NOVARTIS

Clinical Development

AMG334/Erenumab/Aimovig®

AMG334A2401 / NCT03927144

A 12-month prospective, randomized, interventional, global, multi-center, active-controlled study comparing sustained benefit of two treatment paradigms (erenumab qm vs. oral prophylactics) in adult episodic migraine patients

Statistical Analysis Plan (SAP) Amendment

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-May-2019	Prior to DB lock	Creation of final version	N/A - First version	NA
01-Oct-2021	Amendment 1	COVID-19 impact sensitivity analysis	Added analysis to study impact of randomization, study/treatment discontinuations, dose interruptions	Section 2.3.1
			Added analysis to study impact on Protocol deviations	Section 2.3.2
			Added analysis to study impact on demographics	Section 2.3.3
			Added analysis to study impact on primary endpoint	Section 2.5.4
		Visit mapping details	Updated details based on analysis visit instead of dose dates	Section 2.1.1.6
		Protocol amendment PTA phase	Added details about PTA phase and endpoints collected during PTA	Section 1.1, 1.2
		Updated text to clarify randomized treatment	Updated text from “randomized treatment” to “ initially asssigned treatment”	Throughout the SAP
		Sensitivity analyses with corrected stratification factor	Added analysis by correcting strata for mis-stratified subjects	Section 2.5.5
		Analysis for COVID-19 and Hypertension AEs based on SMQ and for	Summary of treatment emergent AEs will be provided for COVID-19 and hypertension data by SMQ levels.	Section 2.8.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		constipation based on CMQ	Summary of treatment emergent AEs will be provided for constipation by CMQ and corresponding preferred term.	
			Summary of exposure adjusted subject incidence rates for treatment emergent AEs and SAEs will be provided by primary system organ class and preferred terms.	Section 2.8.1
		Definitions for study phases	Details added for study phases to provide more clarity on core phase and safety follow up phase data	Section 2.1.1.6
25-Oct-2021	SAP amendment 2	Section 2.5.6	Sensitivity analysis for primary endpoint added for subjects taking prohibited / non-approved medications or polytherapy on initially assigned treatment	Section 2.5.6

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
eCRF	Electronic Case Report Form
EOS	End of Study
FAS	Full Analysis Set
IAT	Initially assigned treatment
IP	Investigational Product
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMD	Monthly Migraine Days
NCI	National Cancer Institute
PD	Protocol Deviation
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
PT	Preferred Term
PTA	Post Trial Access
qm	Monthly once
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAF	Safety Set
SOC	System Organ Class
SoC	Standard of Care
TF	Treatment Failure
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study AMG334A2401, a 12-month phase IV, prospective, randomized, interventional, global, multi-center, active-controlled study comparing sustained benefit of two treatment paradigms (erenumab qm vs. oral prophylactics) in adult episodic migraine patients.

The content of this SAP is based on protocol AMG334A2401 version 02. This SAP includes analysis for core phase data. For extension phase, separate SAP will be developed.

Data will be analyzed by Novartis according to the data analysis section 12 of the study protocol. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Study design

This study uses 2-treatment arm (AMG334 versus standard of care (SoC) oral prophylactic treatment), parallel group randomized (2:1 [AMG334 (70 mg or 140 mg) : SoC oral prophylactic]), open-label in adult patients with episodic migraine who have previously failed 1 or 2 prophylactic migraine treatments. The following periods are included in the study design, with study visits at 4-week intervals after completion of screening:

- Screening period (0-2 weeks): required for all subjects to assess intial eligibility and to obtain informed consent
- Baseline period (4 weeks) – All subjects successfully completing the screening period will be invited to participate. Eligibility for randomization will be assessed based on migraine freqeuncy and diary compiance during this period. Randomization will be stratified by prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during screening / baseline period: 1 treatment failure (TF1) vs 2 treatment failures (TF2). A 30% cap of randomized subjects to the TF2 strata will be implemented. The stratification and 30% cap will be implemented within IRT.
- Open-Label Randomized Treatment Period (52 weeks): All subjects successfully completing the Baseline Period will be invited to participate. Eligible subjects will be randomized 2:1 to one of two treatment arms [AMG334 s.c. q.m. versus SoC oral prophylactic (active comparator)]. Only monotherapy will be allowed in both arms and no concomitant use of other prophylactics for migraine specifically should be used. At the end of this period, the final assessment to address the effect of AMG334 compared to oral prophylactic cycling on the net benefit and related objectives will occur. The last dose for AMG334 will occur at Week 48 (monthly dose) and the last dose for SoC will occur at Week 52.
    - Switching: Treatment (failure) status and decision on whether or not to switch to a new treatment will be checked at every visit and will be based on investigator and subject discretion (based on efficacy/tolerability/satisfaction but not based on prespecified cutoffs for certain parameters). In both arms, switching will be allowed within approved prophylactics in the respective country for prophylaxis of migraine. Subject randomized to AMG334 arm can

switch to oral prophylactics and subject randomized to oral prophylactics arm can switch to only other oral prophylactics and not to AMG334.

