denotes the strata, k=1,..,n_{ij} denotes the subjects within the i^{th} treatment group in the j^{th} strata and $\bar{R}_{\bullet j \bullet}$ is the average rank of all observations in strata j. This form of the test statistic was programmed into the SAS macro used for analyses.

Assuming no ties within the data, the simplified form of the variance, that is

$$\left[\sum_{j=1}^{J} a_j^{\,2} \frac{1}{12} \cdot n_{0j} n_{1j} (n_{0j} + n_{1j} + 1) \right]$$

can be used.

Two weights have been used to combine results over strata:

"Locally best": $a_j = \sqrt{\frac{n_{0j}n_{1j}}{n_{0j}+n_{1j}}} \cdot \frac{1}{n_{0j}+n_{1j}+1}$

"Type II" (used for pooled analyses): $a_j = \sqrt{\frac{n_{0j}n_{1j}}{n_{0j}+n_{1j}}}$.

For large sample sizes (within each strata) the test statistic has a standard normal distribution; therefore the two-sided test would reject the null hypothesis if $|W^*| > u_{\alpha/2}$.

The test can easily be implemented using the SAS, PROC FREQ. The FREQ procedure is used with the TABLE statement options CMH2 and SCORES=MODRIDIT. The second CMH statistic, labeled "Row Mean Scores Differ" is the asymptotic test statistic.
As shown by Koch et al 1982, the Van Elteren test is a member of a general family of Mantel-Haenszel mean score tests. For more information about the Van Elteren test and related testing procedure, refer to Lehmann 1975, Koch et al 1990.

5.4.3 Multiple imputation sensitivity analyses steps

The following steps are followed in order to create the structure of the analysis dataset where missing values and appropriate variables could be imputed.

- Obtain subject id, treatment group, stratification factor, sex, race group, age group, BMI group (subjid trt01pn mmstratn sexn race agemedn bmimedn) from ADBS, ADSL.
- Obtain number of prior migraine prophylactic treatment failed, baseline disease duration group (prophfln durmedn) from ADBS.
- Obtain avisitn paramcd param aval avalc base chg dtype from ADATTACK
- If dtype='BOCF' then expect to obtain aval=. and chg=..
- Ensure the baseline values are included in the chg variables before data transformation, eg if avisitn=2000 is baseline then chg=base; Number of prior migraine prophylactic medication failed (prophfln) should be a dichotomous variable. Therefore, if prophfln gt 3 then prophgrp=1; otherwise prophgrp=0.
- Transpose all the data so you have one observation per subject and each visit becomes a variable within its own right, eg rows where avisitn=2004, 2008, 2012 become the column week4, week8, week 12.
- Impute the missing data for MAR and MNAR separately according to the methods in next steps

MAR multiple imputations steps:

Note that the some variable has missing values and there is a mix of categorical and continuous variables in the modelling of the missing data. Therefore, fully conditional specification (FCS) methods are employed within proc mi to impute the missing data.

- FCS logistic is used for dichotomous variables (mmstratn sexn agemedn bmimedn prophgrp durmedn); discrim is used for categorical variables with more than 2 categories (race); regpmm is used for continuous variables (wk0, wk4, wk8, wk12).
- wk4, wk8 and wk12 represent the chg variable for each of the visits respectively, and wk0 is baseline.

MNAR multiple imputations steps:

- Here is an implementation of the pattern-mixture model approach that uses a control-based pattern imputation and imputing the missing data step-by-step, where the baseline variables inform on any missing baseline efficacy values. The baseline efficacy values then inform on the next visit, which then informs on the next visit and so on until all visits have non-missing data.
- Furthermore, an option is used at post-baseline visits (modelobs= (trt01pn='0'), assuming the treatment code for placebo is 0) to include an adjustment for the fact that any missing data from active treatment subjects will be similar to placebo subjects under the assumption that missing values in the active treatment subjects implies they are no longer on treatment. That is, an imputation model for the missing data in the active treatment group is constructed not from the observed data in the active treatment group but rather from the observed data in the placebo group. This model is also the imputation model that is used to impute missing data in the placebo group.

MAR and MNAR modeling step:

- For the primary endpoint, first, define 50% Responders based on imputed MMD data under the assumption of MAR or MNAR.Then, use the same method as for primary variable - the stratified CMH test to get estimates for numbers of responders in each treatment group and odds ratio at week 12 for each dataset..
- For change from baseline in MMD it is used a linear mixed effects model on imputing data under the assumption of MAR or MNAR. There is no gaps in imputed data, therefore, all the data is available to analyze and can use a fixed effects model looking only at the avisitn=2012/week12 data.

MAR and MNAR combining step:

- The output dataset with the treatment LS means (LSMEANS) and the treatment differences (DIFF) are then sorted, manipulated and read into proc mianalyze to combine the individual sets of imputed results into one set of overall results, see all steps SAS codes in TFLs document.

