NOVARTIS

Clinical Development

AMG 334 (erenumab)

CAMG334A2302 / NCT03333109

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
2-Feb 2018		Initial SAP, version 1.0		
26-Feb-2020		Version 2.0	Amendment 1	Section 2.1.3: definition for cumulative MMD Section 2.12: ANCOVA model for cumulative MMD Section 2.71: add analysis for treatment-related AEs/SAEs Section 2.1.3.1: reference to document "Important derivations in AMG" Section 2.3.1: definition of DBTP completer Section 2.1.1.4: add definition for Treatment Failure of Prior Migraine Prophylactic Medications Section 5.1.5.3.2: remove the number of failed Prior Migraine Prophylactic Medications as covariates as strata is present Table 2-2: update start date to be consistent with baseline definition Table 2-1: remove day 1 (as no more needed, part of baseline visit) Section 2.1.1.1 add EOT definition Table 2-2: safety FU start and end date Table 2-1: FU target day Section 2.1.1: added definition screening value for C-SSRS Section 2.5.5, section 4: added supplementary analysis for long lasting migraine events Section 5.1.2: imputation of end date for concomitant medication

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 5.1.4: imputation of start/end date for alternative migraine therapies
				Section 2.1.1: age is collected and not birth year.
				Definition of BDI-II moved from section 2.1.3.1 to 2.1.3.2
				Section 2.3.2: clarification regarding multiple race. Remove listing with child bearing status. Added stratification of summary of prior migraine prophylactic treatment by medication category. categorical variable added regarding baseline disease characteristics as "Number of prior prophylactic treatment failures"
				Section 2.4.2: prior medications only listed
				Section 2.7.1: summary of SAE by CTCAE removed
				Section 2.7.3: add clarification (newly occurring)
				Section 2.7.4: urine pregnancy results not listed (data not available)
				Section 2.12: added analysis for monthly migraine-specific medication treatments days as per protocol objective
				Section 2.1.3.2 and section 5.1.2: remove part related to flag in eCRF for treatment-emergent (as not in the CRF)
				Section 5.1.5.1: imputation rule for monthly average severity of migraine pain and hours of migraine headache removed as not among the endpoints
				Section 5.1.5.3.2: paragraph about 50% responder as MI analysis not planned for this endpoint
				Section 1: date of study protocol final
				Section 2.1.3.2: add clarification regarding concomitant medication

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.1.3.1: modification of headache, migraine and migraine attack definition for aura-only event (cannot be linked to medication). Reason added in section 4 [redacted] Section 2.7.1: add summary of AE for entire study period Section 2.5.2: 95% CI for LSmeans not displayed in shell Section 2.6.2: testing strategy updated. Clarification on dichotomous endpoint added. Section 2.6.5.1: Clarification added regarding subgroup analysis.

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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
BDI	Beck Depression Inventory
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
DBTP	Double-Blind Treatment Period
EA	Everyday Activities
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EoS	End of Study
[redacted]	[redacted]
FAS	Full Analysis Set
GLMM	Generalized Linear Mixed Model
HIT-6	Headache Impact Test
IRT	Interactive Response Technology
IP	Investigational Product
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
[redacted]	[redacted]
MNAR	Missing Not at Random
[redacted]	[redacted]
NRI	Non-Responder Imputation
PD	Protocol Deviations
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient-Reported Outcomes
PT	Preferred Term
qm	once a month
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

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis according to Section 9 of the study protocol **Protocol v0.0** for AMG 334 Study CAMG334A2302 dated **June 8, 2017** and along with any additional analyses, specifications or deviations from the protocol planned.

The scope of this plan includes the primary, secondary, [redacted] analyses, which will be executed by Novartis internal statisticians and programmers, if not specified differently. Those analyses will be reported in the CSR.

1.1 Study design

This study uses a single-cohort, 3-treatment arm, randomized (2:3:3 [140 mg: 70 mg: placebo]), double-blind study design in adult patients with episodic migraine.

The following periods are included in the study design:

- Screening period of 2 weeks: to assess initial eligibility,
- Baseline period of 4 weeks: All patients successfully completing the Screening period are invited to participate. Final eligibility prior to randomization and dosing will be assessed based on headache frequency and diary compliance during this period,
- Double-blind treatment period (12 weeks): All patients successfully completing the Baseline period are invited to participate. Eligible patients will be randomized to one of three treatment arms. After randomization/Day 1, visits will occur at four week intervals until Week 12, which is the End of Treatment visit.
- Safety follow-up period: the final visit, a Safety Follow-Up visit, will occur 12 weeks later, at Week 24.

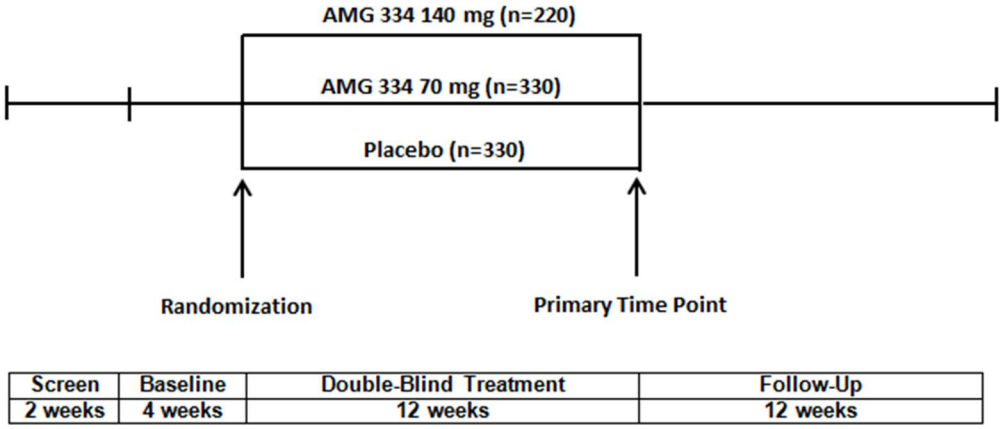
A blinded interim analysis after approximately 50% patients have completed the DBTP (including early withdrawals) will be conducted to re-estimate the sample size by providing information on the variance for this trial relative to the planning assumptions to account for potential higher variability in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

End of Trial (Last Patient Last Visit, LPLV) will occur when all patients have completed their last visit.

Approximatively 880 patients will be randomized (330 in placebo, 330 in AMG334 70mg and 220 in AMG334 140mg), stratified by prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure).

The primary analysis and all other efficacy and safety analyses will be conducted at the end of study after the database lock; i.e., at the time point when all patients have completed their last visit.