- Follow-Up Period (16 weeks) as per protocol version 0 and 1– A follow-up visit 16 weeks after the last dose of treatment (AMG334 or SoC oral prophylactic) will be required as part of routine safety monitoring. As per protocol amendment 2, subject may chose to enter extension phase or discontinue study. This means follow up data will not be available for all subjects.

Extension Phase (as per protocol amendment 2)

- Post-Trial Access Open-Label Treatment Period (52 weeks) - Patients completing visits through week 52 of the Core Phase will be eligible to participate. Patient eligibility will be determined by the investigators opinion as follows: 1) patients treated with erenumab must have benefited from erenumab treatment and 2) patients on Standard of Care (SoC) oral prophylactic must be in need of a treatment switch. PTA to erenumab will be provided for up to 52 weeks (based on continued benefit of erenumab treatment) in all eligible patients; this will ensure erenumab access until country-level launch and subsequent reimbursement decision in all countries. Should a treatment gap exist between the Core and Extension Phase due to a delay of HA/EC approvals or other administrative/logistical reasons, the subject may enter the Extension Phase at a later time. During this treatment gap, the patient would remain in the main study and is allowed to be treated with any medication as deemed appropriate by the investigator to manage the patient's migraines. Upon HA and EC approval of the Extension Phase, the patient will then be administered study drug corresponding to the Week 52 dose and will continue dosing every 4 weeks as per protocol. Patients will be required to follow all protocol requirements for treatments allowed and for prohibited medications (Protocol Section 6.2.2)

End of Trial will occur when the last subject completes their last visit (LPLV) of the study. The primary analysis will occur when the last patient completes the Core Phase, prior to the start of the Extension Phase. The main study report will be prepared and finalized at this time for all data from the Core Phase. An additional study report will be prepared for the Extension Phase after all patients have completed their respective last visit (LPLV) of the Extension Phase and will report data for the Extension Phase.

Approximately 591 subjects will be enrolled into the trial.

There is no planned interim analysis for this study.

Note:

- Treatment discontinuation does not imply study discontinuation. Every effort should be attempted to ensure subjects complete the study visits event if treatment is discontinued. After study completion, post-trial access to AMG334 will be offered to the study participants as needed.
- Some eligibility criteria will be checked at screening visit and some at baseline.
- Treatment disposition form will be filled for the last drug taken by the subject regardless of switching and not only for initially assigned treatment.

- There can be gap between end of first treatment and start of switched treatment.