5.5 Rule of exclusion criteria of analysis sets

The protocol deviations during screening, baseline and treatment periods are defined below (Table 10). The deviation ID, deviation code and it's corresponding text description are

explained in Table 9. Patients exclusion based on protocol deviations and non- protocol deviations criteria are in Table 11.

Table 8 Deviation Codes Description

Deviation code	Text description	Deviation ID
1	SELECTION CRITERIA NOT MET	INCLXX ; EXCLXX
2	PATIENT NOT WITHDRAWN AS PER PROTOCOL	WITHXX
3	PROHIBITED CONCOMITANT MEDICATION	COMDXX
4	TREATMENT DEVIATION	TRTXX
998	OTHER	OTHXX

Table 9 Protocol Deviations

Deviation ID	Description of Deviation
Scr INCL01	Informed consent not signed.
Scr INCL02	Adults <18 to >65 years of age
Scr INCL03	Documented history of migraine (with or without aura) for less 12 months prior to screening according to the International Classification of Headache Disorders-3rd Edition (ICHD-3)
Scr INCL04	< 4 or ≥15 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
Scr INCL05	≥15 days per month of headache symptoms (ie migraine and non-migraine)
Scr INCL06	Not 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)
Scr INCL07	Failed one and failed Or not be suitable for a second of the following: Propranolol or Metoprolol, Topiramate, Flunarizine
Scr INCL08	Failed or not be suitable for Valproate or Divalproex
Bln INCL09	Migraine frequency interval out of 4 to 14 migraine days during the Baseline Epoch, confirmed by the eDiary
Bln INCL10	<80% eDiary compliance during the Baseline Epoch
Scr EXCL01	To be older than 50 years of age at migraine onset
Scr EXCL02	To be unable to differentiate migraine from other headaches
Scr EXCL03	History of cluster headache or hemiplegic migraine headache

Deviation ID	Description of Deviation
Scr EXCL04	*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)
Scr EXCL05	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
Scr EXCL06	Prior Botulinum toxin A treatment in the head/neck region (including cosmetic use or other licensed indications for Botox®) within 4 months prior to randomization
Scr EXCL07	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
Scr EXCL08	Anticipated to require any excluded medication, device or procedure (e.g., nerve block, occipital nerve stimulators, transcranial magnetic stimulation) during the study
Scr EXCL09	Active chronic pain syndromes (e.g., fibromyalgia or chronic pelvic pain)
Scr EXCL10	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)
Scr EXCL11	Evidence of drug or alcohol abuse or dependence within 12 months prior to screening, based on medical records or patient self-report
Scr EXCL12	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
EXCL12B	[redacted] assessment was not performed during the screening and baseline epoch
Scr EXCL13	History of seizure disorder or other significant neurological conditions other than migraine
Scr EXCL14	C-SSRS exclusion criterion met. "yes" on Item 4 or 5 of 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

Deviation ID	Description of Deviation
Scr EXCL15	Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery or other revascularization procedures within 12 months prior to screening
Scr EXCL16	History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
Scr EXCL17	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
Scr EXCL18	Hepatic disease by history or total bilirubin ≥2×ULN or ALT or AST ≥3xULN as assessed by central laboratory at initial screening
Scr EXCL19	Pregnant or nursing (lactating) women
Scr EXCL20	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
Scr EXCL21	Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer
Scr EXCL22	History of hypersensitivity to the study drug or its excipients
Scr EXCL23	Any prior exposure to investigational products targeting the CGRP pathway, including previous AMG 334 studies
Scr EXCL24	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
WITH01	Emergence of certain adverse events, such as malignancy, elevated ALT or AST, liver failure or serious chronic infection and treatment was not discontinued
WITH02	Protocol violation that results in a significant risk to the patient's safety but treatment was not discontinued
TRT01	Patient received damaged or expired study drug
TRT02	Subject missed dosing at two consecutive visits.
TRT03	Subject was randomized but did not receive any study drug
TRT04	Subject received study drug without being randomized into study
TRT06	Partial dose adminsitered
TRT07	Study drug mishandled

Deviation ID	Description of Deviation
TRT08	Patient randomised in wrong strata
COMD01	All oral beta blockers, Topiramate, Flunarizine, Valproate/Divalproex, Antidepressants (amitriptyline, venlafaxine, desvenlafaxine), ACE/ARB (lisinopril, candesartan), Serotonin antagonistic agents (oxetorone, pizotifen, methysergide)
COMD02	Botulinum toxin (in the head and/or neck region)
COMD03	Invasive interventions throughout the study (eg, nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation)
OTH07	Informed consent was signed after the patient entered the study
OTH12	Non-compliance with ICH GCP