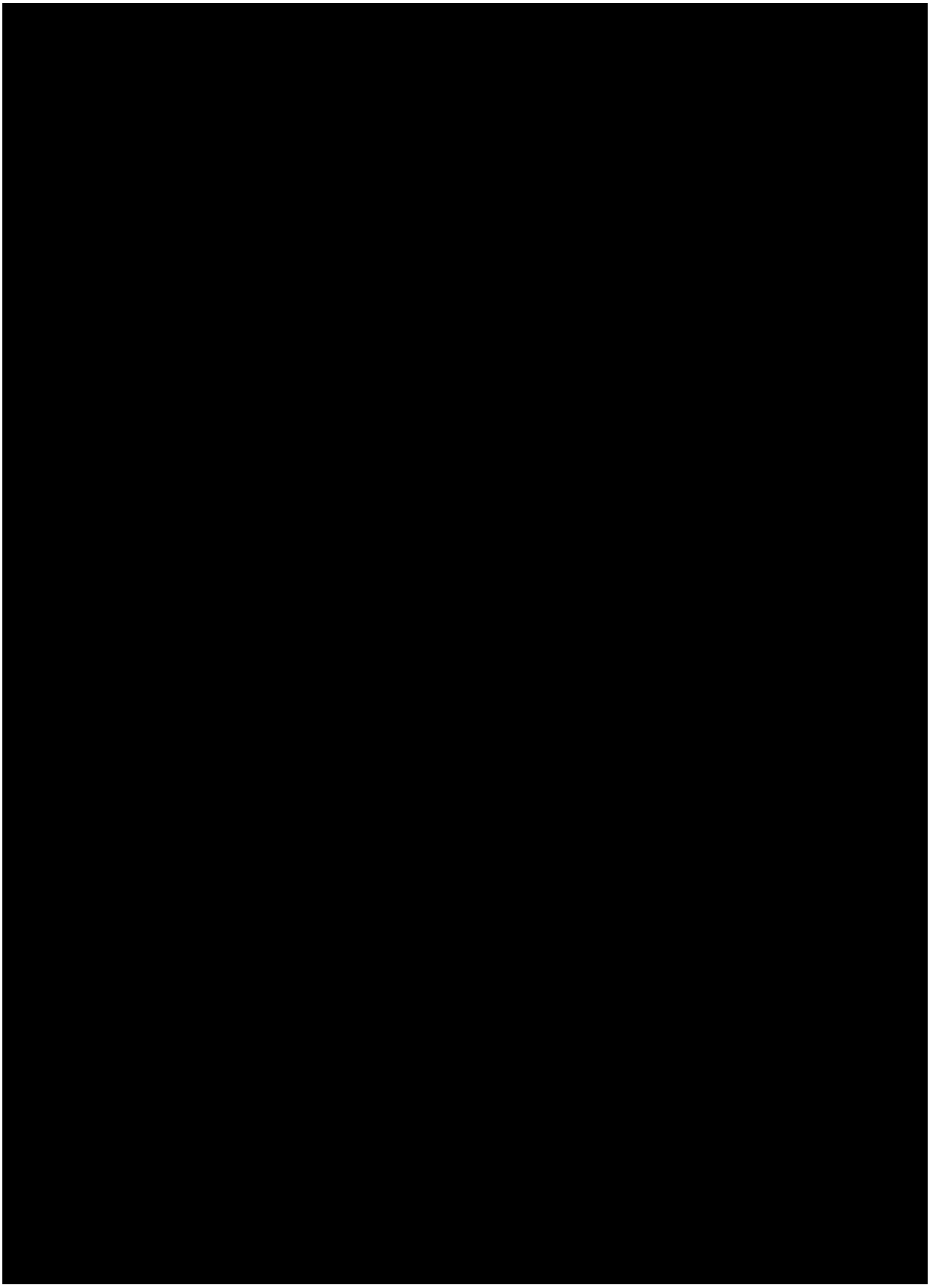
Figure 1-1 Study Design Schematic

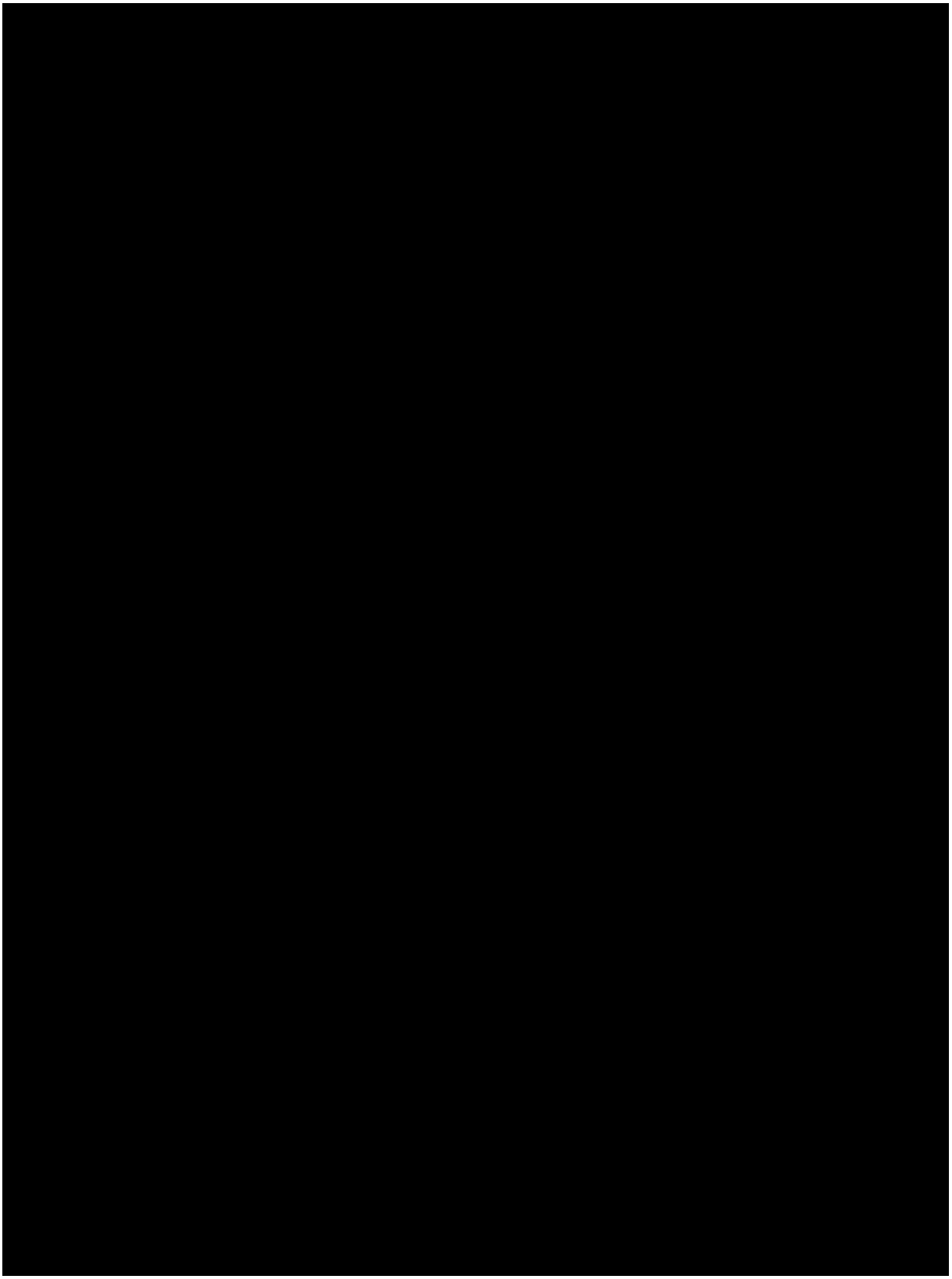


1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

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





[redacted]

2 Statistical methods

2.1 Data analysis general information

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

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

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 arm and presented by country name/center number/patient id (/ visit wherever applicable).

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

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

Randomization will be stratified by prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure). Stratification factor used as covariate in the analysis will use the values used for randomization unless otherwise noted.

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

Final and interim analyses described below will be performed by Novartis, unless otherwise noted.

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), one injection of AMG 334 70 mg and one of placebo or two injections of 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 period.

2.1.1.1 Study dates

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 DBTP

Randomization (Enrollment) Date in DBTP is the date on which a subject is assigned to one of the treatments through IRT in DBTP.

First IP Dose Date

The first IP dose date is the date on which a subject is administered the first dose of IP 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

The last IP dose date for each subject is defined as the latest date IP is administered.

Subject-level End of Study (EOS) Date

The end of study (EOS) date for each subject is defined as the last date on which the subject participated in the study. The date will be recorded on the Study disposition eCRF page.

Subject-level End of Treatment (EOT) Date
The end of treatment (EOT) date for each subject is defined as the end of the treatment phase. The date will be recorded on the Treatment disposition eCRF page.

2.1.1.2 Study points of reference

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.

Baseline

The baseline period for efficacy endpoints collected by the daily eDiary (e.g., monthly migraine days, acute migraine-specific medication days, [redacted] ...) 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 (HIT-6, BDI-II, [redacted]) 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 day 1 (date of first administration of study drug or randomization day if the subject was not dosed after randomization) or on an earlier visit (scheduled or unscheduled) which is the closest to day 1 visit, if the assessment was not done on day 1. In case of multiple assessments on the same day, the first one will be considered for PRO and the latest one for safety; for C-SSRS the first complete assessment performed with the electronic version ("Since last visit" recall period) or supplemental data collected on the CRF page will be used.
Note: Assessments on the day of randomization are assumed to have been taken as per protocol, i.e. if the assessment should be performed before dosing, the assessment will be treated as pre-dose as per protocol. Practically, i.e. that the time part of the date/time entry will be ignored. Exception: In case there is a protocol deviation or a comment that specifically indicates that the assessment has been taken post-dose, the assessment will not be treated as pre-dose.

C-SSRS screening value
Screening value for C-SSRS refers to the last evaluable complete assessment for the recall period "Lifetime" prior or on day 1.

2.1.1.3 Arithmetic calculations

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 2-3. For example, change from baseline in monthly migraine days in the last month (month 3) of the double-blind period will be calculated based on the following:

(Monthly migraine days in the last month of the DBTP) – (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

Response rate 50% (75% / 100%) will be defined as a decrease from baseline score value of at least 50% (75% / 100%).

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).

If the current age 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.

The duration of exposure is computed as min(last DB dose date+27, EoS Date) – First Dose Date+1.

Compliance with the eDiary

The protocol requirement is 80% compliance in 28 days. That means a minimum 23 diaries must be completed within 28 days. Compliance to eDairy at each month is calculated as

- (Number of eDiary entered in baseline period or between IP doses/28days)*100% if the number of actual days in Baseline period or between IP doses interval is <= 28 days
- (Number of eDiary entered in baseline period or between IP doses/ number of actual days in Baseline period or between IP doses interval)*100% if the number of actual days in Baseline period or between IP doses interval is > 28 days

2.1.1.4 Disease characteristics

Treatment Failure of Prior Migraine Prophylactic Medications

Treatment failure of prior migraine prophylactic medications is determined by "Reason for ending medication" as "Lack of efficacy" (with therapeutic dose) or "Lack of tolerability" in the Prior Migraine Prophylactic Medication eCRF page.

Prior migraine prophylactic medications are classified in 7 categories (as per protocol) and one additional category for other migraine prophylactic medications:

- Category 1: Divalproex sodium, sodium valproate
- Category 2: Topiramate
- Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline,
- protriptyline)
- Category 5: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 6: Flunarizine, verapamil
- Category 7: Lisinopril, candesartan
- Category 8: Other migraine prophylactic medication (for example: Botulinum toxin)

For medications entered as free text, categorisation will be provided by clinical team, confirmed by Medical Lead, prior DBL.

The number of failed prior prophylactic treatments is the number of categories with at least one failed prior migraine prophylactic medication.

2.1.2 Visit and analysis windows

Visit window

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, ECG, C-SSRS and some PROs collected during office visits (HIT-6, [redacted], BDI-II, [redacted]) before dose is administered.

Table 2-1 Study Visit Windows

Study visit	Target Day	Study Day
Baseline	See baseline assessment of the Study (Section 2.1.1.2, baseline definition)	
Week 4	28	16-43
Week 8	56	44-71
Week 12	84	72-99
Safety follow-up	Safety follow-up should be excluded from the analysis visit windows described above and summarized under 'safety follow-up' for safety analyses only. Refers to Table 2-2. Target day: last IP dose date + 16 weeks	

For safety endpoints (like lab, vital signs) except ECG, when assessment value for scheduled visit and unscheduled visit are both present within the same analysis window, scheduled visit value should be used. Unscheduled visit will only be used when there is no measurement from the scheduled visit in the defined window. In case of multiple assessment values among the same type of visit (ie, scheduled vs. unscheduled) within the same analysis window, the closest to the scheduled visit day will be used. In case of equal distances (e.g same day), 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 ECG, the same strategy will be applied except that no prioritization of scheduled vs unscheduled visit will be made.

In case of multiple assessments on the same day for PROs (including C-SSRS), the first assessment will be used. For C-SSRS, the first complete assessment performed with the electronic version ("Since last visit" recall period) or supplemental data collected on the CRF page will be used. In case of multiple days with assessments within an analysis window (for post-baseline visit) for PROs and C-SSRS, the day the closest to the scheduled visit day will be used.

Study phases

For safety analyses which are summarized by study phase (AE, antibody, laboratory, vital signs, ECG and C-SSRS), or during the entire study (anti-AMG334 antibody), analysis windows will be set up based on study phase:

Table 2-2 Study Phases for Safety analysis

Study Phase	Start Time Point	End Time Point

Double-blind Treatment Period	For AE, concomitant medications: Study Day 1 Otherwise: Study Day 2	For AE, concomitant medications: MIN (EoS date, last IP dose date + 27 days) Otherwise: MIN(EoS Date, MAX(last IP dose date + 27 days, EoT date+14 days))
Safety follow-up	For AE, concomitant medications: last IP dose date + 28 days Otherwise: MAX(last IP dose date + 28 days, EoT date+15 days)	For AE, concomitant medications: MIN(EoS Date, last IP dose date + 16 weeks) Otherwise: MIN(EoS Date, last IP dose date + 16 weeks +14 days)
Entire Study	For AE, concomitant medications: Study Day 1 Otherwise: Study Day 2	For AE, concomitant medications: MIN(EoS Date, last IP dose date + 16 weeks) Otherwise: MIN(EoS Date, last IP dose date + 16 weeks +14 days)

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

Monthly Interval for Efficacy Endpoints (from eDiary)

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 EOT visit (week 12 visit).

Table 2-3 Study Intervals for Efficacy Endpoints

Study Phase	**Assessment Time point**	**Interval Based on Dose Dates**	
		Start date	**End date**
Baseline Period	Baseline	From eDiary device assignment date (or Week -4 visit)	Day prior to study day 1
Double-Blind Treatment Period	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 DBTP 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)	MIN (Study day 84, EoS) if Week 8 dose is not received MIN (Week 8 dose date + 27, EoS) if week 8 dose is received

2.1.3 Definition of terms included in study endpoints

2.1.3.1 Efficacy endpoints

Please refer to the document "Important derivations in AMG" (in CREDI: AMG334A/Administrative files/CIS (Clinical Information Sciences)/Biostatistics) for more detail on the derivations.

eDiary Day

A day in which a subject uses the eDiary.

Information Day

A day which is either a headache day or an eDiary day.

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). Please see exceptions in Appendix 5.11. 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 (i.e., triptan or ergotamine) during aura (as part of an headache), 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 5.1.5 (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 period

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

Migraine Attack

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

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours will be considered as one attack and not two.

b) An attack treated successfully with migrainespecific medication but with relapse within 48 hours will be considered as one attack.

c) A migraine attack lasting more than 48 hours will be counted as one attack.

Monthly Migraine Attacks

Number of migraine attacks between each monthly IP dose. Monthly migraine attacks at baseline are the number of migraine attacks in baseline period. Days without eDiary data are handled by proration according to Section 5.1.5.

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). Please see exceptions in Appendix 5.11. A qualified headache is defined as**:**

- a qualified migraine headache 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.

Unknown medications (entered as 'Other' in the eDiary and not identified) will not be counted as acute headache treatment. Sensitivity analysis might be performed as appropriate.

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 5.1.5.

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 5.1.5.

Unknown medications (entered as 'Other' in the eDiary and not identified) will not be counted as acute headache treatment. Sensitivity analysis might be performed as appropriate.