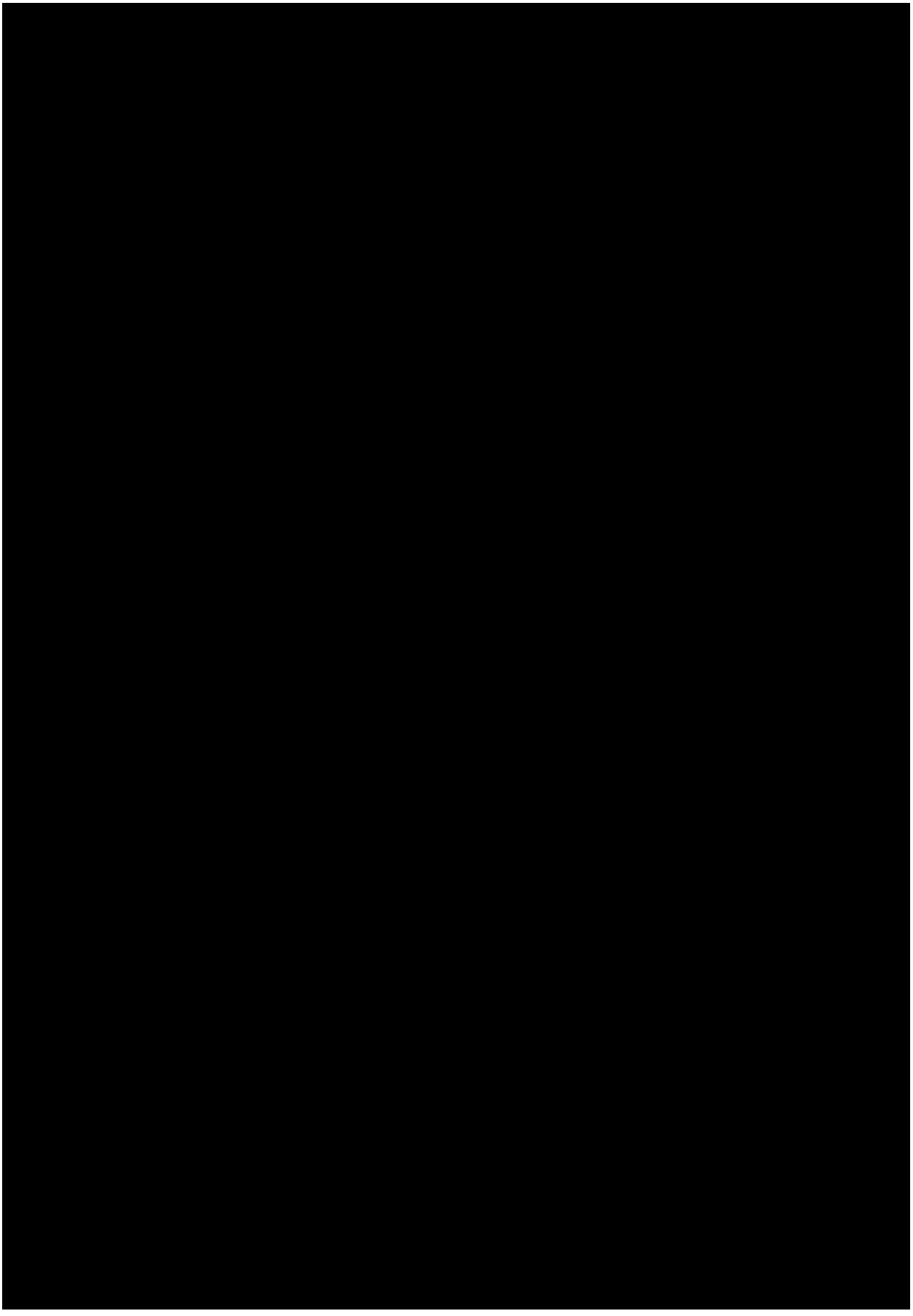
1.2 Study objectives and endpoints

In the table below and throughout this SAP Month 6 is equivalent to Week 24, and Month 12 is equivalent to Week 52. Also, all analysis is planned for initially assigned treatment where initially assigned treatment is refers to randomized treatment.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the superiority of subcutaenous erenumab compared to oral prophylactic(s) on sustained benefit defined as % subjects completing one-year on the initially assigned treatment and achieving at least a 50% reduction from baseline in monthly migraine days at month 12.	• Proportion of subjects who complete initially assigned treatment and achieve at least 50% reduction from baseline in monthly migraine days at Month 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of erenumab compared to oral prophylactic(s) on overall subject retention defined as % subjects completing study on the initially assigned treatment	• Proportion of subjects completing the study at Month 12 on the initially assigned treatment
• To evaluate the effect of erenumab compared to oral prophylactic(s) on the change from baseline in monthly migraine days during the treatment period	• Cumulative average change from baseline on the monthly migraine days during the treatment period for the subjects on initially assigned treatment (Months 1-12)
• To evaluate the effect of erenumab compared to oral prophylactic(s) on the subject's assessment of the change in clinical status since the start of treatment as measured by the Patients' Global Impression of Change (PGIC) Scale	• Proportion of responders (PGI-I score >= 5) as measured by PGIC at month 12 for subjects completing the treatment period at Month 12 on initially assigned treatment

[redacted]



2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis or a designated CRO. The current version of SAS or R software or later available versions will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis of study data will be established after last subject completes or discontinues core phase that is when all subjects either complete week 52 on core phase or complete FU or discontinue early prior to week 52. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of center: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

2.1.1.1 Study treatment

Subjects will be randomized to one of the following treatment groups:

- Erenumab labelled as AMG334 (70mg or 140mg): pre-filled 1mL syringes (PFS) containing 70mg/1mL of AMG334. Note: if and when 140mg/1mL PFS become available, the dose may be administered by a single injection.
- Comparator: locally approved oral prophylactic migraine medication.

For this trial, study treatment refers to AMG334 or oral prophylactics as assigned to a subject at randomization.

Unless otherwise specified, analysis will be presented by initially assigned treatment i.e. randomized treatment.

2.1.1.2 Study dates

- **Date of first administration study treatment**

The date of first administration of study treatment is derived as the date on which a subject is administered the first nonzero dose of study treatment following randomization, which may be the same day or after the randomization date. For subjects who are randomized but not dosed with study treatment after randomization, date of first administration of study treatment is considered missing.

- **Date of last administration of study treatment**

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered.

2.1.1.3 Study day

Study Day 1 is defined as the first dose date of study treatment during initially assigned treatment period. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization. Also, for subjects who are randomized but not dosed during initially assigned treatment period and received dose in switched period, 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.

