NOVARTIS

Clinical Development

AMG 334 (erenumab)

CAMG334A2304 / NCT03867201

A 12-week phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of once monthly subcutaneous erenumab 70 mg in adult chronic migraine subjects

Statistical Analysis Plan (SAP)

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18-Feb-2021	SAP Amendment 1	The COVID-19 related analysis, [redacted] and Chinese subgroup related analyses were added.	2.2 Analysis sets 2.2.1 Subgroup of interest 2.3.1 Subject disposition 2.3.2 Demographic variables and other baseline characteristics [redacted]
20-Aug-2021	SAP Amendment 2	Update start/end time point for study phases; Add shift table for hypertension and elevated blood pressure	2.1 Data analysis general information 2.7.4.2 Vital signs and weight

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List of abbreviations

AE	Adverse Event
ADA	Anti-Drug Antibody
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
COVID-19	COronaVIrus Disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DB	Double-Blind Treatment
DBL	Database Lock
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EoS	End of Study
EQ-5D-5L	EuroQol, 5 dimensions, 5 levels scale
FAS	Full Analysis Set
GLMM	Generalized Linear Mixed Model
[redacted]	[redacted]
IRT	Interactive Response Technology
IP	Investigational Product
IPW	Inverse Probability Weighting
LOCF	Last Observation Carried Forward
LPLV	Last Subject Last Visit
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Multiple Imputation
MIN	Minimum function
mMIDAS	Modified Migraine Disability Assessment
MNAR	Missing Not at Random
[redacted]	[redacted]
NRI	Non-Responder Imputation
OLE	Open-label extension
PD	Protocol Deviations

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Subject-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
VS	Vital Signs
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 12 of the study protocol **(v02)** for AMG 334 Study CAMG334A2304 dated 26 **Jan 2021** 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, 2-treatment arm, randomized (1:1 [70 mg: placebo]), double-blind study design in adult subjects with chronic migraine (see Figure 1-1).

The following periods are included in the study design:

- Screening period of 2 weeks: to assess initial eligibility,
- Baseline period of 4 weeks: All subjects 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 (DB) period of 12 weeks: All subjects successfully completing the Baseline period are invited to participate. Eligible subjects will be randomized to one of two treatment arms. At the end of this period, the final assessment to address the efficacy-related objectives will occur.
- Post double-blind treatment follow-up of 12 weeks: for subjects discontinuing treatment during the double-blind treatment period and willing to return for the subsequent scheduled follow-up (FUP) visits, until the Week 12 follow-up visit.
- Safety follow-up period of 8 weeks: a Safety Follow-Up visit, will occur 8 weeks after the 12 weeks' DB, at Week 20 for subjects who complete the double-blind treatment period (including complete post treatment follow-up visits) but not enter into the open-label treatment period. For subjects who discontinue double-blinded period (NOT willing to return for scheduled visits until week 12), they will be suggest to complete safety follow-up visit 12 weeks after the last dose.
- Open-label treatment extension (OLE) period (until launch of erenumab in the country or until June 2021 in Korea): all subjects completing the double-blind treatment period on study drug are invited to participate. Eligible subjects who consent to participate in this open-label treatment period will receive erenumab until it is launched in the country or until June 2021 in Korea, in order to ensure continued drug access.

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

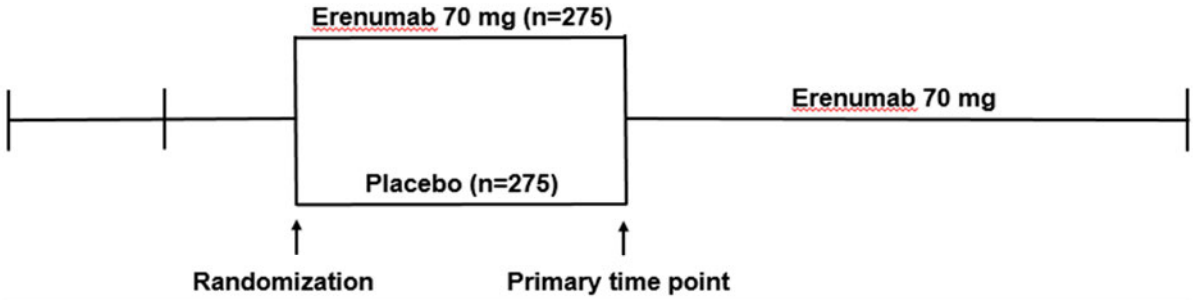
Approximatively 550 subjects will be randomized (275 in placebo, 275 in AMG334 70mg), stratified by prior prophylactic migraine medication treatment failure (prior prophylactic

migraine treatment failure due to efficacy or tolerability vs. no prior prophylactic migraine treatment failure) and medication overuse (yes vs. no).

Two interim analyses (IA) are planned for this study.

- A blinded IA, after approximately 50% (275) of subjects have completed the double-blind treatment period (including early withdrawals), will be conducted to re-estimate the sample size.
- An unblinded IA will be conducted at the time of 70% (385, based on the currently planned sample size 550 if no need for sample size increase after the blinded IA) of subjects have completed the double-blind treatment period (including early withdrawals), to determine whether the study will stop early or continue to the final primary analysis (full sample size).

Figure 1-1 Study Design Schematic



Screening	Baseline	Double-Blind Treatment	Open-Label Treatment (if applicable)
2 weeks	4 weeks	12 weeks	Until launch of erenumab in the country or until June 2021 in Korea

Note: For subjects not entering the Open-Label Treatment period, Safety Follow-Up visit will occur 8 weeks after last visit of the Double-Blind Treatment period

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 erenumab compared to placebo on the change from baseline in monthly migraine days, in subjects with chronic migraine	• Change from baseline in monthly migraine days during the last 4 weeks of the 12-week treatment period
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of erenumab compared to placebo on change from baseline in migraine-related disability and productivity as measured by the modified Migraine Disability Assessment (mMIDAS)	• Change from baseline in migraine-related disability and productivity as measured by the mMIDAS during the last 4 weeks of the 12-week treatment period

Objective(s)	Endpoint(s)
• To evaluate the effect of erenumab 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 during the last 4 weeks of the 12-week treatment period
• To evaluate the effect of erenumab compared to placebo on the change from baseline in monthly acute headache medication days	• Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period
• To evaluate the safety and tolerability of erenumab	• Adverse events, clinical laboratory values, vital signs, and anti-AMG 334 antibodies

[redacted]

2 Statistical methods

2.1 Data analysis general information

Data from the study will be analyzed based on the study phase as defined in Table 2-1. The full scope of data analysis defined in this document is pertinent to both DB period (including safety follow-up), and OLE period. The sub-scope of data analysis for the unblinded interim readout is defined in section 2.12.