Monthly Acute Migraine-Specific Medication Treatment Days

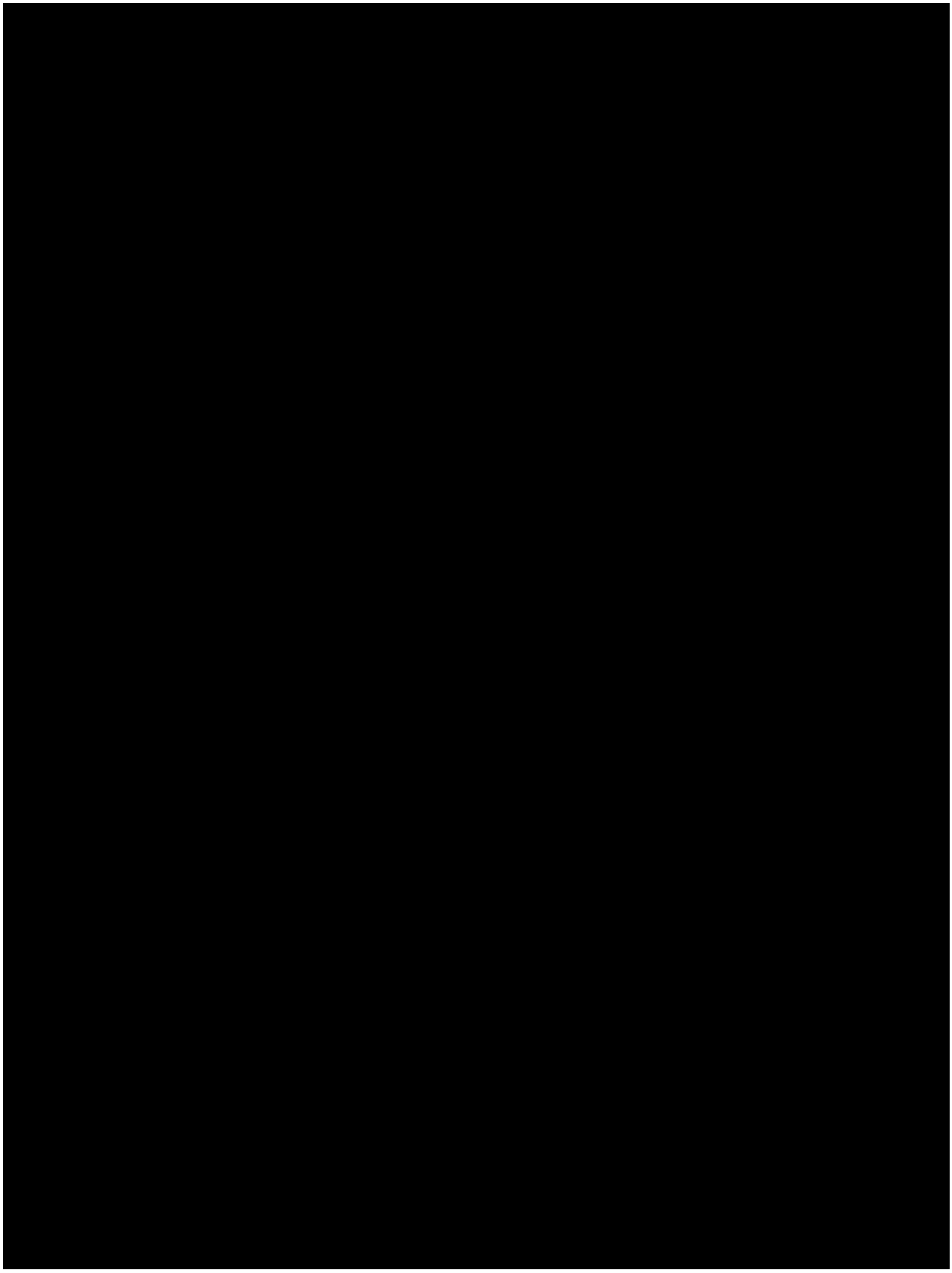
Number of days on which acute migraine-specific medications are used as recorded in eDiary between each monthly IP dose. Migraine-Specific medications include two categories of medications: triptan-based migraine medications and ergotamine-based migraine medications. Monthly migraine-specific medication 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 5.1.5.

Cumulative Monthly Migraine Days

Cumulative monthly migraine days during DBTP is sum of qualified monthly migraine headache days during the entire DBTP normalized into the 28-days period. If eDiary compliance>=50% then the cumulative monthly migraine days are calculated according to the formula:

28*(Total number of observed eDairy migraine days /Number of information days during DBTP);

If eDiary compliance is <50%, it is set up to missing.



[redacted]

Headache Impact Test (HIT-6)

The Headache Impact Test (HIT-6) is a short-form self-administered questionnaire based on the Internet-HIT question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a patient's clinical status over a short period of time. Six questions cover:

- severe pain,
- limitation of daily activity (household, work, school and social),
- wanting to lie down when headache is experienced,
- feeling too tired to work or do daily activities because of headache,
- feeling fed up or irritated because of headache, and
- headache limiting ability to concentrate or work on daily activities.

Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always." And, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided for each HIT-6 item. These points are summed using special algorithm to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 score are categorized into 4 grades, representing little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78) due to headache. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.
Subjects will complete the HIT-6 using the eDiary. Please refer to Appendix D for details.

Achievement of at least a 5 point reduction from baseline in the last month of the DBTP

The achievement of at least a 5 point reduction from baseline in the total HIT-6 score is calculated based on the following:
If (total HIT-6 score in the last month of the DBTP - baseline total HIT-6 score) is less than or equal to -5.

[redacted]

2.1.3.2 Safety endpoints

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 (Table 2-2). 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.

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 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.

Treatment-Emergent Serious Adverse Event

A treatment-emergent serious 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.

Treatment-Related Serious Adverse Event

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

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: Screening and Since Last Visit. The C-SSRS consists of a maximum of 20 items to evaluate suicidal behavior and suicidal ideation.

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. A concomitant medication for the DBTP is a concomitant medication that was taken at least once during the DBTP (defined in Table 2-2). A concomitant medication for the FU is a concomitant medication that was taken at least once during the FU (defined in Table 2-2).

In case the end date is missing and patient entered the FU, the medication will be classified as concomittant medication for DBTP and FU (and prior medication if start date prior first dose

of the randomized study medication). In case the end date is missing and the patient didn't enter the FU, the medication will be classified as concomittant medication for DBTP (and prior medication if start date prior first dose of the randomized study medication).

2.2 Analysis sets

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

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

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

As a general rule, the actual treatment is the randomized treatment. Only in case a patient received an incorrect dose at all the visits (up to DBTP completion or discontinuation), the actual treatment is the one received.

Rule of exclusion criteria of analysis sets is presented in Appendix 5.5.

2.2.1 Subgroup of interest

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

- prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure)
- Number of prior prophylactic migraine treatment failure medications: >=2,<2
- Age (< median vs ≥ median)
- BMI (< median vs ≥ median)
- Sex (Male vs Female)
- Region (see appendix E):
    - Asia (excluding India, Taiwan, Korea)
    - India
    - Taiwan
    - Korea
    - Others

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

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Randomized
Subjects are considered randomized if they have been assigned a randomization number.
Exposed to Investigational Product
Subjects are defined as being exposed to IP if they receive at least one dose of IP.
Completing the DBTP
Subjects are defined as completing the DBTP if they complete all visits and the EOT assessments. Subjects are defined as DBTP discontinuers if the Subject Status is not ticked as "Completed" for the study disposition page during DBTP or if they missed any visit.
Completing the Double-Blind Investigational Product
Subjects are defined as completing double-blind IP if they receive the week 8 IP dose.
It will be derived from Treatment Disposition Form with "Completed" as subject status.
Completing the Study
Subjects are defined as completing study if they complete the safety follow-up visit (week 24)**.** It will be derived from Study Disposition Form with "Completed" as subject status.

Patient disposition will be summarized on RAS. The number and percentage (based on the number of patients within each randomized treatment arm) of patients who complete the study will be displayed by randomized treatment and overall. The primary reason for premature study discontinuation will be displayed by randomized treatment and overall.

Double-blind treatment period completion will be summarized in the same manner and in the same table as patient disposition (study completion). The number and proportion of patients, who complete the DBTP or discontinue the study before week 12 visit along with the primary reason for DBTP discontinuation will be presented.

Treatment completion will be summarized in the same manner as patient disposition. The number and proportion of patients, who complete the Double-Blind Investigational Product or discontinue the study drug prematurely along with the primary reason for study drug discontinuation will be presented.

Disposition and treatment completion data will also be presented in listings.

The total number of patients screened and the number of patients screened, but not randomized (discontinued prior to screening phase completion or prior to baseline phase completion) will be summarized, including the reason for screening failure.

Demographic data and the reason for non- inclusion into the study will be listed for screened/baseline patients who discontinued from study prior to randomization.

The number of patients within each of the analysis sets used in the study will be given.

The number of patients with PDs according to the applicable SOP will be presented. The results of the PDs will be grouped using the broad categories defined in the applicable SOP, which currently are:

- Eligibility: Patient did not satisfy entry criteria
- Withdrawal: Patient developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Study Drug: Patient received the wrong treatment or incorrect dose
- Concomitant Medication: Patient took a prohibited concomitant medication
- Other GCP deviation

A complete list of the PDs can be found in the Edit Check Specifications document in CREDI.

Patients with PDs and non-PDs leading to data exclusion from analysis sets will be listed.

2.3.2 Demographic variables and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized for each randomized treatment group and for all participants (total) using RAS.

At baseline (end of the baseline period; see Section 2.1.1.2, baseline definition), the following demographic and baseline characteristics will be summarized:

- Categorical variables:
  - Sex
  - Ethnicity
  - Race
  - Acute headache medication (none, migraine-specific/non migraine-specific) during baseline phase
  - Strata*: Prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure).
  - Aura status during baseline: Migraine with aura (ever experienced a migraine with aura during the baseline period), migraine without aura (never experienced any migraine with aura during the baseline period)
  - Number of prior prophylactic treatment failures based on the treatment category – (0, 1, 2, 3, 4, >4)
  - Beck Depression Inventory (BDI)-II total score severity grade (minimal depression (0-13), mild depression (14-19))

- Continuous variables:
  - Age
  - Height (cm)
  - Weight (kg)

- Body Mass Index (BMI, kg/m2)
- Age at onset of migraine (years)
- Disease duration of migraine with or without aura (years)
- Monthly migraine days during baseline phase
- Monthly migraine attacks during baseline phase
- Monthly headache days during baseline phase
- Monthly acute migraine-specific medication use in days during baseline phase
- Monthly acute headache medication use in days during baseline phase

*value used for randomization.

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

If multiple races have been reported for a subject, the subject will be categorized as multiple and in each selected race category .

The number of patients per country for each treatment group will be presented.
Summary of prior migraine prophylactic treatment and reasons for discontinuation will be presented by treatment group and by medication category (as defined in section 2.1.1.4).

Subject demographics and baseline characteristics including stratification factor and ethnicity will be listed by treatment.

Subject disease history characteristics (listed below) collected on the "Headache and Migraine Frequency History" CRF page will be listed by treatment:

- Age at onset of migraine (years)
- Disease duration of migraine with or without aura (years) – derived.
- Frequency of migraines over the past 3 months (average days per month subject had migraines)

2.3.3 Frequency of headache (migraine and non-migraine) over the past 3 months (average days per month subject had headache)Medical history

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

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 randomized treatment group and for all participants (total) using RAS (randomized analysis set). The SOCs will be presented in alphabetical order. Preferred terms will be ordered within each SOC by decreasing order of frequency in the AMG334 140mg arm.

Relevant medical history and current medical conditions will be listed by treatment.

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

2.4.1 Study treatment / compliance

Exposure will be calculated for patients in the SAF and is defined as the number of investigational product doses received (planned to be 2 injections per dose) by patient.

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The proportion of patients who received 1, 2 or 3 doses will be provided.

A listing with the investigational drug (AMG 334 or placebo) injections administered will be provided.

The duration of exposure since first injection will be summarized descriptively by treatment group.

At each visit, the number and percentage of patients receiving an investigational drug (AMG 334 or placebo) dose will be summarized by treatment group. Additionally, the number and percentage of patients with dose change and reason for dose change will be summarized by treatment group and by visit.

2.4.2 Prior, concomitant and post therapies

The number and percentage of participants receiving concomitant (during the double-blind treatment period) medications, and significant non-drug therapy will be summarized by SOC, preferred term (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment arm, and be listed. The use of concomitant medications and significant non-drug therapy during the follow-up period will be summarized in the same way, in a separate table, but will be listed in the same listing. Medications and significant non-drug therapies prior to start of study drug by treatment will only be listed.