Table 10 Patient Classification

Analysis Set	*PD ID that cause patients to be excluded*	*Non-PD criteria that cause patients to be excluded*
RAS	*NA*	Not randomized;
FAS	*NA*	Mistakenly randomized and no double-blind study drug taken; No post-baseline measurement in primary efficacy endpoint during DBTE;
SAF	*NA*	No double-blind study drug taken;

5.6 Appendix A: Vital signs notable criteria

Table 11 Vital Signs Notable Criteria

Vital Sign Variable	Notable Criteria
Pulse (beats/min)	> 120bpm or Increase of ≥15 bpm from baseline or < 50bpm or Decrease of ≥15 bpm from baseline
Systolic BP (mmHg)	>180 mm Hg or Increase of ≥20 mm Hg from baseline Or < 90 mm Hg or Decrease of ≥ 20 mm Hg from baseline
Diastolic BP (mmHg)	> 105 mmHg or Increase of ≥ 15 mm Hg from baseline Or < 50 mmHg or Decrease of ≥ 15 mm Hg from baseline

5.7 Appendix B: Clinically notable laboratory values

Table 12 Clinically Notable Laboratory Values

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

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

5.8 Appendix C: Criteria for ECG abnormalities

Table 13 ECG Abnormality Ranges

ECG Parameter	Abnormality Flags	
	Absolute	Relative*
RR Interval	Low: < 600 msec ; High: > 1200 msec	Low: ≤ -20%; High: ≥ 20%
PR interval	Low: < 120 msec ; High: > 200 msec	Low: ≤ -20%; High: ≥ 20%
QRS Interval	Low: < 60 msec ; High: > 109 msec	Low: ≤ -20%; High: ≥ 20%
QT Interval	Low: < 320 msec ; High: > 450 msec	Low: ≤ -20%; High: ≥ 20%
QTcB Interval (Bazett's correction)	Low: < 320 msec ; High: > 450 msec	Low: ≤ -20%; High: ≥ 20%
QTcF Interval (Fridericia's correction)	Low: < 320 msec ; High: > 450 msec	Low: ≤ -20%; High: ≥ 20%
*Relative change from previous measurement in percent (%)		

5.9 Appendix D: Visit schedules and assessments

Table 14 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)						
[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	X							

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**	
Completion Form								
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.

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.

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.

5.10 Appendix E: Patient-reported Outcome Forms/Instruments

E.1 Migraine Physical Function Impact Diary (MPFID, Version 2.0) scoring

Overview

The Migraine Physical Function Impact Diary (MPFID) is a 13-item self-administered disease-specific patient-reported outcome (PRO) instrument measuring physical functioning. The recall period is the past 24 hours.

MPFID has two domains, Impact on Everyday Activities (EA; 7 items) and Physical Impairment (PI; 5 items), and one stand-alone global question which provides an assessment of overall impact on everyday activities (G-EA).

Subjects respond to items using a 5-point scale. Responses are assigned scores from 1 to 5, where 5 represents the greatest impact.

• Frequency item responses range from:

o None of the time = 1, All of the time = 5

• Difficulty item responses range from:

o Not difficult = 1, Extremely difficult = 5

o Without any difficulty = 1, Unable to do = 5

There is a scale score for each of the two domains (EA, PI) and a score for the stand-alone item (G-EA). Higher scores represent greater impact of migraine (ie, higher burden).

Domain and Global Item Scores

To calculate the two MPFID domain scores (EA, PI), scores for each item are summed across each individual domain. The table below provides details about scoring:

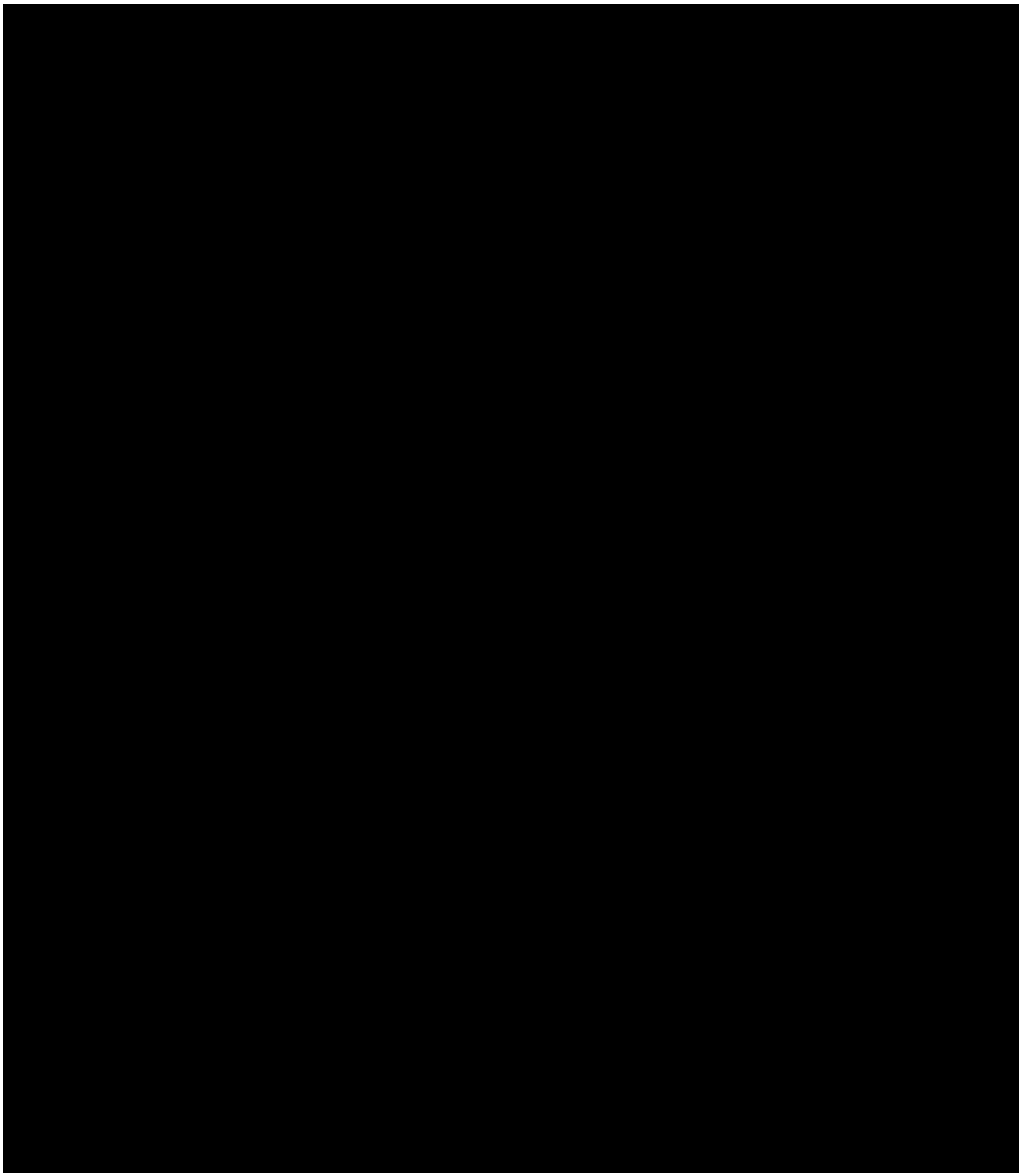
Domain/ Global Item	***Number* of Items in Domain**	***Sum* of Item Values**	**Lowest and Highest Possible *Sum* of Item Values (Raw Scores)**	**Final Domain/ Global Item Score Range**
Impact of Migraine on Everyday Activities (EA; items 1-7)	7	1+2+3+4+5+6+7	7, 35	0-100
Global Item: Overall Impact on Everyday Activities (G-EA; item 8)	1	8	1,5	0-100
Physical Impairment (PI;	5	9+10+11+12+13	5, 25	0-100