Table 2-1 Study Phases for data analysis

Study Phase	Start Time Point	End Time Point
DB Period (including Safety follow-up)	Study Day 1 (after the 1st DB IP Dose)	For subject who won't join in OLE: end of study date; For subject who join in OLE: the End of Treatment visit in DB period (the last visit scheduled in DB Period)
OLE Period (applicable for subjects continuing OLE treatment)	The End of Treatment Visit in DB Period + 1	For subject who join in OLE: end of study date

*In general, if the End of Treatment visit date of DB period and the 1st OLE IP injection are on the same day, then the AE or CM which occurs on that day will be considered to belong to DB

period. [redacted]

In the case of a positive unblinded IA read-out (success), an interim CSR based on the 70% subjects (DB period completers or early withdrawers up to the unblinded IA cutoff) who are included in the unblinded IA analysis will be generated. The primary analysis will be performed for DB period. Ongoing DB period subjects at the time of unblinded IA cutoff will not be included in this interim CSR. Their data will be reported in an addendum for the interim CSR, when all subjects completed their last visit in DB period. In this interim CSR addendum, those ongoing subjects together with the 70% subjects who have been included in the interim CSR, will be analyzed again and data will be mainly presented by summary statistics. The interim CSR and its addendum will be prepared for regulatory submission.

In case the trial needs to continue enrollment to full sample size as all enrolled subjects have completed DB period, the primary database lock will then be performed. One interim CSR based on all data from DB period and safety follow up collected up to the cutoff timepoint for the primary lock will be prepared for regulatory submission.

At the end of OLE period, a final CSR for data from OLE will be prepared supplementally.

Unless otherwise stated, summary tables/listings/figures will be presented for each treatment arm in the respective analysis set. In general data of interest will be listed by treatment arm and by country name/center number/subject id (/visit wherever applicable). For OLE period, data will be displayed by the treatment arm as in DB period as well as overall.

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.

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 (yes vs. no) and medication overuse (yes vs. no). Stratification factors used as covariates 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 9.4 or higher.

The full scope of analysis described below will be performed by Novartis. The unblinded IA read-out will be performed by the independent statistical analysis team outside Novartis, for the requirement of Data Monitoring Committee (DMC) meeting. The process in details are defined in DMC Charter.

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

One injection of AMG 334 70 mg and one 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 DB treatment period. For the open-label treatment period each pre-filled syringe will be packaged individually in open-label fashion. This open-label study treatment will be labeled as AMG334 70 mg.

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

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

First DB IP Dose Date

The first DB 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 (most of the time) or after the randomization date. For subjects who are randomized but never dosed with double-blind IP after randomization, First DB IP Dose Date is considered missing.

Last DB IP Dose Date

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

First OLE IP Dose Date

The first OLE IP dose date is the date on which a subject is administered the first OLE dose of IP on or after Week 12. The first OLE IP dose date will only be applicable for subjects who enter OLE period.

Last OLE IP Dose Date

The last OLE IP dose date for each subject is defined as the latest date IP is administered during OLE period, which is applicable for subjects who enter OLE period.

Subject-level End of DB Treatment (EOT_DB) Date

The end of DB treatment date for each subject is defined as the end of the treatment in DB period. The date will be recorded on the Treatment disposition eCRF page.

Subject-level End of OLE Treatment (EOT_OLE) Date

The end of OLE treatment date for each subject is defined as the end of the treatment in OLE period. The date will be recorded on the Open-label Treatment disposition eCRF page.

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.

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 subject for daily data capture) and the day prior to study day 1 (study day 1 is not included).

A baseline for PRO [redacted], BDI-II, MIDAS) 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 2-2. For example, change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period will be calculated based on the following:

(Monthly migraine days in the last 4 weeks of the 12-week treatment period) – (monthly migraine days during the baseline period)

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% [redacted] will be defined as a decrease from baseline score value of at least 50% [redacted]

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 in days for DB Period is computed as min (last DB treatment dose date + 27, EOT visit, cutoff date) – First Dose Date + 1.

The duration of exposure in days for OLE Period is computed as min (last OLE treatment dose date + 27, EOS date) – First OLE Dose date + 1

Compliance with the eDiary

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

The protocol requirement is 80% compliance in 28 days at baseline period. That means minimum 23 diaries must be completed within 28 days.

2.1.2 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. Those medications are classified in 13 categories (as per protocol section 6.2.2):

- 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: Flunarizine, verapamil, cinnarizine
- Category 6: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine,
- desvenlafaxine, duloxetine, milnacipran)
- Category 7: Botulinum toxin
- Category 8: Lisinopril, candesartan
- Category 9: Pregabalin, gabapentin
- Category 10: Zonisamide
- Category 11: Memantine
- Category 12: Pizotifen
- Category 13: Cao Wu Jia Su Pian, Du Liang Ruan Jiao Nang

For medications entered as free text, categorisation will be provided by clinical team prior DBL. The number of failed prior prophylactic treatments is the number of categories with at least one failed prior migraine prophylactic medication.

2.1.3 Visit and analysis windows

Visit window for DB period

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 data captured in DB period - lab, vital signs, ECG, C-SSRS and some PROs collected during office visits ([redacted] BDI-II, mMIDAS) before dose is administered.

Table 2-2 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 (for safety endpoints)	Safety follow-up should be excluded from the analysis visit windows described above and summarized under 'safety follow-up visit' for safety analyses only. Target day: last IP dose date + 12 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.