Use of other non-pharmacological treatments and traditional techniques (such as acupuncture, traditional and herbal medicine) during the baseline phase and the DBTP will be summarized by category of medication for each treatment group in a separate table.
Use of acute headache medication during the baseline phase and the DBTP will be summarized by category of medication for each treatment group.

2.4.3 Prohibited treatment

Analysis of concomitant medications, procedures that are prohibited as per protocol (see protocol Section 5.5.8) and given during the conduct of the study will be addressed by the currently planned outputs for the protocol deviations.

No separate outputs will be produced related specifically to prohibited medications.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

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

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

The primary endpoint of the study will be first tested for each of AMG 334 70 mg and 140 mg compared to placebo, respectively.

- Null Hypothesis: In subject with episodic migraine, the AMG 334 treatment group is the same as placebo, in terms of the reduction from baseline in mean monthly migraine days in the last month (month 3) of the DBTP
- Alternative Hypothesis: In subject with episodic migraine, the AMG 334 treatment group is different from placebo, in terms of the reduction from baseline in mean monthly migraine days in the last month (month 3) of the DBTP

A hierarchical gate-keeping procedure and the Hochberg method will be used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints. See further details in protocol Section 9.5 and Section 2.6.2 of this document.

2.5.3 Handling of missing values/censoring/discontinuations

For the primary analysis, missing data will not be imputed, but various sensitivity analyses (see below) under missing at random and missing not at random assumptions will be performed.

2.5.4 Sensitivity analyses

Analysis of the primary efficacy variable at week 12 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 (baseline observations carried forward 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 during the DBTP (the imputation methods are described in Section 5.1.5.3).

2.5.5 Supplementary analyses

See Section 2.6.5 for subgroup analysis.

Blinded review of the data identified a number of cases of long lasting headache/ migraine event in multiple patients across different time points during the study. Some subjects reported headaches lasting more than 10 days.

According to the ICHD-3, migraine events are typically of duration 4-72 hours. At time of the assessment of the impact, a significant proportion of events greater than 96 hours were confirmed as due to data entry error or device problems. After further discussion with the Clinical Trial Team (CTT), it was decided to perform supplementary analyses to assess the impact of long lasting headaches (greater than 96 hours) on primary endpoint following adjustment of the duration of these events.

Definition of the modified Monthly migraine days (mMMD):

A modified 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). Please see exceptions in Appendix 5.11. In case the event is lasting more than 96h, days of that event beyond 96h after the start date of the headache event will not be counted as migraine day, eDiary day or information day except if on the end date another headache started (in that case that day only is still counted).

The modified Monthly migraine days is the number of modified migraine days between each monthly IP dose that are normalized in a 28-day interval using the modified number of information days (if the number of modified eDiary days>=14).

For example if a subject had a long-lasting headache starting on 1st June2019 at 11:45pm (Day 1) and ending on 9th June 2019 at 10:30am (Day 9). Projecting forward 96 hours would give the end of the episode as 05June2018 11:45pm (Day 5). Suppose the subject took migraine-specific medications only on Day 6 and no pain/symptoms were associated with the event. Then the event is still classified as a migraine event. Suppose another migraine event started on 9th June 2019 at 5:35pm (Day 9). Only days 2,3,4,5 and day 9 (due to the other event) will contribute to mMMD and to the number of modified information days. If any eDiary reported on those days (day 1, 2, 3, 4, 5, 9) then they will contribute to the number of modified eDiary days.

The change from baseline in mMMD at each month of the DBTP will be analysed in the same way as the primary endpoint (summary statistics, linear mixed effects repeated measures model).

If the supplementary analysis leads to a different conclusion than the primary analysis, further analysis might be considered.

Blinded review of the data identified that due to an issue in the vendor derivation a few cases of patients who were randomized althought the baseline MMD was higher than 14 days. Supplementary analysis will be performed on the subgroup of patients with baseline MMD<15

to assess the impact of those deviations on the primary analysis results for primary endpoints. If the supplementary analysis leads to a different conclusion than the primary analysis, further analysis might be considered.

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2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

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

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

2.6.2 Statistical hypothesis, model, and method of analysis

Analysis of secondary efficacy endpoints will utilize the FAS except for the analysis of change from baseline in monthly acute migraine-specific treatment days in Month 3 of the DBTP, which will be conducted based on the subgroup of patients who used acute migraine-specific medication during baseline. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

The above continuous change from baseline efficacy endpoints will be analyzed using a linear mixed effects repeated measures model with treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. If applicable, in the repeated statement, an unstructured covariance matrix will be used.

The dichotomous endpoint (Proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month of DBTP) will be analyzed based on Cochran-Mantel-Haenszel (CMH) test after patients who have missing monthly migraine day data at Month 3 of the DBTP imputed as non-responders.

The description of the models can be found in Section 5.4.

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

A hierarchical gate-keeping procedure and the Hochberg method will be used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints. The primary endpoint, the change from baseline in monthly migraine days

to the last 4 weeks of the 12-week double-blind treatment period, will be initially tested at a 2-sided significance level of 0.025 for each of the AMG 334 treatment group (140 mg and 70 mg) compared to the placebo group, respectively. If the primary endpoint and all secondary endpoints are statistically significant for an AMG 334 treatment group, the corresponding significance level will be carried over to the primary endpoint for the other AMG 334 treatment group, and the primary endpoint will be re-compared to the placebo group at a 2-sided significance level of 0.05 (full alpha). If the primary endpoint of one dose group is statistically significant but not all the secondary endpoints, only half of the initial alpha of the dose (0.0125) can be transferred to the primary endpoint of the other dose.

Figure 2-1a describes the originally planned testing sequence. But based on the observed data, the testing strategy as per figure 2-1b is thought be more appropriate and will be used for analysis.

Figure 2-1a Hierarchical Testing Procedure

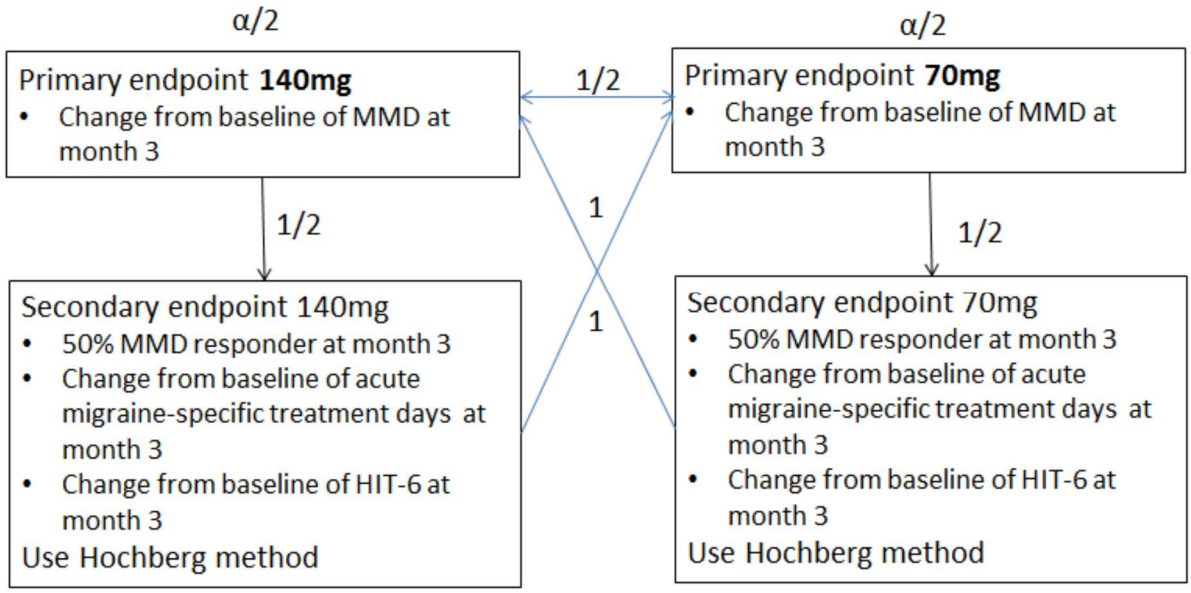
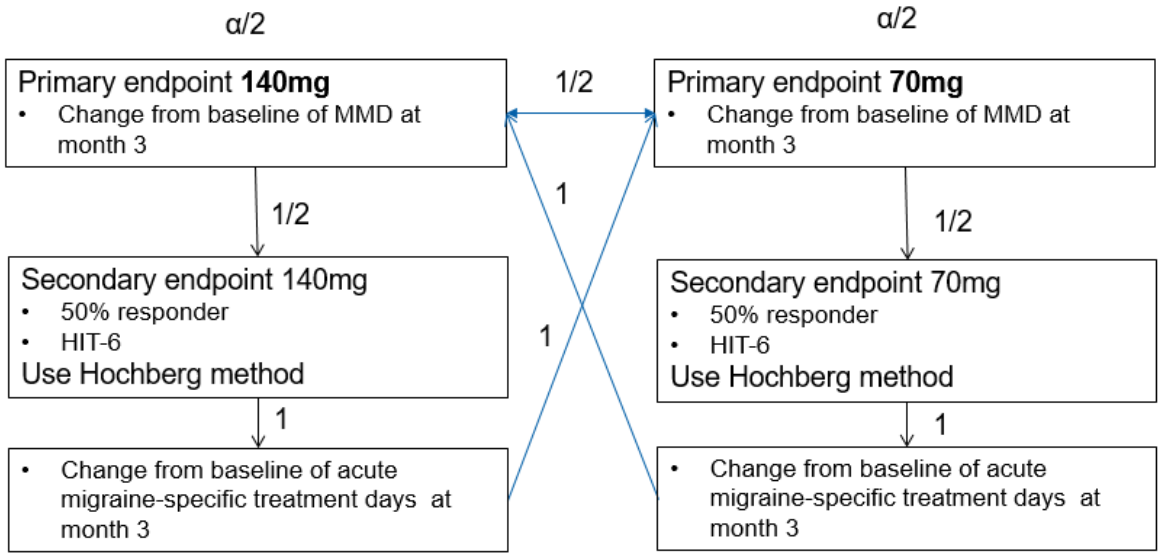


Figure 2-2b Hierarchical Testing Procedure - Updated



2.6.3 Handling of missing values/censoring/discontinuations

For the proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month of DBTP (Month 3), the missing data will be imputed as non-responder (NRI).

2.6.4 Sensitivity analyses

In order to assess the robustness of the analysis for the secondary endpoint "Proportion of patients who achieve at least a 50% reduction from baseline in monthly migraine days in the last month of DBTP (Month 3)", next analysis will be done:

- Logistic regression analysis will be used to get odds ratio of each AMG 334 group vs placebo in the 50% response rate after the missing data are imputed as non-response.

In all cases, the odds ratio of each treatment group compared to placebo group with associated 95% confidence intervals and p-values will be provided.

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

Table 2-4 Summary of secondary efficacy Endpoints and Analysis Methods during DBTP

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis

The achievement of at least a 50% reduction from baseline in monthly migraine days in the last month of the double-blind period	*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	*Analysis method III*, NRI: analyze using a logistic regression model that includes treatment and stratification factor as fixed effects and baseline monthly migraine days as covariate
Change from baseline in monthly acute migraine-specific medication treatment days in the last month of the double-blind period	*Analysis method II:* 1. Summary statistics by visit using observed data 2. Least squares mean at each time point calculated based on a linear mixed effects repeated measures model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit using observed data. In repeated statement, an unstructured covariance matrix structure will be used. 3. Test pairwise treatment difference (each AMG 334 dose group vs placebo), using a contrast from the model above.	N.A.
Change from baseline in headache impact scores as measured by the HIT-6 in the last month of the double-blind period	*Analysis method II.*	N.A.