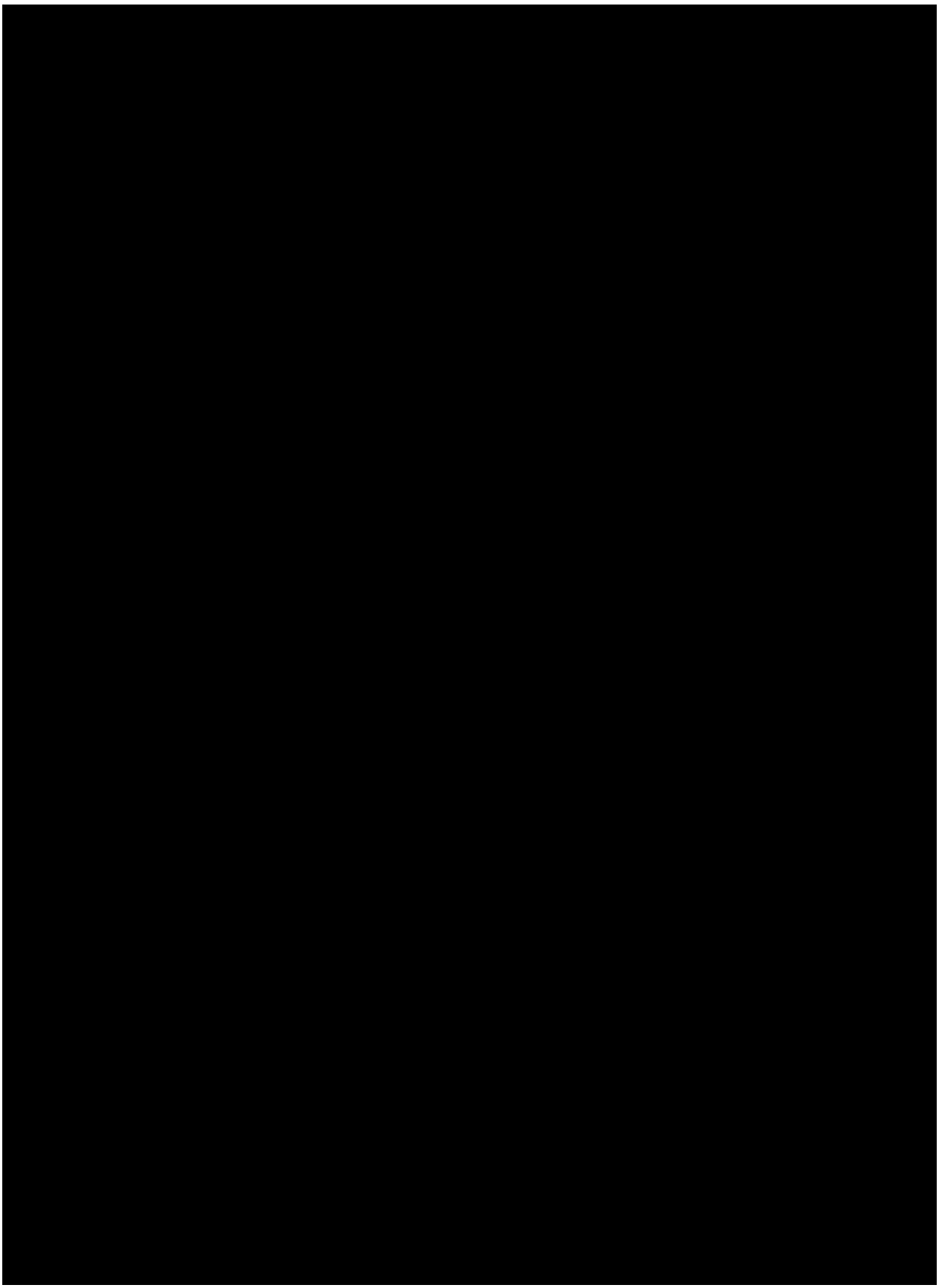
items 9-13)				

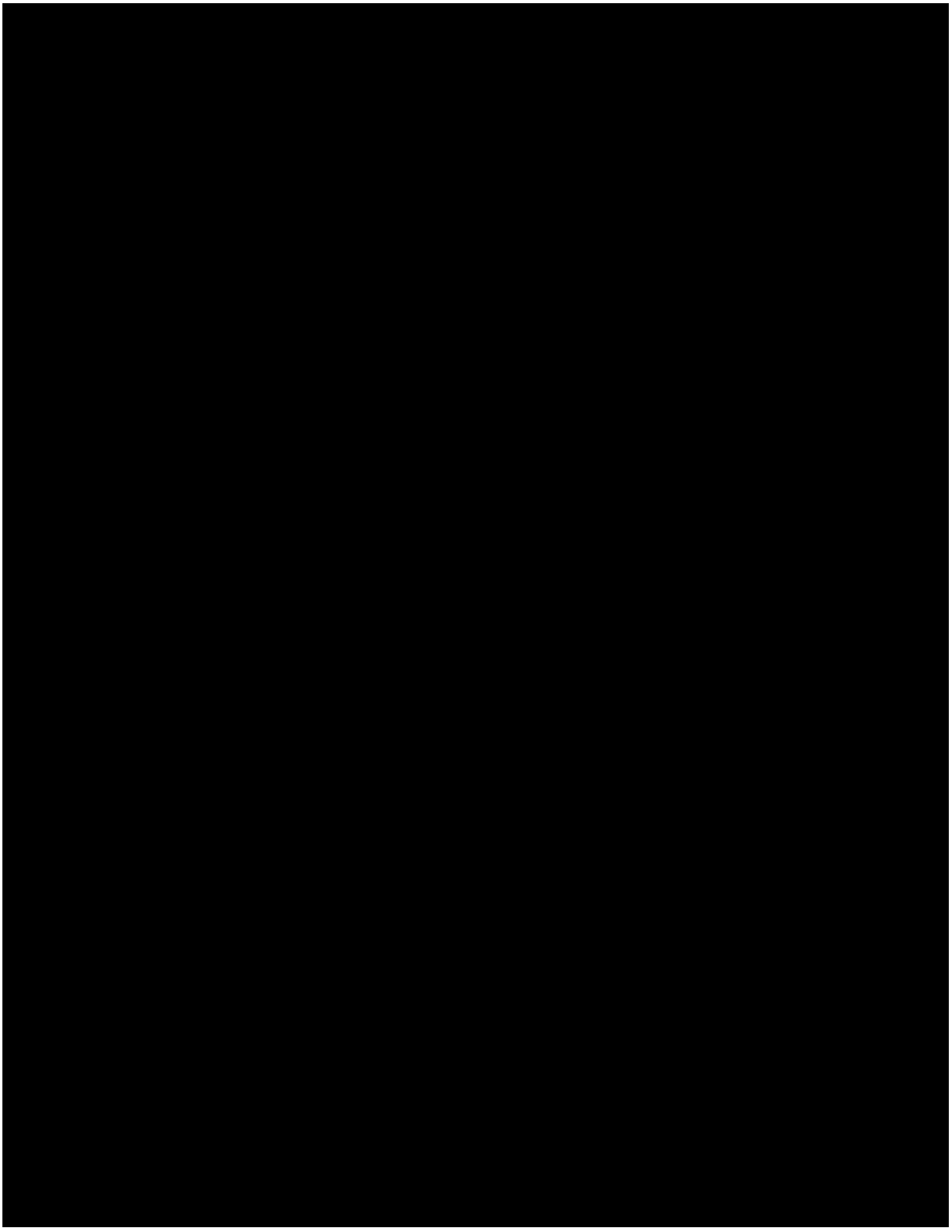
The formula below will be used to transform raw domain score values into a 0-100 scale. This will provide MPFID domain scores that range from 0 to 100, where higher score values are indicative of greater migraine impact. No total score is created for the MPFID.
Formula for calculating MPFID domain scores:

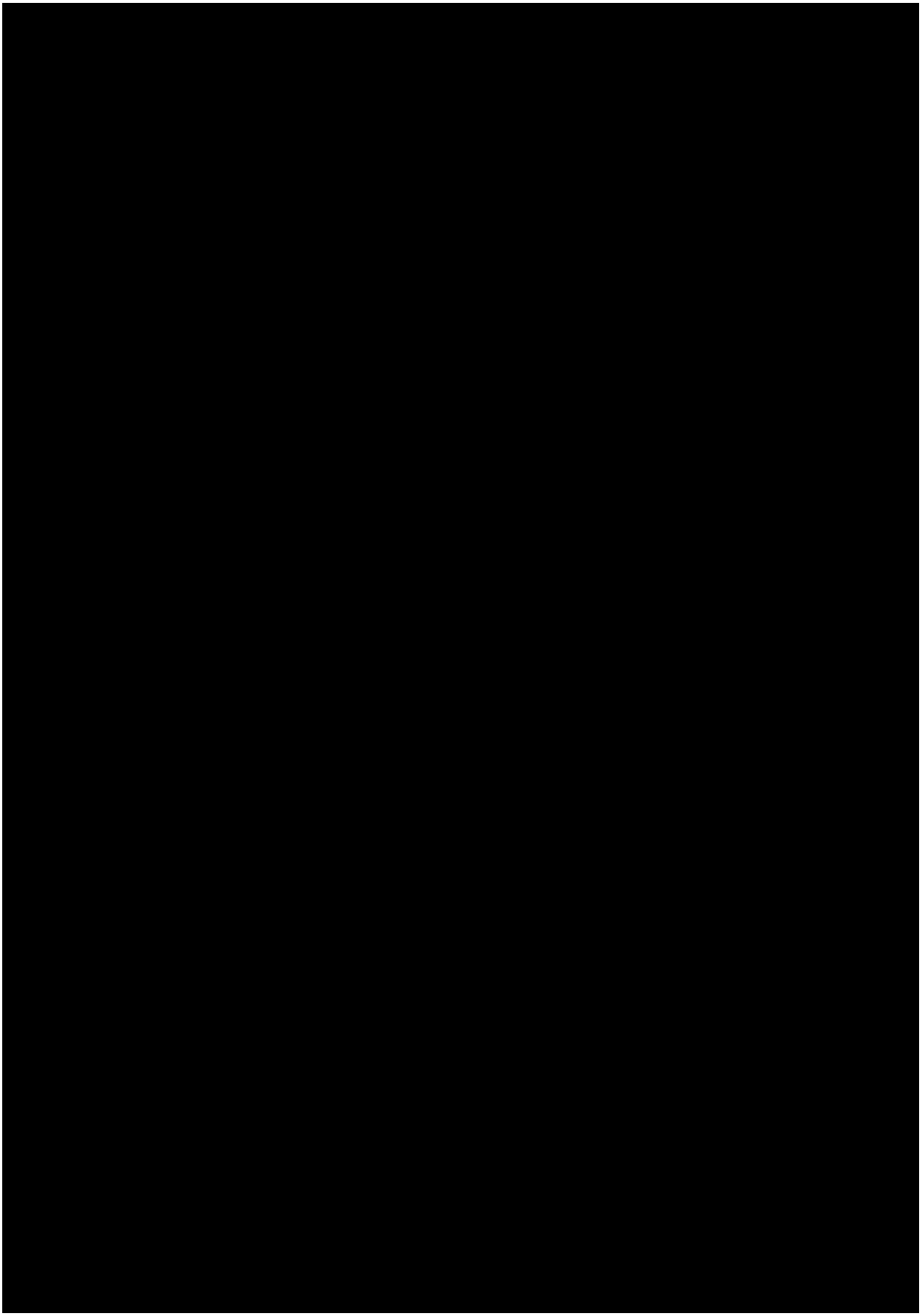
$$\text{Transformed score} = \frac{\text{(raw score - lowest possible raw score)}}{\text{highest possible raw score - lowest possible raw score}} * 100$$