[redacted]

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 period (Week -4 visit) up to the End of Treatment in DB period (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
DB 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 assessments during treatment period 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 + 28, EoS) if week 8 dose is received

2.1.4 Definition of terms included in study endpoints

2.1.4.1 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. Derivations will be based on eDairy data and done by analysis team.

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 subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). Please see exceptions in Appendix 5.10. A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 4 continuous hours, 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 subject took ANY acute medication (simple analgesics [NSAIDs, acetaminophen], combination analgesics, triptans or ergot-derivative) during aura, or to treat a moderate or severe headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. Opioid-containing analgesic and butalbital-containing analgesic are excluded in allowed acute medication categories.

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).

Modified Migraine Disability Assessment (mMIDAS)

The modified Migraine Disability Assessment Questionnaire (mMIDAS) is a 5-item self-administered questionnaire that sums the number of productive days lost over the past month in two settings: the workplace and the home. The mMIDAS also assesses disability in family, social, and leisure activities. The mMIDAS score is the sum of missed days due to a headache from paid work, housework, and non-work (family, social, leisure) activities; and days at paid work or house work where productivity was reduced by at least half. **The total score is**

multiplied by 3 and categorized into 4 severity grades: Grade I = 0 - 5 (defined as minimal or infrequent disability), Grade II = 6 - 10 (mild or infrequent disability), Grade III = 11 - 20 (moderate disability), and Grade IV = 21 and over (severe disability). The recall period is the past one month.

Subjects will complete the mMIDAS monthly using the eDiary. Please refer to Appendix 5.9 for scoring algorithm.

Achievement of at least a certain percentage reduction from baseline in monthly migraine days

Calculated based on the following: (monthly migraine days at each timepoint post-baseline - baseline monthly migraine days*100/baseline monthly migraine day.

At least a 50% reduction at month [redacted] will be evaluated.

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.

[redacted]

Headache Day

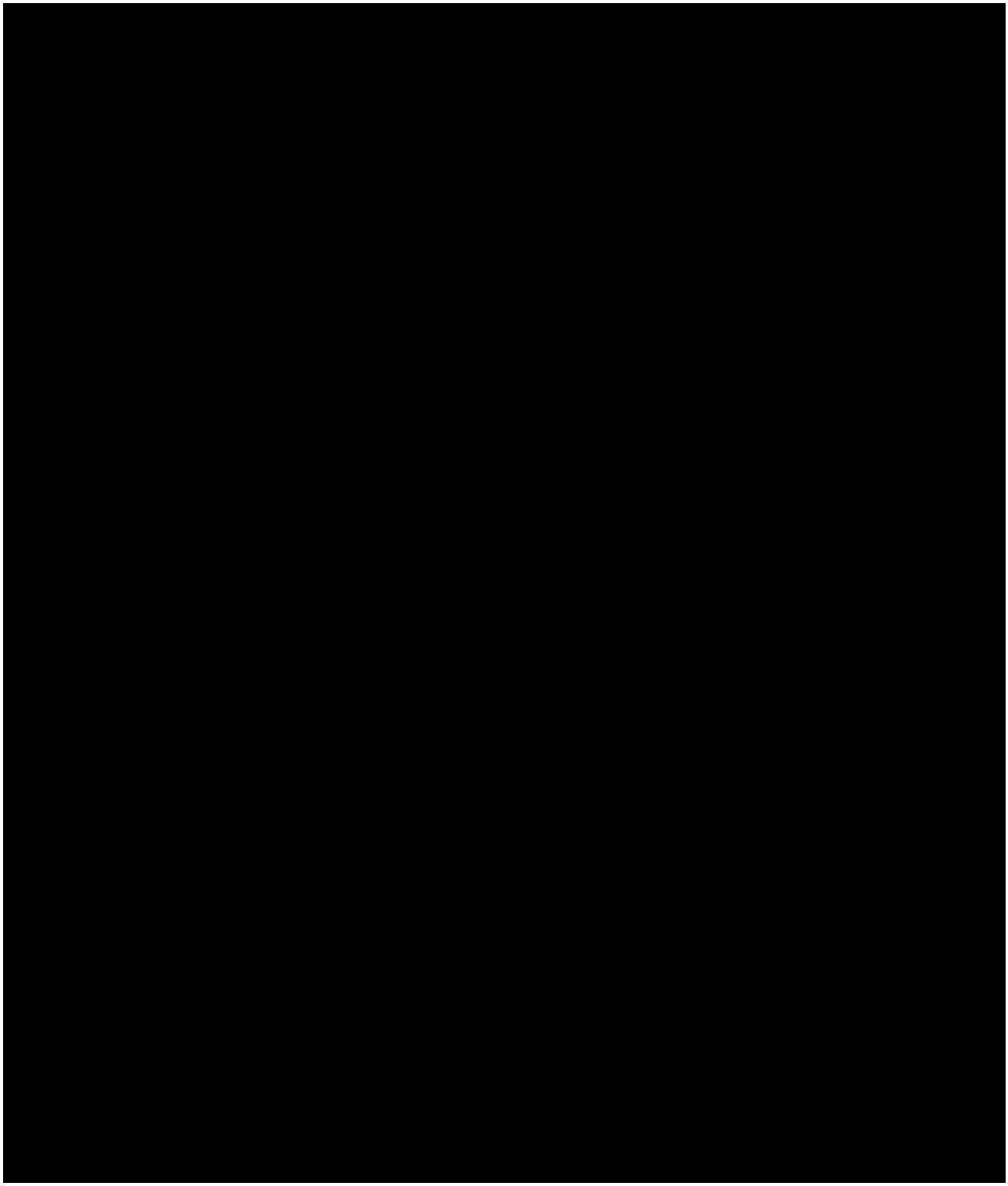
A headache day is any calendar day in which the subject experiences a qualified migraine or non-migraine headache (initial onset, continuation or recurrence of the headache). Please see exceptions in Appendix 5.10. A qualified headache is defined as:

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or

- a qualified non-migraine headache, which is a headache that lasts ≥ 4 continuous hours and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered.