2.6.5 Supplementary analyses

2.6.5.1 Subgroup analyses

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

- Prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure)
- Number of prior prophylactic migraine treatment failure medications: >=2,<2
- Age (< median vs ≥ median)
- BMI (< median vs ≥ median)
- Sex (Male vs Female)
- Region:
    - Asia (excluding India, Taiwan, Korea)
    - India
    - Taiwan
    - Korea
    - Others

The effect of other baseline 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 purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses are performed for primary and secondary efficacy endpoints using the same method as primary analysis method but performed within each subgroup of interest. The treatment difference (or odds ratio) with associated 95% confidence intervals and p-values will be reported within each subgroup.

Note: if the subgroup is the stratification factor (Prior prophylactic migraine medication treatment failure) then the stratification factor will not be included in the model.

The heterogeneity of the treatment effect across the subgroups will be evaluated for the primary and secondary endpoints by examining the treatment by subgroup interaction at primary time point (Week 12) and a p-value will be presented. For continuous endpoints, the primary analysis model with the addition of subgroup and treatment group by subgroup interaction as two additional effects will be used. For endpoint based on proportions, a logistic regression model that includes treatment group, stratification factor, baseline value, subgroup and treatment group by subgroup interaction will be used.

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 only summary statistics will be performed.

The least square means for each treatment group, SE's, difference of LSMs compared to placebo group, and associated 95% CIs for each subgroup and the nominal p-value for subgroup by treatment interaction will be calculated.

The outcome will be displayed in separate forest plot for each endpoint (one symbol for placebo vs AMG334 70mg, one symbol for placebo vs AMG334 140mg, in a combined plot), presenting the following information:

- The number of patients within each subgroup level / treatment arm
- Supporting information such as least squares mean by treatment and subgroup level
- The treatment effect estimate and two-sided 95% confidence interval within each subgroup level (using the BY statement for the primary analysis model).
- The directions which favor placebo or AMG 334 will be indicated.
- For pre-specified subgroup analyses, the p-value for the treatment*subgroup term.

2.7 Safety analyses

For safety endpoints, all randomized subjects who received at least one dose of investigational product (i.e., utilizing the SAF) will be analyzed based on the actual treatment received (defined as the randomized treatment unless a subject has received the incorrect dose the entire DBTP).

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

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

Missing data will not be imputed for safety endpoints.

2.7.1 Adverse events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 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 or higher. All adverse event tables will be summarized by treatment group.

For all AEs tables presented by SOC and PT (and grade), the SOCs will be presented in alphabetical order and PTs will be ordered within the SOC by decreasing order of frequency in the AMG 334 140 mg treatment group.

AE tables by preferred term only will be sorted in descending order of frequency in the AMG 334 140 mg treatment group.

Note, for exposure-adjusted AEs the sorting will be based on the exposure-adjusted subject incidence rate.

Overall subject incidence of AEs and exposure-adjusted subject incidence will be summarized for all treatment-emergent AEs (TEAEs), serious AEs, AEs leading to discontinuation of study treatment and deaths for the DBTP. Summary will be repeated for the safety follow-up period and for the entire study period using subject incidence.

Subject incidence and exposure-adjusted subject incidence of all treatment-emergent AEs, serious AEs, AEs leading to discontinuation of study treatment, serious AEs leading to discontinuation of study treatment and deaths will be tabulated by system organ class and preferred term for DBTP. Summaries will be repeated for the safety follow-up period using subject incidence.

In addition, subject incidence and exposure-adjusted subject incidence of all treatment-emergent AEs will be tabulated by SOC, PT and CTCAE grade for the DBTP. Summaries will be repeated for the safety follow-up period using subject incidence.

Subject incidence and exposure-adjusted subject incidence of all TEAEs and serious AEs will be tabulated by PT for the DBTP. Summaries will be repeated for the safety follow-up period using subject incidence.

Subject incidence all treatment-related AEs and serious treatment-related AEs will be tabulated by SOC and PT for the DBTP.

All AEs, deaths (see Section 2.7.2 for details), SAEs and AEs leading to permanent study drug discontinuation will be listed separately.

2.7.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.7.2 Deaths

Deaths will be listed by treatment including the start date of the study treatment, the last date on study treatment, the death date and the primary cause (and contributing cause if any) for death.

2.7.3 Laboratory data

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

Subject incidence of newly occurring liver enzyme abnormalities (including AST, ALT, Total Bilirubin (TBL) and Alkaline Phosphatase (ALP)) will also be summarized by treatment group and study phase (separately for the DBTP and follow-up period.).

Shift from baseline for some liver enzyme level categories (specified in the TFL shells; for e.g. ALP<=1 x ULN) will also be provided by treatment group and study phase (separately for the DBTP and follow-up period).

Clinically notable laboratory values will be flagged and listed by treatment.

Parameters measured in the urine at screening including urine drug tests (if applicable) will be listed.

2.7.4 Other safety data

Serum pregnancy test results (if applicable) will be listed for female patients.

2.7.4.1 ECG data

The ECG measurements from this clinical study will be 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 (see Table 5-5) will be summarized by treatment group and by visit, for the DBTP.

ECG measurements will be listed by treatment.

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.

2.7.4.2 Vital signs and weight

The analyses of vital signs (systolic/diastolic blood pressure, pulse rate) and weight will include summary statistics of change from baseline by treatment group and by visit, for DBTP and for safety follow-up period.

The number and percentage of patients with clinically relevant abnormality (see Table 5-3) at any post-baseline visit will be presented, separately for DBTP and for safety follow-up period.

Patient listings (including systolic/diastolic blood pressure, pulse rate and temperature measurements) will be provided and values outside these critical value ranges will be flagged.

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

The number and percentage of subjects reporting any suicidal ideation or any suicidal behavior will be summarized descriptively by treatment group and by visit, for DBTP and for safety follow-up period, respectively.

Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group for DBTP and for safety follow-up period, respectively.

No statistical testing will be performed on C-SSRS.

2.7.4.4 Anti – AMG 334 Antibody Formation - Immunogenicity (IG) analysis set

The number and percentage of subjects who are positive for anti-AMG 334 antibodies at baseline (Day 1, pre-dose) and who develop anti-AMG 334 antibodies (binding and, if positive, neutralizing) at any time during the study (after signing informed consent and up to the end of the DBTP) will be tabulated by treatment group.

In addition, the number and percentage of patients who develop anti-AMG 334 antibodies at any time post-dose during the DBTP (Visit 130, 150 and 1999) will be tabulated by treatment group.

The list of subjects with positive at any time will be provided.

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.

2.7.4.4.1 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 sample: Determinant sample where ADA confirmatory assay is positive.
- ADA-positive NAb sample: Determinant sample where NAb ADA 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 signal greater than the ADA-positive baseline signal.

2.7.4.4.2 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 time point (including baseline), will be provided using the Immunogenicity prevalence set. For summaries by time point, the denominator is the number of patients at that time point 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 time point (including positive samples) and patient ADA status

2.10 Patient-reported outcomes

The eDiary will collect the following patient-reported outcomes:

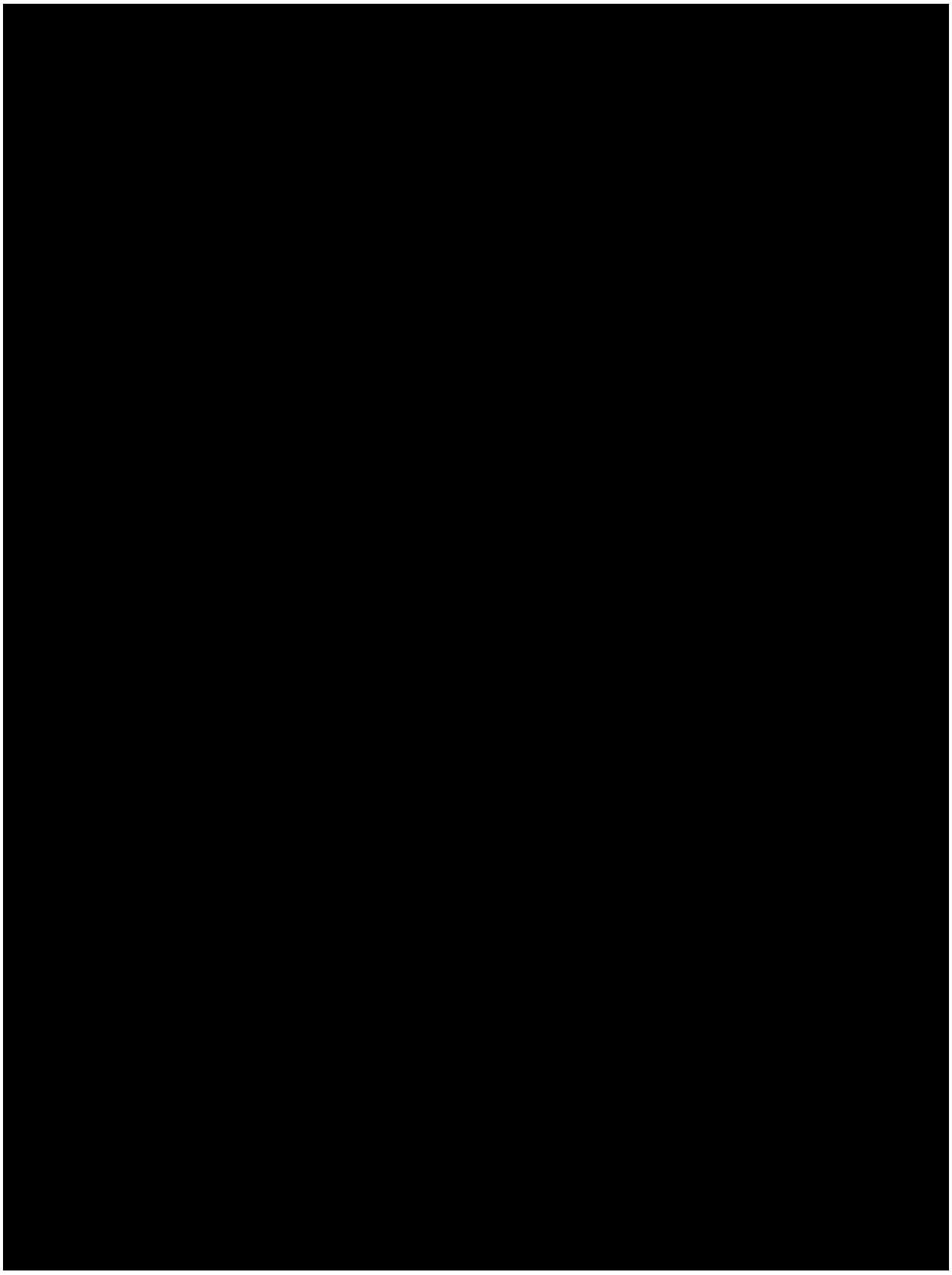
- HIT-6, monthly
- [redacted]
- [redacted]
- Beck Depression Inventory, screening
- [redacted]

Change from baseline in headache impact scores as measured by the HIT-6 in Month 3 of the DBTP is among the secondary endpoints (see Section 2.6).

[redacted]

Beck Depression Inventory is collected only at screening and reported in baseline disease characteristics (see Section 2.3.2).

[redacted]



2.13 Interim analysis

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

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

3 Sample size calculation

A treatment difference of -1.79 days for change from baseline in monthly migraine days in Month 3 between AMG 334 140mg and placebo was observed in study 20120296 (STRIVE).

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

Assuming a treatment effect similar to the effect observed in previous studies with AMG 334 in episodic migraine, the treatment difference in terms of change from baseline on monthly migraine days during week 9-12 (primary variable) for erenumab 140mg vs. placebo and 70mg vs. placebo is assumed at -1.5 days and -1.1 days, respectively. The common standard deviation of the primary variable is assumed at 4. Given a 2:3:3 randomization ratio among erenumab 140mg, 70mg, and placebo, a total of 880 subjects (including 10% drop out rate) would enable

both doses to achieve higher than 90% power under overall 0.05 full alpha level to detect the designed treatment difference. In addition, the sample size will also ensure the trial to have adequate power to detect treatment difference under initial 2-sided 0.025 alpha level assigned to each dose (equally split between the erenumab two doses).