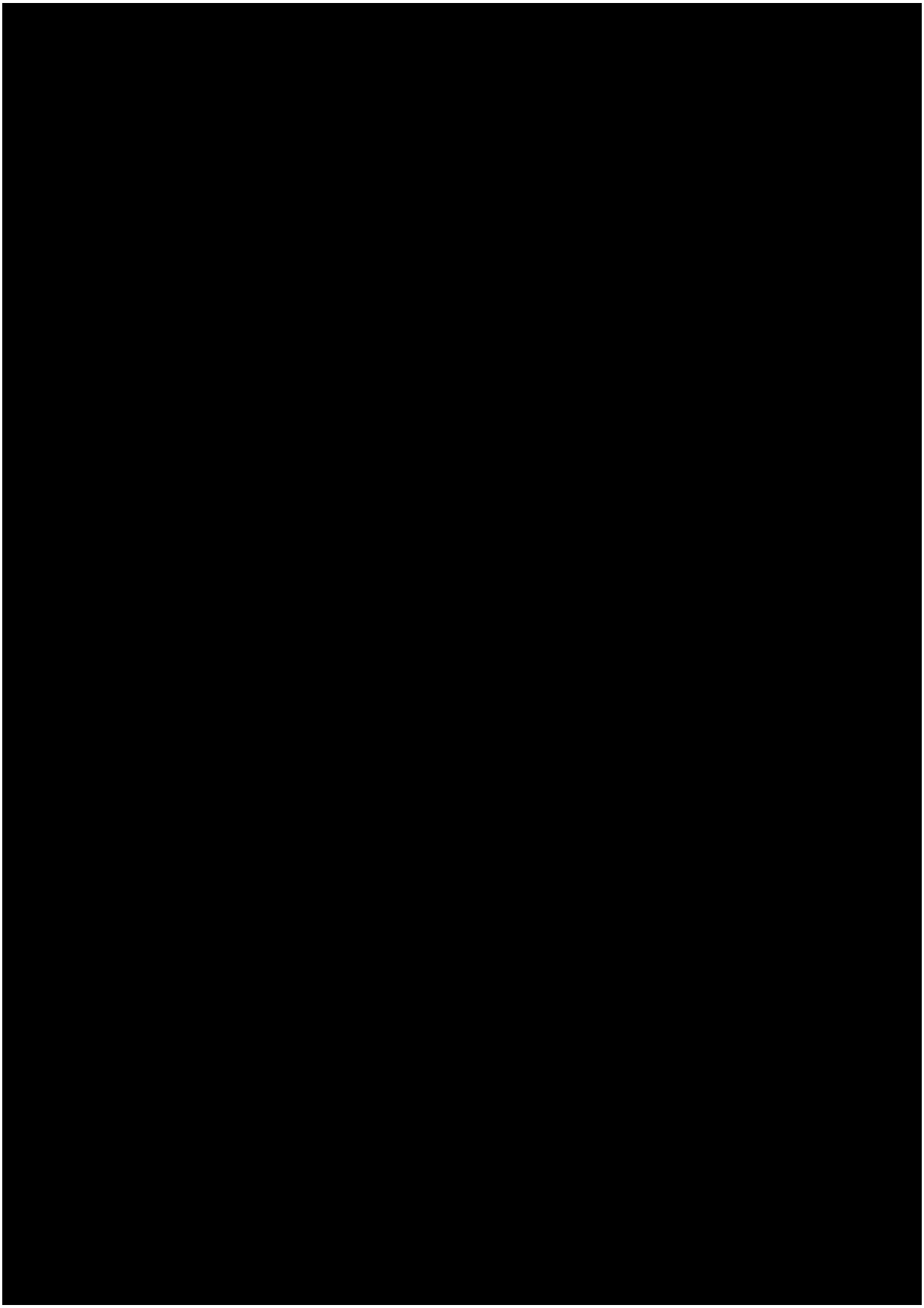
Imputing Missing Data and Sensitivity Analyses for MPFID Domain Scores
For each MPFID daily diary domain, if <50% of the items within a domain are missing, the mean of the item scores that are present for that day will be used to impute a score for the missing item(s). If ≥50% of the items that make up a domain are missing, no domain score will be calculated; the domain will be considered missing. This relatively simple approach has previously been shown to yield unbiased and robust estimates, and compared favorably with more complicated methods of single-imputation and regression-based methods (Fairclough and Cella 1996).