The headache day will be flagged in eDiary data.

[redacted]



2.1.4.2 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 up to the last available visit. 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 end of study.

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.

Adverse Event leading to discontinuation of study treatment

An AE leading to discontinuation of study treatment will be identified by the item “Action Taken With Study Treatment” on AE page of CRF when it’s reported as “Drug withdrawn”.

Serious Adverse Event leading to discontinuation of study treatment

An SAE that is considered to lead to discontinuation of study treatment.

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, 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 study will be a concomitant medication.

2.1.4.3 Other endpoints at Baseline

Beck Depression Inventory (BDI)-II

The BDI-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is calculated by special algorithm and categorized into 4 severity grades: minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63). Subjects will complete the BDI-II using the eDiary at screening visit. The recall period is the preceding two weeks, including the day of completion. The BDI-II will only be reported during screening period.

Please refer to Appendix 5.9 for details.

[redacted]

2.2 Analysis sets

The following analysis sets are defined for the double-blind treatment period:

The **Full Analysis Set (FAS)** 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, important protocol deviations (IPDs), and efficacy analyses will utilize this analysis set.

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

The following analysis set is defined for the open-label treatment period:

The **Open-label treatment analysis set (OAS)** will consist of all subjects who consented to enter into the open-label treatment period and who have taken at least one dose of erenumab during the open-label treatment period. This analysis set will be used when summarizing data collected during the open-label treatment period.

[redacted]

2.2.1 Subgroup of interest

The primary and secondary efficacy endpoints, safety endpoints (adverse events, clinical laboratory values, vital signs, and anti-AMG 334 antibodies), as well as the demographics and baseline characteristics, and the prior migraine prophylactic medication usage information will be analyzed for Chinese subgroup (recruited from China mainland and 3 qualified sites from Taiwan). This is to evaluate the consistency of efficacy and safety effects in Chinese population vs overall population.

In addition, the effect in the following subgroup analysis by baseline characteristic will be investigated with respect to the primary and secondary efficacy analyses as well:

- Prior prophylactic migraine medication treatment failure (Yes or No)
- Medication overuse at Baseline: Yes, No

- Baseline MMD (< median vs ≥ median)
- Disease duration (< median vs ≥ median)
- Age (< median vs ≥ median)
- BMI (< median vs ≥ median)
- Sex (Male vs Female)
- Region

The impact of other baseline variables, may be 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 it 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 and the p-value for the interaction term will be reported. 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 factors, 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 adjusted mean changes from baseline, SE's, and 95% CIs for each subgroup and the nominal p-value for subgroup by treatment interaction will be calculated.
The outcome will be displayed in separate forest plot for each endpoint with 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 (erenumab 70mg vs. placebo) 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.
- p-value for the treatment*subgroup interaction term.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject 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 DB Treatment

Subjects are defined as completing the treatment period if they receive the week 8 IP dose. It will be derived from Treatment Disposition Form with "Completed" as subject status.

Completing the DB period

Subjects are defined as completing the DB period if they complete all visits up to EOT assessments at Week 12.

Entering into the OLE Period

Subjects are considered entering into OLE period if they complete the DB period and sign on ICF for OLE period.

Completing the Study

Subjects are defined as completing DB period if they complete the safety follow-up visit (week 20), or continue with OLE treatment until the end of study**.** It will be derived from Study Disposition Form with "Completed" as subject status.

Subject disposition for DB period will be displayed by randomized treatment and overall on FAS, in terms of:

- the number and percentage (based on the number of subjects within each randomized treatment arm) of subjects who complete the DB treatment, or discontinue the DB treatment prematurely along with the primary reason
- the number and percentage of subjects who has completed DB period and enter into OLE period or safety follow-up visit
- the number and proportion of subjects, who complete the DB period, or discontinue the DB period prematurely along with the primary reason for study

The subject disposition for OLE period will be summarized on OAS, in terms of:

- the number and percentage of subjects who complete the OLE treatment, or discontinue the OLE treatment prematurely along with the primary reason
- the number and percentage of subjects who complete the OLE period, or discontinue the OLE period prematurely along with the primary reason

In addition, the total number of subjects screened and the number of subjects screened, but not randomized (discontinued prior to screening phase completion or prior to baseline period completion) will be summarized, including the reason for non-inclusion into the study.

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

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

- Eligibility: Subject did not satisfy entry criteria
- Withdrawal: Subject developed study/treatment withdrawal criteria during the study, but was not withdrawn
- Study Drug: Subject received the wrong treatment or incorrect dose
- Concomitant Medication: Subject 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.

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

To evaluate the impact of COVID-19 on trial integrity, the number of subjects randomized during COVID-19 pandemic period, the number of subjects under DB period during COVID-19 pandemic, as well as the number of subjects who reported COVID-19 related PDs during DB period will be summarized.

The COVID-19 related PDs will be grouped in summary by following categories which was defined by clinical trial team with reference to COVID-19 guidance released by Novartis:

- Missed visit due to COVID-19
- Visit done outside of study site due to COVID-19
- Assessment/procedure changed due to COVID-19
- Non-compliance with baseline period duration due to COVID-19
- Non-compliance with no re-screening post-baseline failure due to COVID-19
- Discontinuation due to COVID-19
- Treatment not given or delayed due to COVID-19
- Changes in drug supply method (self-administration) due to COVID-19

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 subjects (total) using FAS.

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 (yes, none) during baseline period
  - Strata*: Prior prophylactic migraine medication treatment failure (prior prophylactic migraine treatment failure, due to efficacy or tolerability, vs no prior prophylactic migraine treatment failure).
  - Strata*: Medication overuse at Baseline (yes, vs no)
  - The number of prior prophylactic migraine treatment category (by counting the category defined in section 2.1.2)
  - The number of prior prophylactic migraine treatment failure (by counting the category defined in section 2.1.2)
  - 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)
  - Beck Depression Inventory (BDI)-II total score severity grade (minimal depression (0-13), mild depression (14-19), moderate depression (20-28))
- Continuous variables:
  - Age
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI, kg/m^2)
  - Age at onset of migraine (years)
  - Disease duration of migraine with or without aura (years)
  - Monthly migraine days during baseline period
  - [redacted]
  - Monthly acute headache medication days during baseline period

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

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

To evaluate the impact of COVID-19 on study population, the demographic and baseline characteristics will be summarized in the same manner, respectively for subjects who are randomized pre-COVID-19, and subjects who are randomized during COVID-19.