4 Change to protocol specified analyses

The following analyses will be performed and are not planned in the protocol

- To explore if the treatment effect varies across subgroups of interest, subgroup analysis will be performed for the primary and secondary efficacy endpoints for the following subgroups: age, gender, BMI, prior prophylactic migraine medication treatment failure (stratification factor), number of prior prophylactic migraine treatment failure medications (>=2,<2) and region.
- Given monthly migraine days is the key endpoint for the study, additional sensitivity analysis using logistic regression model will be performed for the 50% responder analysis as well.
- To evaluate the effect of AMG 334 compared to placebo on the change from baseline in HIT-6 total score during the entire DBTP (and not only at Month 3): change from baseline will be analyzed using Method II (see Table 2-4) and categorized HIT-6 score will be summarized by shift tables from baseline to the last month of the double-blind period.
- To assess the impact of long-lasting migraine events on the primary analysis, supplementary analysis has been added for the change from baseline in MMD.
- To assess the impact of patients with baseline MMD>=15 on the primary analysis results for the primary and secondary endpoints, supplementary analysis on patients with baseline MMD<15 has been added.
- Due to the eDiary device set-up, it is not possible to link a medication to an aura without headache (as no id available that link between medication taken and aura or headache event and no start/end date was collected for aura without headache event). Therefore, it is not possible to know if patient took a migraine-specific medication to treat an aura without headache and to count those days as migraine days (and thus headache days).
- During the blinded review of the baseline data, it was spotted that approx 60% of the patients didn't use any migraine-specific medication during the baseline period. Therefore, the secondary objective "To evaluate the effect of AMG 334 compared to placebo on the change from baseline in monthly acute migraine-specific medication treatment days" was exchanged [redacted] and the testing strategy (Figure 9-1 in protocol) was replaced by a testing strategy where the endpoint MMSMD (monthly migraine-specific medication days) is tested after 50% responder and HIT-6.

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 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
	Day/Month	01Jan	Default to Study Day 1 if an event started the same year as Study Day 1
	Day/Month/Year	No imputation	

For concomitant medication, incomplete end date will be imputed as follow:

Missing	Imputed date
Day	The earliest of (last day of the month, date of death).
Day/Month	The earliest of the (31DECYYYY, date of death).

Day/Month/Year	No imputation

If the imputed end date is less than the existing start date, use the start date as the imputed end date.

5.1.3 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 imputed birth date please use: date of informed consent-age-1.

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.

5.1.4 Post therapies date imputation

5.1.5 For alternative migraine therapies taken during the treatment period, the start date and end date will be imputed in the same way as concomittant medication (section 5.1.2). Other imputations

5.1.5.1 eDiary data

The eDiary includes the following clinical outcome assessments:

- Incidence of headache (i.e., migraine with or without aura or non-migraine headache)
- Time of onset of headache
- Time of resolution of headache
- Pain severity per headache
- Symptoms (e.g., 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 [redacted] HIT-6.

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, migraine attacks, 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]

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 5.1.5.3.

Briefly, handling missing and incomplete eDiary data is summarized by next rules:

Monthly Endpoint	**Condition**	**Proration Method (does not need to be rounded)**
Monthly frequency measurements (including migraine days, headache days, migraine attacks, 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]

[redacted]

Missing PROs (HIT-6 [redacted]) scheduled to be collected at office visit at certain assessment will not be imputed.

5.1.5.2 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 5.1.5.1 since only subject with ≥ 80% compliance of eDiary use during baseline will be eligible for randomization.

5.1.5.3 Missing Post-baseline Evaluation in Double-Blind Treatment Period

Primary analysis of continuous efficacy endpoints during the 12-week randomized DBTP will be conducted using the linear mixed effects repeated measures model on observed data without imputation (see Section 5.4.1).

In the sensitivity analysis on primary and secondary efficacy endpoints during the 12-week DBTP, 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. See below for more details.

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 [redacted] efficacy endpoints (responder [Yes/No] based on ≥50%, ≥75% and 100% reduction from baseline in monthly migraine days, [redacted], achievement of at least a 5-point reduction from baseline in HIT-6 total score) during double-blind treatment phase will be imputed as non-responder at each corresponding time point.

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 the proportion of missing data in primary endpoint is high (e.g., > 20% for primary analysis at week 12) or if imbalance occurs amongst the treatment groups, 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 (e.g., due to measurement or sample processing error)

Additional sensitivity analyses, including those based on alternative missing data assumptions, will be performed as deemed appropriate and necessary.

5.1.5.3.1 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.

5.1.5.3.2 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 (trt01pn), stratification factor (prior migraine prophylactic treatment failed, a dichotomous variable), sex, race group, age group, BMI group, disease duration at baseline from ADBS or ADSL.
- Obtain avisitn paramcd param aval avalc base chg dtype from ADATTACK
- Perform minor data manipulation, as required, to reinstate the missing data, eg if dtype="LOCF" then aval=., avalc=" " and chg=..
- Ensure the baseline values are included in the chg variables before data transformation, e.g. if avisitn=2000 then chg=base.
- Transpose all the data so you have one observation per subject and each visit becomes a variable within its own right, e.g. rows where avisitn=2004, 2008, 2012 become the column wk4, wk8, wk12.
- Impute the missing data for MAR and MNAR separately according to the methods in next steps

MAR multiple imputations steps:

Note that some variables (for ex., duration of migraine) might have 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; discrim is used for categorical variables with more than 2 categories; regpmm is used for continuous variables.
- wk0, wk4, wk8 and wk12 represent the chg variable for each of the visits respectively, where 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= (trt01p='Placebo')) 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 change from baseline in MMD analysis, it uses a linear mixed effects repeated measures 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.

5.2 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 5 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.

Grade 5 – Death related to AE.

5.3 Laboratory parameters derivations

CTCAE grading for the laboratory toxicity will be derived 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

5.4 Statistical models

5.4.1 Primary analysis

The primary endpoints of the study will be first tested for each of AMG 334 70 mg and 140 mg compared to placebo, respectively.

- Null Hypothesis: In subject with episodic migraine, the AMG 334 treatment group is the same as placebo, in terms of the reduction from baseline in mean monthly migraine days in the last month (month 3) of the DBTP
- Alternative Hypothesis : In subject with episodic migraine, the AMG 334 treatment group is different from placebo, in terms of the reduction from baseline in mean monthly migraine days in the last month (month 3) of the DBTP

It will be analyzed using a linear mixed effects repeated measures model with treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit. In repeated statement, an unstructured covariance matrix will be used.

5.4.2 Secondary analysis

5.4.2.1 Method I

The first secondary 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 Period, for each of AMG 334 70 mg and 140 mg compared to placebo, respectively.

- Null Hypothesis: In subject with episodic migraine, the AMG 334 treatment group is inferior or the same as placebo, in terms of 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 Period
- Alternative Hypothesis : In subject with episodic migraine, the AMG 334 treatment group is superior to placebo, in terms of 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 Period

More precisely, 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.

Test statistic:

After the missing data are imputed as non-response, a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata will be used under a significance level of alpha/2, one-sided (alpha, two-sided; See further details in protocol Section 9.5 and Section 2.6.2 of this document for the value of alpha) to evaluate the association between the 50% responder rate and the treatment. The estimated common odds ratio, confidence intervals and p-values will be reported.

Sensitivity analysis:

- 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.

The odds ratio of treatment group compared to placebo group with associated 95% confidence intervals and 2-sided p-values will be provided.

5.4.2.2 Method II

The secondary continuous endpoints of the study will be first tested for each of AMG 334 70 mg and 140 mg compared to placebo, respectively.

- Null Hypothesis: In subject with episodic migraine, the AMG 334 treatment group is same as placebo, in terms of the reduction from baseline in the continuous endpoint of interest in the last month (month 3) of the DBTP
- Alternative Hypothesis : In subject with episodic migraine, the AMG 334 treatment group is different from placebo, in terms of the reduction from baseline in the continuous endpoint of interest days in the last month (month 3) of the DBTP

It will be analyzed using a linear mixed effects repeated measure model with treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit. In repeated statement an unstructured covariance matrix will be used.

5.4.3 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.

5.5 Rule of exclusion criteria of analysis sets

The protocol deviations resulting in participants' exclusion from analysis sets are defined below (Table 5-2). A complete list of the PDs can be found in the Edit Check Specifications document in CREDI.

Table 5-1 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 5-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAS	NA	Not randomized
FAS	NA	Not randomized
		Not in the randomized set;
		No double-blind study drug taken;
		No change from baseline measurement in monthly migraine day during the DBTP
SAF	NA	No double-blind study drug taken

5.6 Appendix A: Vital signs notable criteria

Table 5-3 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 5-4 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

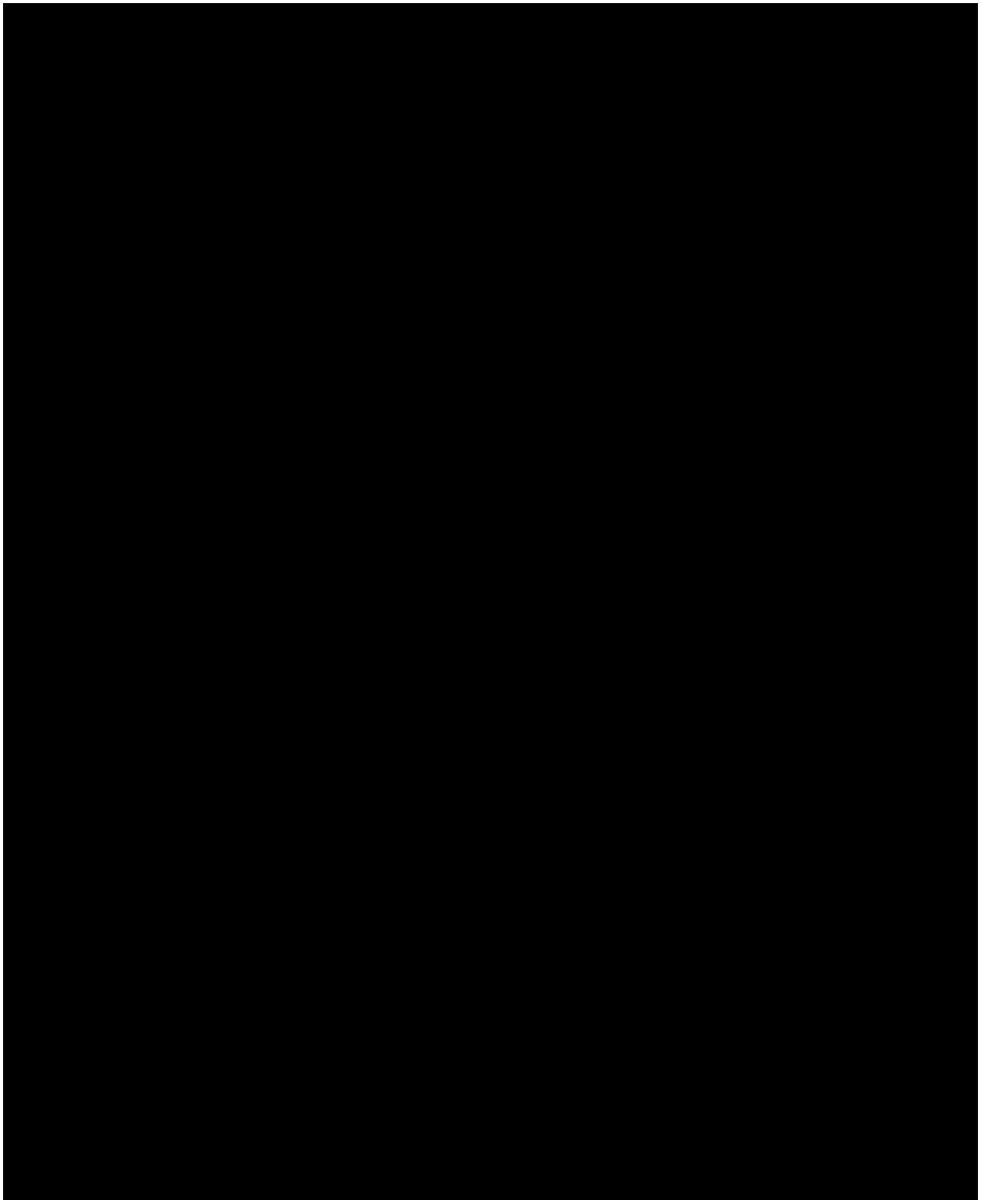
Note: Only selected lab parameters which have potential to be sensitive to AMG 334 exposure are listed.