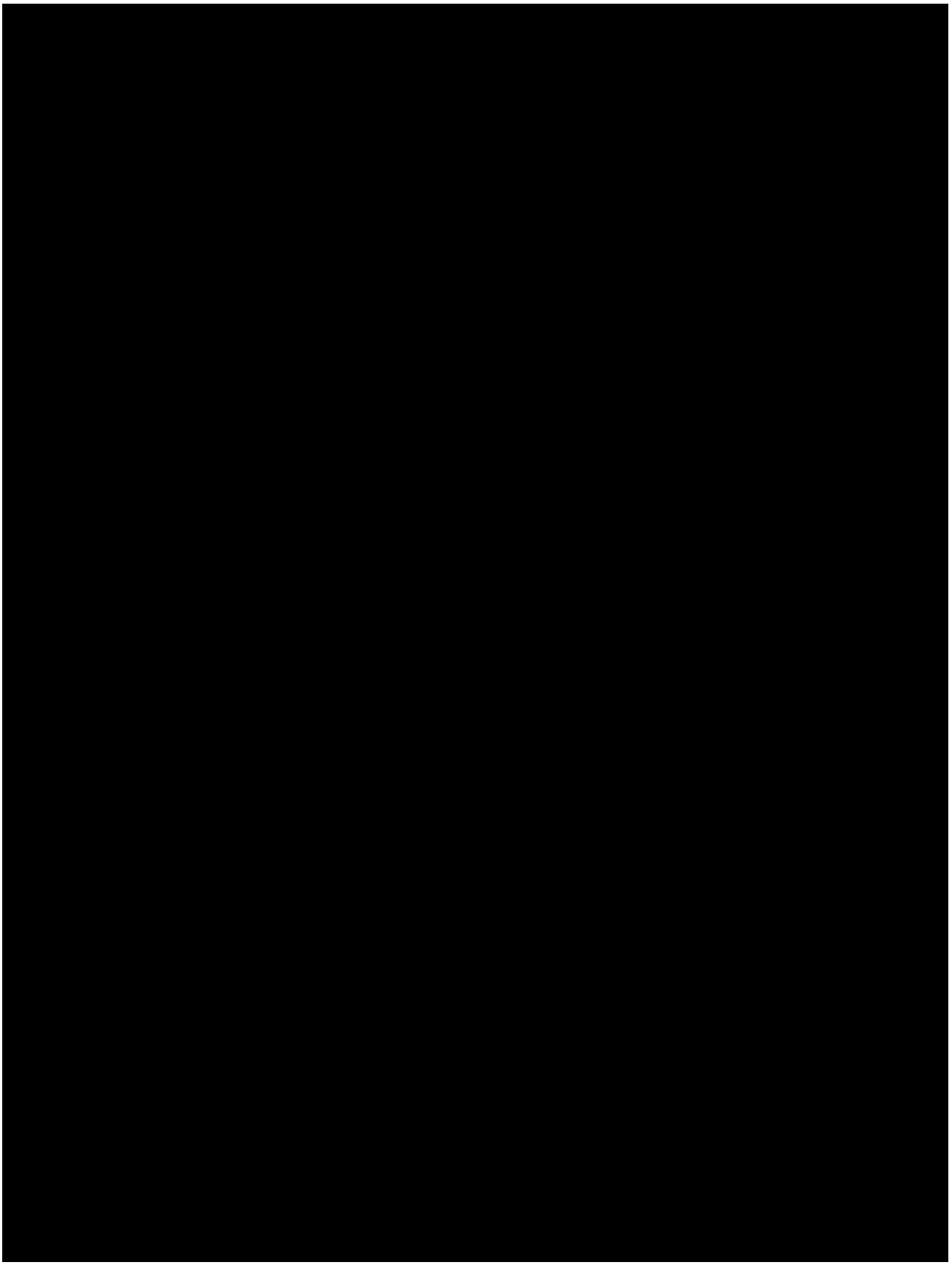












5.11 Appendix F: Geographic regions

Geographic Region	**Country**
Europe	Denmark
	Sweden
	Finland
	Norway
	France
	Germany
	Spain
	UK
	Italy
	Netherlands
	Belgium
	Czech R
	Greece
	Switzerland
Australia	Australia

5.12 Appendix G: Prohibited treatments

Use of the treatments displayed in Table 17 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 15 Prohibited Treatments

Treatment	Prohibition period
All oral beta blockers	Within 5 half-lives of the start of the baseline epoch and throughout the study when used for migraine prophylaxis
Topiramate	
Flunarizine	
Valproate/Divalproex	
Antidepressants (amitriptyline, venlafaxine, desvenlafaxine)	
ACE/ARB (lisinopril, candesartan)	
Serotonin antagonistic agents (oxetorone, pizotifen, methysergide)	
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

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