The number of subjects 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 2.1.2).

Subject demographics and baseline characteristics including stratification factors, ethnicity and child bearing status 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)
- Frequency of headache (migraine and non-migraine) over the past 3 months (average days per month subject had headache)

2.3.3 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 subjects (total) using FAS (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 70 mg 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 subjects in the SAF and is defined as the number of investigational product injections received (planned to be 1 injection per dose) by subject.

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. The proportion of subjects who received 1, 2 or 3 injections 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 subjects receiving an investigational drug (AMG 334 or placebo) dose will be summarized by treatment group. Additionally, the number and percentage of subjects 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 subjects receiving concomitant 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.

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

Use of acute headache medication during the baseline period and the treatment period 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 4 weeks of the 12-week treatment period.

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 endpoint of the study will be tested for erenumab 70 mg compared to placebo.

Null hypothesis: There is no difference between erenumab 70 mg group and placebo group, in terms of change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period.

Alternative hypothesis: There is a difference between erenumab 70 mg group and placebo group, in terms of change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period.

The null hypothesis will be rejected if the observed p-value for the between-group comparison is less than the significant level adjusted according to the alpha spending function with the

O'Brien-Flemming approach. The nominal p-value threshold will be calculated upon the exact information collected in the interim analysis, considering the alpha-level spent at interim analysis and considering the actual correlation among the test statistics, in order to achieve a cumulative type I error smaller than the desired significance level (i.e. smaller than the 5% for a two-sided test).

The primary efficacy endpoint variable will be analyzed using a linear mixed effects repeated measures model based on observed monthly data during treatment period. with treatment, scheduled visit, treatment by visit interaction, and the stratification factors and baseline values as covariates. If applicable, unstructured covariance structure is assumed. Least squares means (LSMs) for treatment groups and its associated 95% confidence intervals, difference of LSMs compared to placebo group and the associated 95% confidence interval of the difference, as well as the nominal two-sided p-values, will be tabulated by visit and treatment.

2.5.3 Handling of missing values/censoring/discontinuations

For the primary analysis, missing data will not be imputed.

2.5.4 Sensitivity analyses

Multiple imputation (MI) techniques applying missing at random (MAR) and missing not at random (MNAR) approaches will be used to assess the impact of missing values on the interpretation of the results during study. In addition, the baseline observations carried forward (BOCF) method will also be used. After imputation, the primary efficacy variable at week 12 will be analyzed using an analysis of covariance (ANCOVA) model including treatment group and stratification factor as fixed effects in the model with baseline value as covariate.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

The secondary efficacy variables are:

- Change from baseline in migraine-related disability and productivity as measured by the mMIDAS during the last 4 weeks of the 12-week treatment period
- Proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period
- Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period

2.6.2 Statistical hypothesis, model, and method of analysis

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

The above continuous change from baseline efficacy endpoints will be analyzed using a linear mixed effects repeated measures model similar to the primary efficacy variable.

The dichotomous endpoint (Proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period) will be analyzed based on Cochran-Mantel-Haenszel (CMH) test after subjects who have missing monthly migraine day data at the last 4 weeks 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.

2.6.3 Handling of missing values/censoring/discontinuations

For the proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period, 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 subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of 12-week treatment period", a logistic regression analysis that includes treatment and stratification factors as fixed effects and baseline migraine days as covariate, will be used to get odds ratio of AMG 334 group vs placebo in the 50% response rate after the missing data are imputed as non-response.

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

2.7 Safety analyses

For safety endpoints in DB period, 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 treatment period).

[redacted]

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

Missing data will not be imputed for safety endpoints.

The safety analysis for DB period [redacted] will be displayed separately and pertinent to all safety endpoints below, unless other specified.

2.7.1 Adverse events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 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.

The overall subject incidence of AEs and exposure-adjusted subject incidence will be summarized for all TEAEs, AEs leading to discontinuation of study treatment, all treatment-related AEs, SAEs, SAEs leading to discontinuation of study treatment, treatment-related SAEs and deaths as defined in **Table 2-4**.

Table 2-4 AE Summaries of subject incidence and exposure-adjusted subject incidence

Category	Summary by SOC and PT	Summary by SOC, PT and maximum CTCAE grade	Summary by PT only
All TEAEs	Y	Y	Y
SAEs	Y	Y	Y
AEs leading to discontinuation of study treatment	Y		
All treatment-related AEs	Y		
SAEs leading to discontinuation of study treatment	Y		
Treatment-related SAEs	Y		
Deaths	Y		

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.

AE tables by preferred term only will be sorted in descending order of frequency.

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

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

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.

[redacted]

2.7.2 Deaths

Deaths will be listed by actual treatment arm 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 for DB period only.

For both DB period [redacted] period, following analyses will be provided by treatment arm:

- the subject incidence of liver enzyme abnormalities (including AST, ALT, Total Bilirubin (TBL) and Alkaline Phosphatase (ALP))
- shift from baseline for some liver enzyme level categories (specified in the TFL shells; for e.g. ALP≤1 x ULN)
- clinically notable laboratory values will be flagged and listed.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging 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.

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 DB period.

The number and percentage of subjects with clinically relevant abnormality (see Table 5-3) at any post-baseline visit will be presented for both DB period [redacted].

The number and percentage of subjects with hypertension/worsening hypertension or elevated blood pressure at post-baseline will be provided by as change from baseline in category of with/without hypertension or elevated blood pressure at baseline.