5.8 Appendix C: Criteria for ECG abnormalities

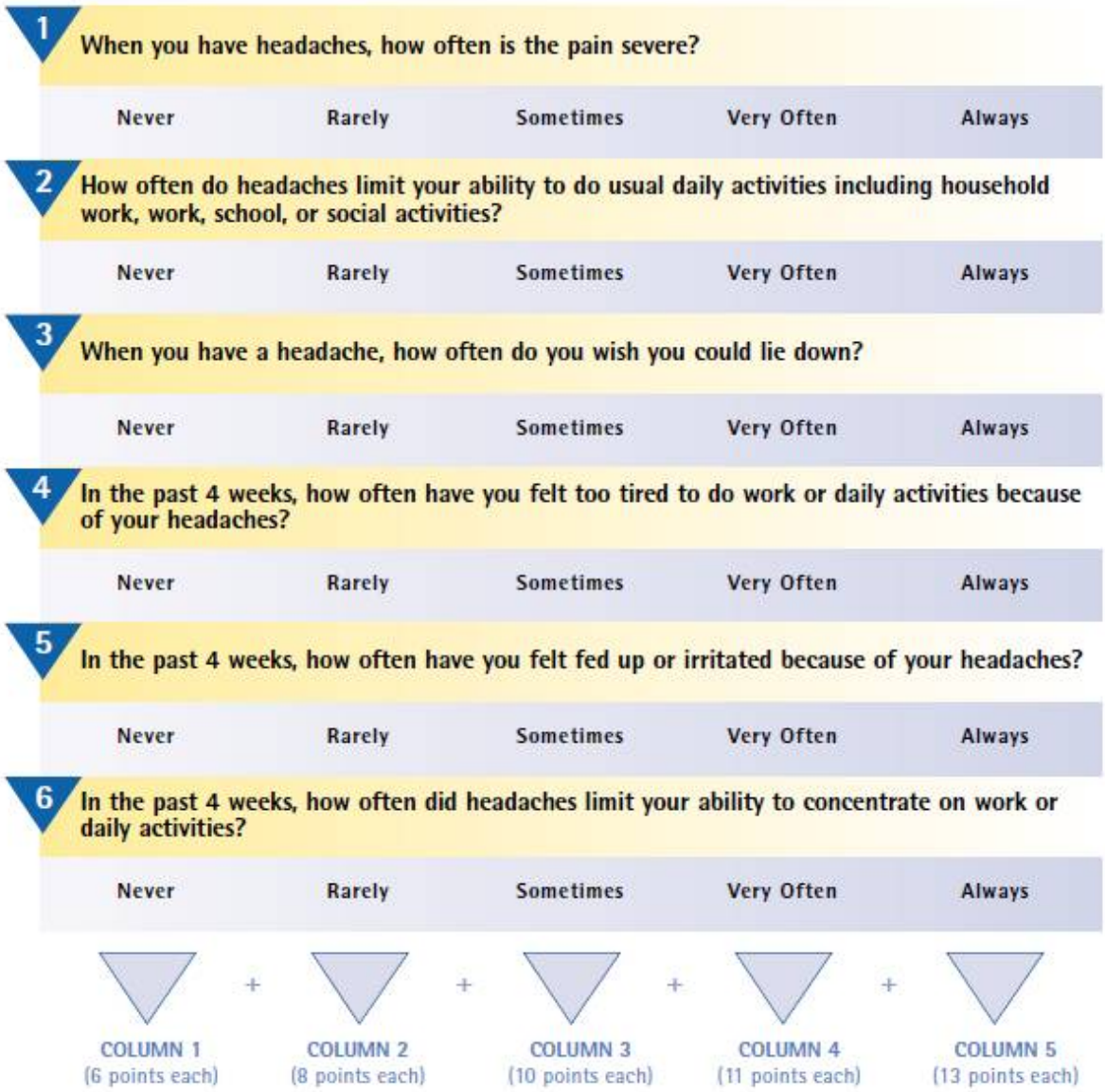
Table 5-5 ECG Abnormality Ranges

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: Patient-reported Outcome Forms/Instruments

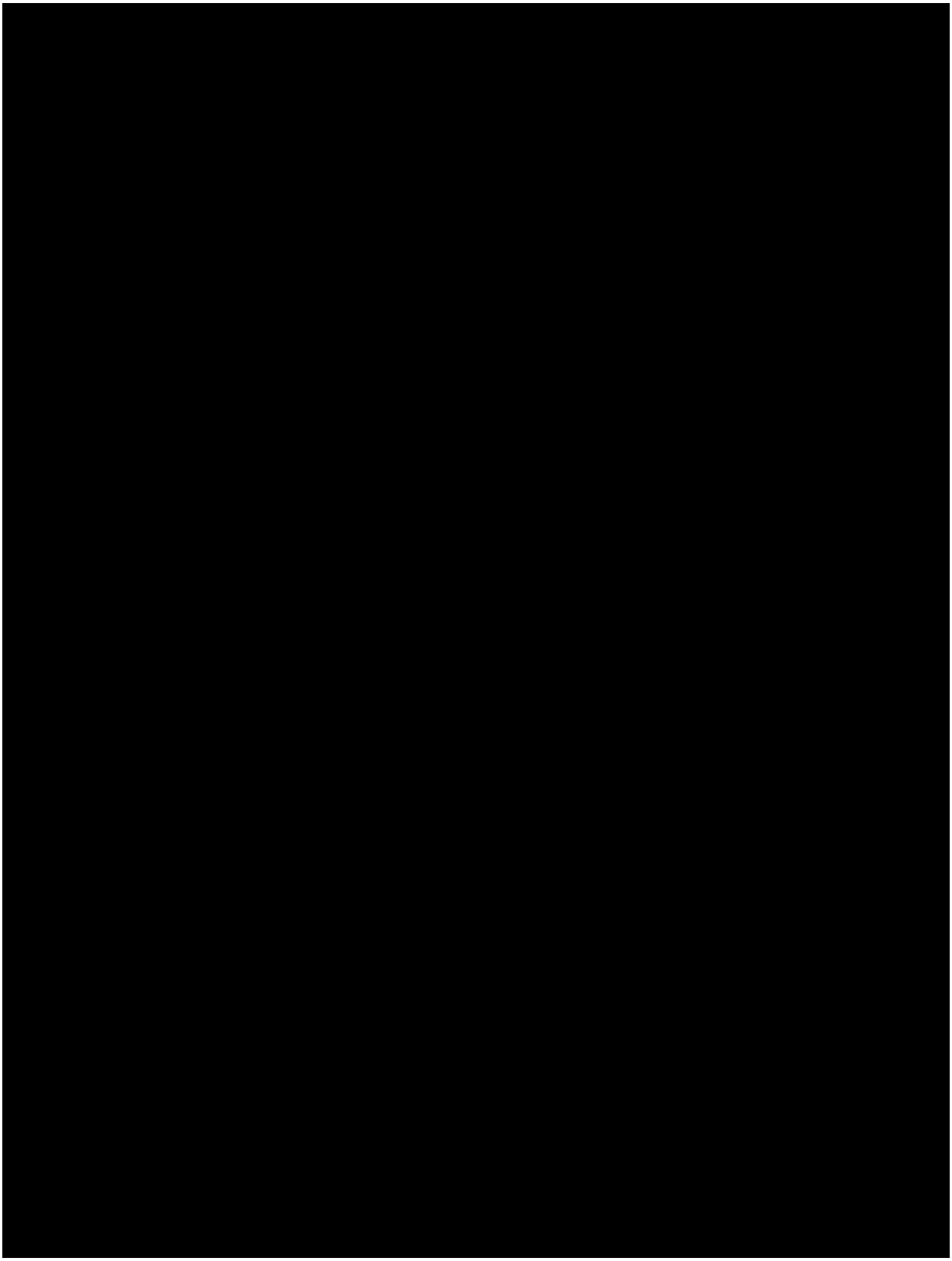


5.9.2 Headache Impact Test (HIT-6) scoring



Scoring:
Scoring of HIT-6 total score is computed by QualityMetrics software with total score ranging from 36 to 78. HIT-6 scores are categorized into 4 grades, representing little or no impact (49 or less), some impact (50-55), substantial impact (56-59), and severe impact (60-78) due to headache.

[redacted]



5.9.4 Beck Depression Inventory -II (BDI-II) scoring

Beck Depression Inventory – II (BDI-II)

This instrument consists of 21 items, each with 4 or 6 statements regarding symptoms of depression. One statement is selected for each item. Each statement has an associated value. Two of the items' values are recoded for scoring, while the others retain their original value.

Group	Original value	Rescored value
1 – 15, 17, 19 - 21	0 1 2 3	0 1 2 3
16, 18	0 1 2 3 4 5 6	0 1 1 2 2 3 3

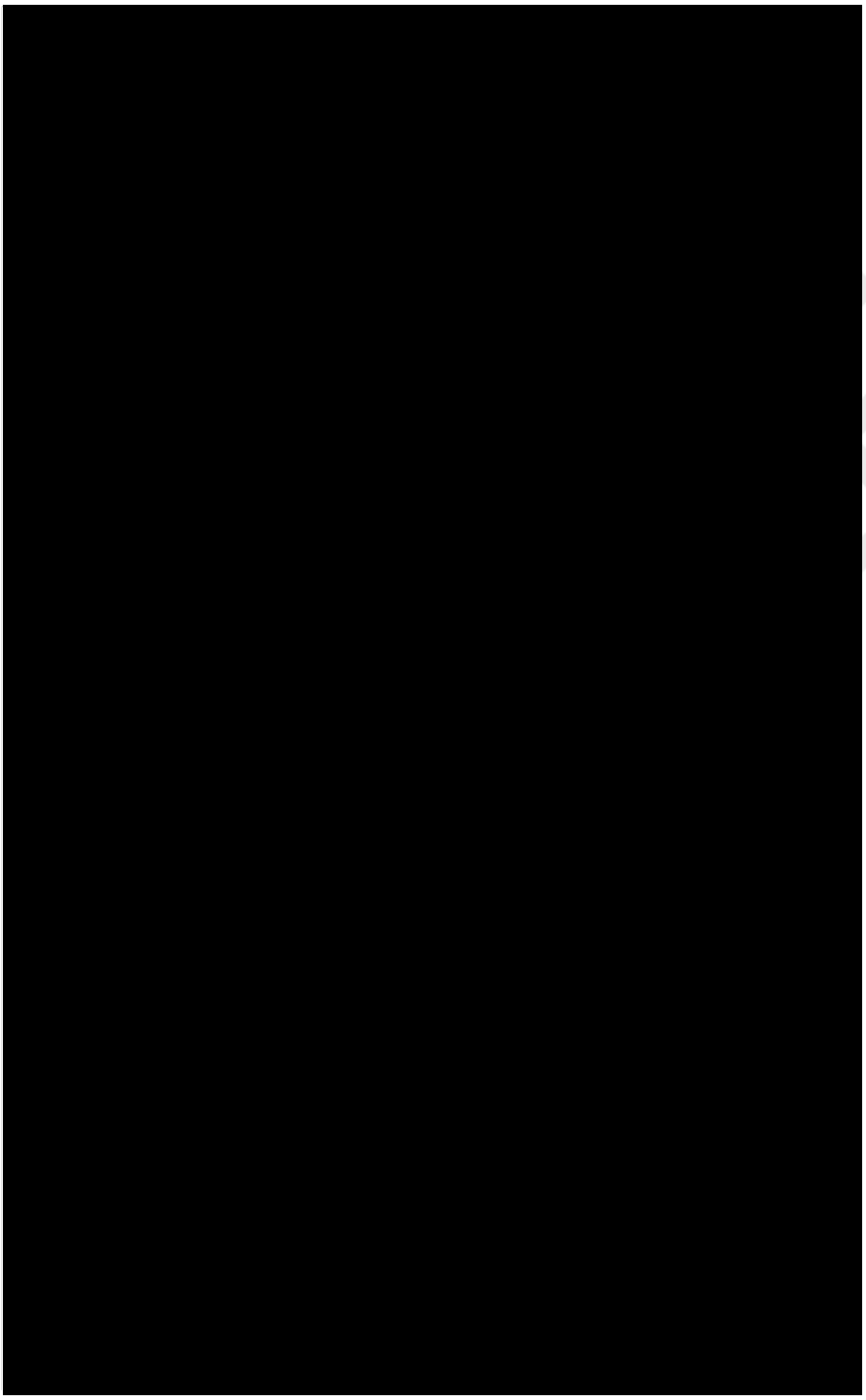
Score
A single score is calculated by adding up the (rescored) values of the 21 items. The range of values is 0 – 63.