- Hypertension at baseline will be identified from medical history based on SMQ narrow list
- Elevated blood pressure at baseline is defined as Systolic Blood Pressure (SBP) ≥140 mmHg or Diastolic Blood Pressure (DBP) ≥90mmHg

- Hypertension/worsening hypertension at post-baseline will be identified from AE based on SMQ narrow list
- Elevated blood pressure at post-Baseline is defined as two consecutive visits meeting increase of ≥20 mm Hg in SBP or increase of ≥15 mm Hg in DBP

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

C-SSRS will be collected during DB period and safety follow-up period.

The number and percentage of subjects reporting any suicidal ideation or any suicidal behavior will be summarized descriptively by treatment group and by visit.

Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline will be provided by treatment group by visit.

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 DB period (after signing informed consent and up to the end of DB period or safety follow-uo) will be tabulated by treatment group.

In addition, the number and percentage of subjects who develop anti-AMG 334 antibodies at any time post-dose will be tabulated by treatment group.

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

The Immunogenicity prevalence set includes all subjects 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 Subject ADA status

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

- Treatment-boosted ADA-positive: number and percent of subjects with at least one treatment-boosted ADA-positive sample. The denominator is the number of subjects with an ADA-positive sample at baseline.
- Treatment-induced ADA-positive: number and percent of subjects with at least one treatment-induced ADA-positive sample. The denominator is the number of subjects with an ADA-negative sample at baseline.
- ADA-negative: number and percent of subjects with no treatment-induced or treatment-boosted ADA-positive sample.
- ADA incidence (i.e. % ADA-positive): number and percent of subjects 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 subjects at that time point with determinant samples:

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

[redacted]

[redacted]

2.10 Subject-reported outcomes

The eDiary will collect the following subject-reported outcomes during DB period:

- Modified MIDAS, monthly
- [redacted]
- [redacted]
- Beck Depression Inventory, screening
- [redacted]

Change from baseline in migraine-related disability and productivity as measured by the mMIDAS during the last 4 weeks of the 12-week treatment period 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).

2.11 Other [redacted] analyses

[redacted]

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

[redacted]

Figure (line plot with confidence interval) will be produced showing the change from baseline in the secondary endpoints (mMIDAS total score and monthly acute headache medication treatment days) at the end of each month by treatment.

Figure (bar plot) will be produced showing the responder rate (at least 50% reduction from baseline in monthly migraine days) at the end of each month by treatment.

[redacted]

2.12 Interim analysis

2.12.1 Blinded Sample Size Re-estimation

To account for potential larger than expected variability during the trial, a blinded interim assessment is planned after about 50% of subjects finish 12 weeks' DB treatment or early withdraw. Only the standard deviation of the primary variable, change from baseline in monthly migraine days in the last 4 weeks, 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 if the standard deviation is larger than 6.8.

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.

2.12.2 Unblinded Interim Analysis

An unblinded IA will be conducted after 70% (385) of subjects have completed the DB treatment period (including early withdrawals), to determine whether the study will stop early or continue to the primary analysis (full sample size in DB period). The following data analysis (excluding OLE period) will be included in IA read-out.

- Subject disposition (as defined in Section 2.3.1)
- Demographics and baseline characteristics (as defined in Section 2.3.2)
- Study treatment / Compliance (as defined in Section 2.4.1)
- The primary and sensitive analysis on key efficacy endpoints:
  - The change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period (as defined in Section 2.5)
  - Proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)
  - Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)

  - Change from baseline in migraine-related disability and productivity as measured by modified MIDAS during the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)

- The primary analysis on key safety endpoints:
  - Adverse events (as defined in Section 2.7.1)
  - Laboratory evaluations - Hematology, Chemistry and Urinalysis (as defined in Section 2.7.3)
  - ECG evaluations (as defined in Section 2.7.4.1)
  - Vital signs (as defined in Section 2.7.4.2)
- Subgroup analysis in Chinese sub-population: repeat the primary analysis for following efficacy endpoints and safety endpoints
  - The change from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period (as defined in Section 2.5). Sensitive analyses for primary endpoint will not be conducted for Chinese sub-population.
  - Proportion of subjects who achieve at least a 50% reduction from baseline in monthly migraine days in the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)
  - Change from baseline in monthly acute headache medication days during the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)
  - Change from baseline in migraine-related disability and productivity as measured by modified MIDAS during the last 4 weeks of the 12-week treatment period (as defined in Section 2.6)
  - Adverse events (as defined in Section 2.7.1)

3 Sample size calculation

The planned total sample size in this proposed China-centric phase 3 study is 550 subjects. The key assumptions in calculating the sample size are based on prior results from erenumab global pivotal study. A treatment difference in terms of change from baseline on MMDs during Week 9-12 (primary endpoint) for erenumab 70 mg vs. placebo is assumed at -2.0 days. The common standard deviation of the primary variable is assumed at 6.8. Given a 1:1 randomization ratio among erenumab 70 mg and placebo, it requires a total of 550 subjects (including 10% drop out rate) to achieve approximate 90% power to demonstrate the treatment difference of erenumab 70 mg compared with placebo under two-sided 0.05 alpha level. The impact of spending alpha at unblinded interim analysis on sample size and power is relatively negligible. Having this interim analysis with alpha spending at 0.014 two-sided, at final analysis an observed p-value ≤ 0.046 two-sided would be required (given that the interim analysis was performed when 70% subject finished treatment or early withdraw). With that said, the overall power will be maintained at approximately 88% with planned sample size.

The sample size for Chinese sub-population will make sure the consistency of treatment effect between Chinese and total population. The methods for consistency assessment are proposed as,

$Pr(D_{china} / D_{overall} > 0.5) > 95\%$,

which means that this China study should have high probability (>95%) to demonstrate consistency where the treatment effect (treatment difference of erenumab compared with placebo) observed in the Chinese population should be as high as at least 50% of the treatment effect observed in the overall study population in the prospective trial, assuming there is no difference between the Chinese population assessed in the trial and the overall population.

To meet the above criteria, approximately350 (out of 550 for the overall study) Chinese subjects will be recruited.