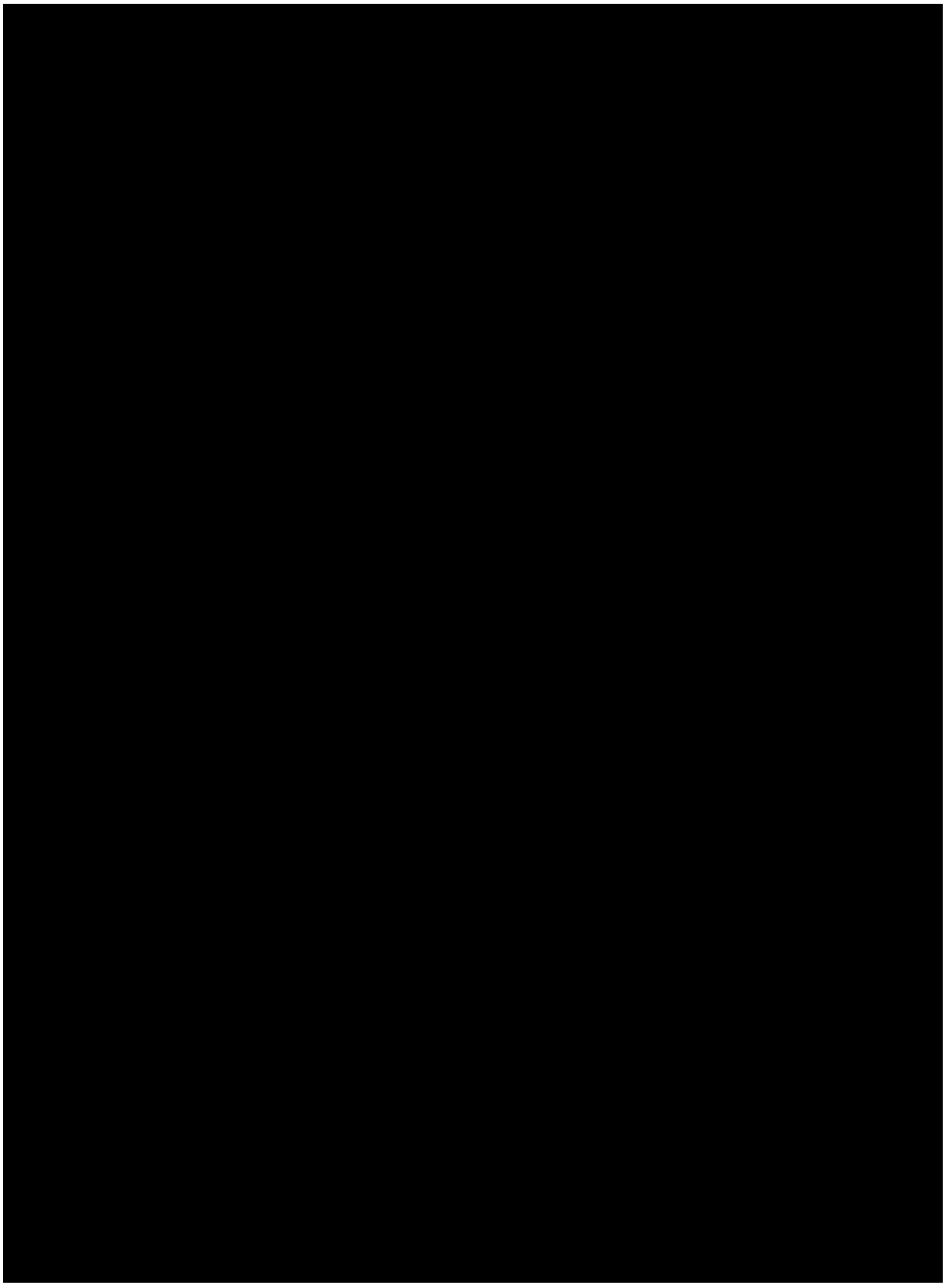
Missing values:
if more than 2 items have missing values, the total BDI score will be missing. If one or two items are missing, their score can be imputed with the mean of the non-missing scores before summing.

Interpretation:
0 – 13: minimal depression
14 – 19: mild depression
20 – 28: moderate depression
29 – 63: severe depression

Missing data:

If more than 2 items have missing values, the total BDI score will be missing. If one or two items are missing, their score can be imputed with the mean of the non-missing scores before summing.





[redacted]

5.10 Appendix E: Geographic regions

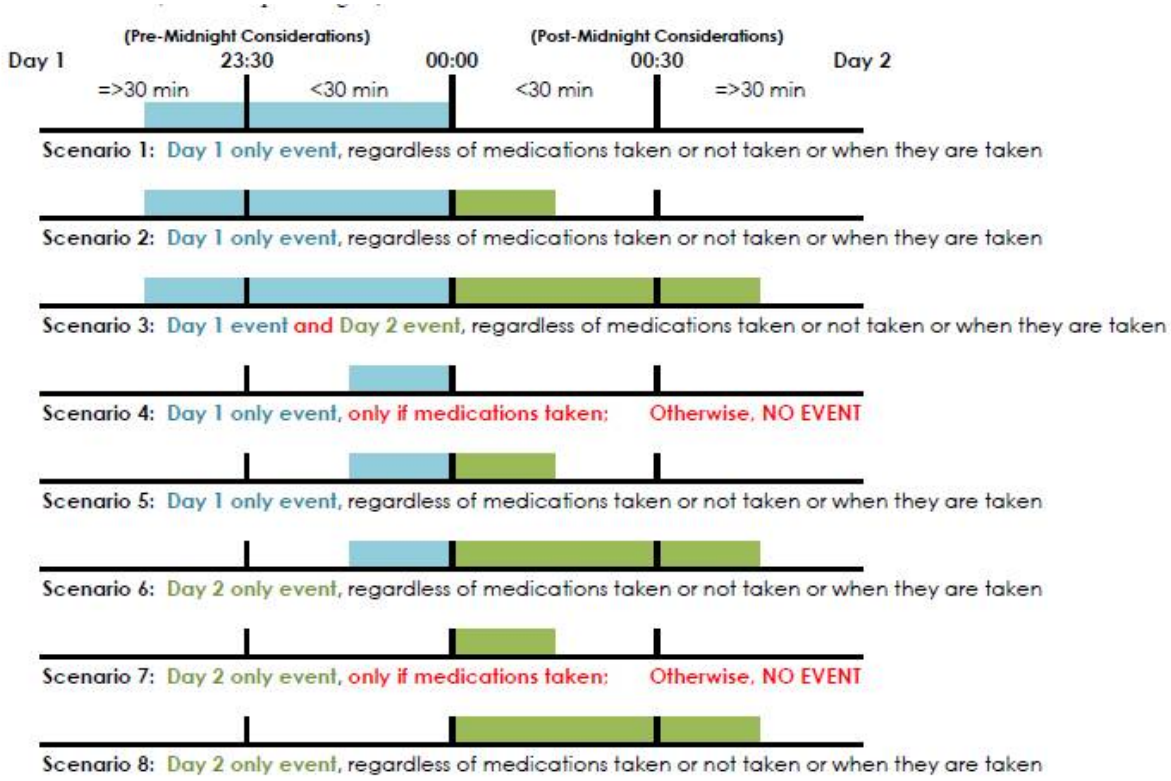
Table 5-6 Geographic regions

Geographic region	Country
India	India
Taiwan	Taiwan
Korea	Rep of Korea
Asia (excluding India, Taiwan, Korea)	Malaysia
	Singapore
	Thailand
	Vietnam
	Philippines
Other	Lebanon
	Argentina
	Mexico

5.11 Appendix F: MMD derivation, exceptions

5.11.1 Assigning Headache and Migraine Days to Events Spanning Midnight

The diagram below shows all of the possible scenarios for time-based determination of assignment of events to days when the events span midnight

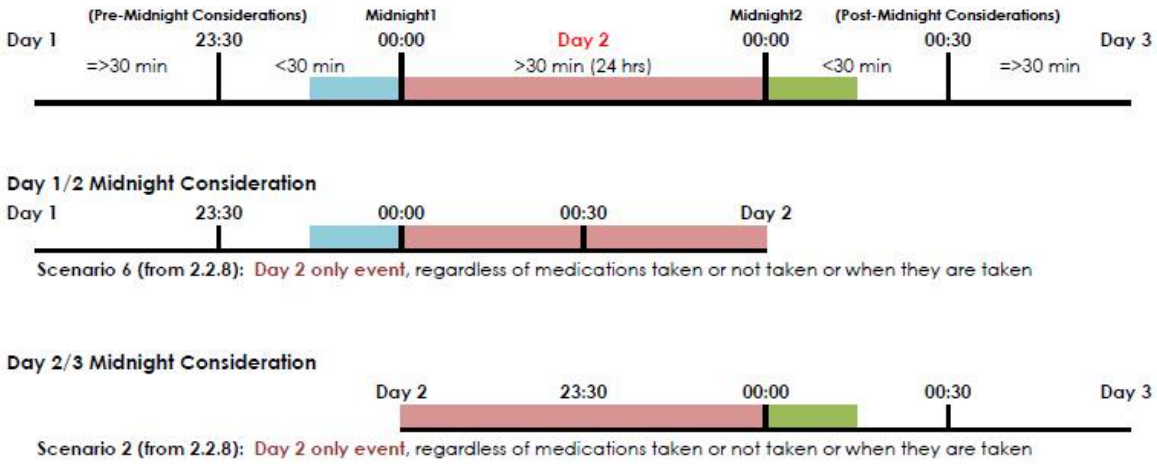


5.11.2 Spanning Midnight Rules for Multi-Day Events Longer Than Two Days

When an event spans two or more full days, with "tail" conditions (event lasts for less than 30 minutes or less on one side of midnight or the other), the "tail" conditions must be checked separately at each end of the event (beginning and end) to determine which days are included in the event expanse. The example below shows an event spanning 3 days. For events spanning more than 3 days, where there are n total days of the event, the endpoints would be Day 1 (Day 1 in the example below), Day n (Day 3 in the example below), and Days 2 to n-1 (Day 2 in the example below).

Example

A headache event starts 28 minutes before midnight (Day 1), extends across a full day (Day 2), and ends 25 minutes after the next midnight (Day 3)



In this example, because the midnight scenario between Day 1 and Day 2 (Scenario 6) determines that Day 1 will NOT be counted as a headache/migraine day, and the midnight scenario between Day 2 and Day 3 (Scenario 2) determines that Day 3 will NOT be counted as a headache/migraine day, the event that started on Day 1 and ended on Day 3 will only count as a headache/migraine day on Day 2.

6 Reference

[redacted]
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