At the interim analysis, as long as China population takes the majority of the overall population, there should have high likelihood to demonstrate the consistency as well.

4 Change to protocol specified analyses

Not applicable.

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	

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 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

Not applicable.

5.1.5 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
- Acute medication taken to treat headache, aura-only event, or both headache and aura

As well as, subject-reported outcomes (PROs) measures of [redacted], modified MIDAS, [redacted], [redacted]

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following method:

1. For monthly intervals with ≥ 14 days of eDiary days (including retrospective eDiary days) in each interval:
    a. Monthly frequency measurements (including migraine days, [redacted], 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.

    [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, [redacted] acute headache 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]	[redacted]

Missing PROs [redacted] mMIDAS [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 Treatment Period

Primary analysis of continuous efficacy endpoints during the 12-week DB treatment period 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 efficacy endpoint during the 12-week DB treatment period, 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 primary efficacy endpoint 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%, ≥53%, [redacted] reduction from baseline in monthly migraine days) during treatment period 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 factors (prior migraine prophylactic treatment failed, medication overuse), sex, race group, age group, BMI group from ADSL
- Obtain number of prior migraine prophylactic treatment failed and baseline disease duration from ADBS
- 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="BOCF" then aval=., avalc=" " and chg=.
- Ensure the baseline values are included in the chg variables, 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.
- If necessary, for the 50% Responders analysis, it is based on imputed MMD data under the assumption of MAR or MNAR. Then, use the same method as for primary analysis - the stratified CMH test to get estimates for numbers of responders in each treatment group and odds ratio at week 12 for each dataset.

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 Statistical models

5.3.1 Van Elteren Test for Continuous Response Variable with Strata

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

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

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

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

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

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

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

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

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

can be used.

Two weights have been used to combine results over strata:

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

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

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

The test can easily be implemented using the SAS, PROC FREQ. The FREQ procedure is used with the TABLE statement options CMH2 and SCORES=MODRIDIT. The second CMH statistic, labeled "Row Mean Scores Differ" is the asymptotic test statistic.

As shown by Koch et al 1982, the Van Elteren test is a member of a general family of Mantel-Haenszel mean score tests. For more information about the Van Elteren test and related testing procedure, refer to Lehmann 1975, Koch et al 1990.

5.4 Rule of exclusion criteria of analysis sets

The protocol deviations resulting in subjects' 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	SUBJECT 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
FAS	NA	Not randomized
SAF	NA	No double-blind study drug taken
[redacted]	[redacted]	[redacted]

5.5 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

5.6 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.

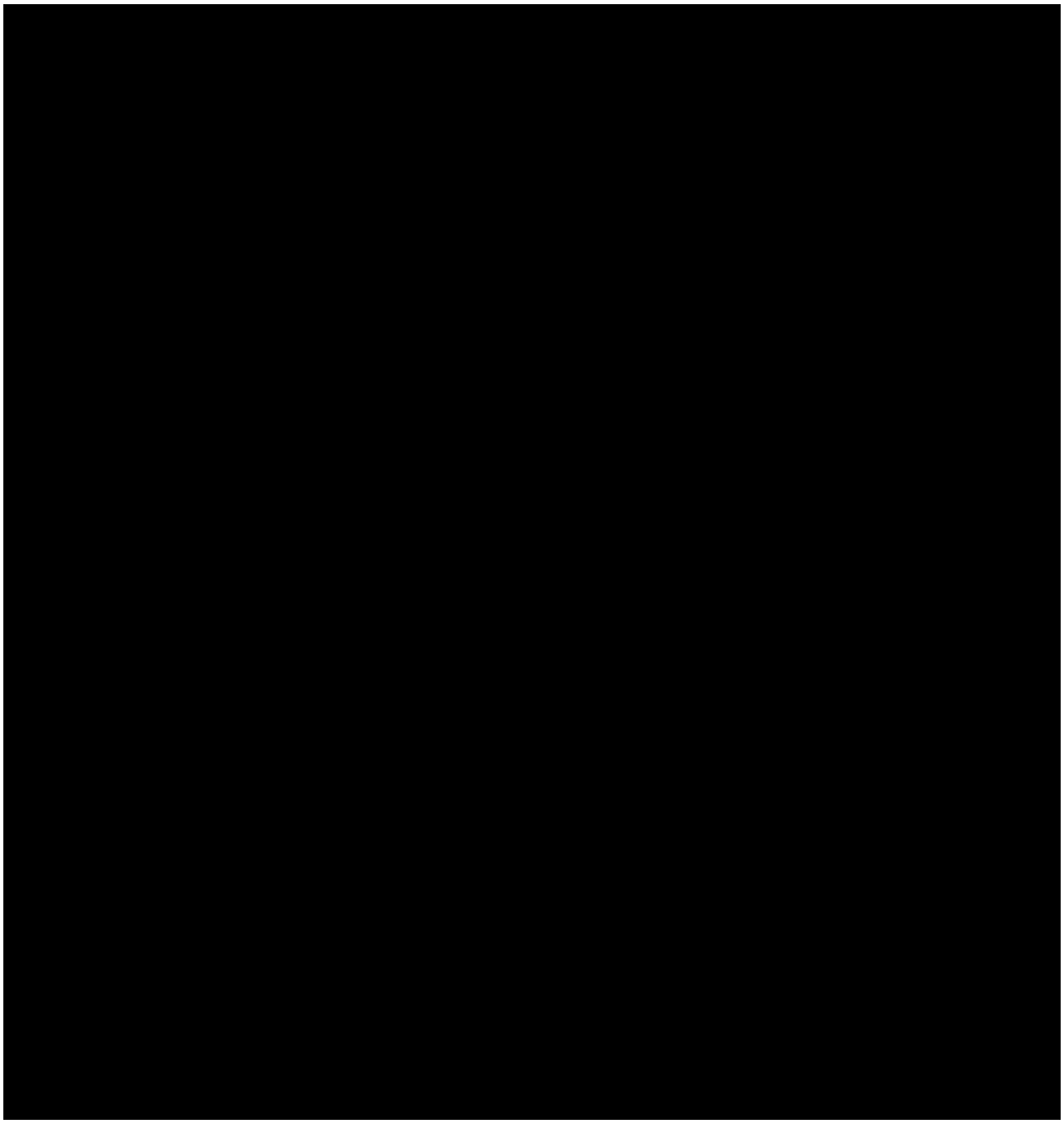
5.7 Appendix C: Criteria for ECG abnormalities

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 (%)		

5.8 Appendix D: Subject-reported Outcome Forms/Instruments



5.8.3 Modified Migraine Disability Assessment (MIDAS) Questionnaire

mMIDAS questions

Please answer the following questions about ALL of the headaches you have had over the Last 1 month. Select your answer in the box next to each question. Select zero if you did

not have the activity in the last 1 month.

_____ 1. On how many days in the last 1 month did you miss work or school because of your headaches?

_____ 2. How many days in the last 1 month was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 1 month did you not do household work because of your headaches?

_____ 4. How many days in the last 1 month was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 1 month did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

Scoring:

The mMIDAS total score is the sum of the number of days from question 1 to 5.

In order to assign disability grades, multiply the total score on the MIDAS by 3 and then assign the grade based on following table.

MIDAS Grade	Definition	MIDAS Score
I	Minimal or infrequent disability	**0 - 5**
II	Mild or infrequent disability	**6 - 10**
III	Moderate disability	**11 - 20**
IV	Severe disability	**21 and over**

MIDAS absenteeism domain score is the sum of the number of days from questions 1, 3 and 5.

MIDAS presenteeism domain score is the sum of the number of days from questions 2 and 4.

Missing data:

We score the instrument if 3 out of 5 questions are scored. We do not allow skip patterns so only 4 and/or 5 can be missing in order to calculate mMIDAS total score. If question 4 and/or 5 are missing, then use the number from 2 to impute into 4 and a mean from 1 and 3 for 5.

5.8.4 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

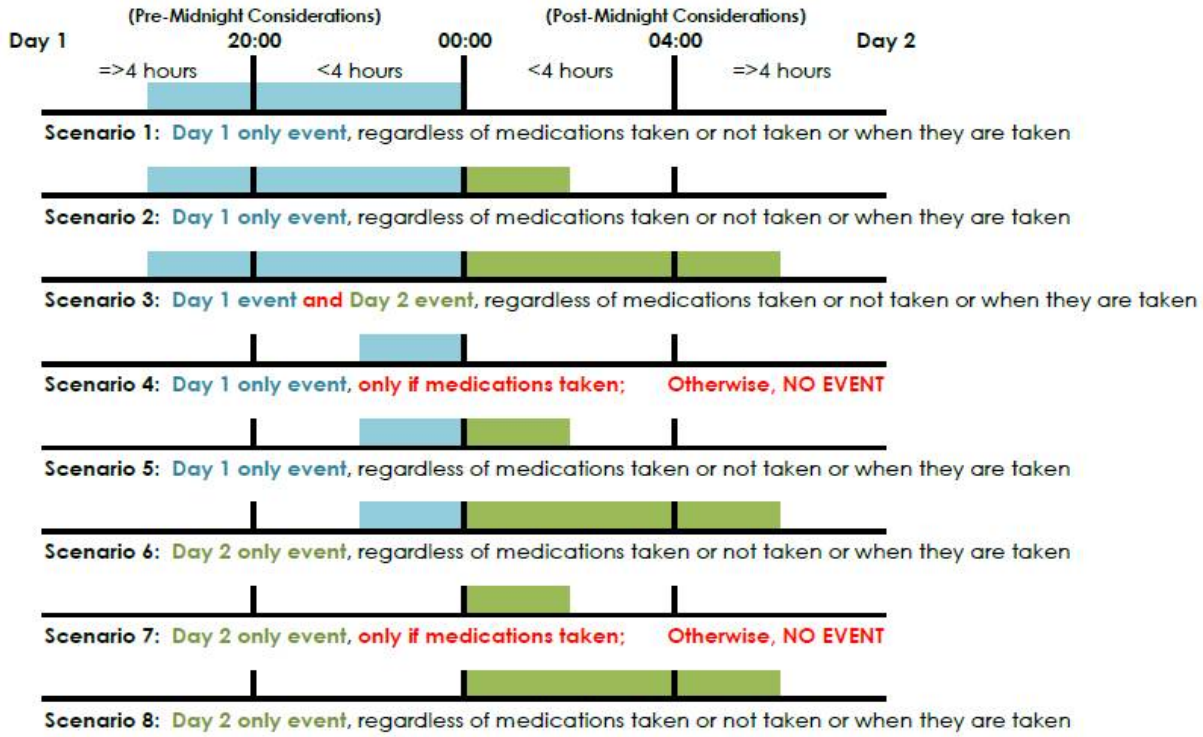
Missing data:

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.

5.9 Appendix E: MMD derivation, exceptions

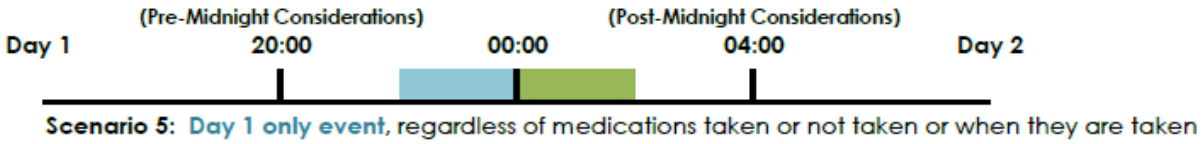
5.9.1 Assigning Headache and Migraine Days to Events Spanning Midnight

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



Example

A headache starts 20 minutes before midnight (Day 1), a triptan is taken at 15 minutes after the midnight (Day 2).



In this case, the midnight Scenario 5 is applied so that Day 1 will be counted as headache/migraine day only.

5.9.2 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 4 hrs 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.

Example

A headache event starts 2 hrs before midnight (Day 1), extends across a full day (Day 2), and ends 3 hrs 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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