The study day will be displayed in the data listings.

2.1.1.4 Baseline

The baseline period for efficacy analysis 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 subject reported outcome (PRO) and safety (including Columbia-Suicide Severity Rating Scale (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 value obtained on the day of the randomization (Day 1, Visit 101), or on an earlier visit (scheduled or unscheduled) which is the closest to Visit 101, if Visit 101 is missing or the assessment was not done at baseline.

Baseline weight and height are taken from vital signs screening visit.

eCSSRS is collected at screening or before randomisation and patients should complete "lifetime assessment eCSSRS questionnaire" at screening and if need arises during the course of the trial complete "since last contact eCSSRS questionnaire". Hence, we do not have "Evaluation timeframe" (TMFRM) variable collected and baseline eCSSRS will correspond to the last evaluable measurement prior to the first administration of the study drug, irrespective of re-screening. For this analysis, each subject can only be counted once for each event. However, a subject can be counted in several different events.

2.1.1.5 Post-baseline measurement

Post baseline measurements are defined as those assessments after the start of study treatment.

2.1.1.6 Visit remapping and assessment windows

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. Also note that month 6 is equivalent to week 24, and month 12 is equivalent to week 52.

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

Table 2-1 Study visit windows

Study visit	Target Day	Study Day
Baseline	Please refer to Section 2.1.1.4.	
Week 4	28	16-43

Week 8	56	44-71
Week 12	84	72-99
Week 16	112	100-127
Week 20	140	128-155
Week 24	168	156-183
Week 28	196	184-198
Week 32	224	199-239
Week 36	252	240-267
Week 40	280	268-295
Week 44	308	296-323
Week 48	336	324-351
Week 52	364	352-379
Safety follow up	Safety follow-up should be excluded from the analysis visit windows described above and summarized under 'safety follow-up' for safety analyses only. Refer to Table 2.2.	

Note: xx: target day then study day window: (xx-12 days) up to (xx+ 15 days)

For efficacy parameters: If more than one visit (including the unscheduled visits) fall within the same defined window with non-missing measurements, scheduled visit will be used regardless of the distance from the target day. Unscheduled visit will only be used when there is no measurement from scheduled visit in the defined window. The closest visit to the target day among the same type of visit (i.e., closest of all scheduled visits or if no scheduled visits, closest of all unscheduled) will be considered for analysis. If two assessment dates are equidistant from the target date, the latter assessment will be considered for analysis. The exception is an assessment at early study withdrawal visits along with another assessment within a window. In such cases the early-withdrawal assessment will be used.

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

Table 2-2 Study intervals for safety analysis

	Start time point	**End time point**

Core phase	Treatment start date	1. Subject completes 52 weeks on core phase treatment i.e. if trt disposition reason is "COMPLETED" on DS domain a. If subject does not enter PTA phase then use week 52 visit date b. If subject enters PTA phase then i. Subject enters PTA on week 52 visit date then use a day prior to week 52 visit date ii. Subject enter PTA phase after week 52 then use week 52 visit date 2. Subject completes 52 weeks on core phase but discontinues treatment early i.e. core phase treatment disposition reason is not equal to "COMPLETED on DS domain a. If subject does not enter PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day ii. if week 52 visit date < = treatment end date plus 27/1 day then use week 52 visit date b. If subject enters PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day ii. if week 52 visit date < = treatment end date plus 27/1 day then use a day prior to first dose in PTA phase 3. Subject discontinues treatment early and does not complete 52 weeks on core phase i.e. core phase trt disposition reason is not equal to "COMPLETED on DS domain and Week 52 visit date is not available in SV domain and study disposition reason is equal not to "COMPLETED" on DS domain a. If treatment disposition date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day b. If treatment disposition date < = treatment end date plus 27/1 day then use treatment disposition date
Safety follow up	Core phase end plus 1 day	a) If subject does not enter PTA phase then use study disposition date; b) If subject enters PTA phase then use a day prior to first dose in PTA phase
PTA phase	First erenumab injection	1. If subject completes 52 weeks on PTA phase then use min (trt disposition or study disposition date)

	date in PTA phase	2. If subject discontinues prior to completing 52 weeks on treatment in PTA phase i.e. treatment disposition reason is not equal to "COMPLETED" on DS domain then a. If treatment disposition date > treatment end date plus 27 day then use trt end date plus 27 day b. If treatment disposition date < = treatment end date plus 27 day then use trt disposition date

	Start time point	**End time point**
Initially assigned treatment (IAT) period (core phase)	Treatment start date	1. Subject completes 52 weeks on IAT i.e. core phase treatment disposition reason is "COMPLETED" and week 52 visit date is non-missing in SV domain and date of switching is missing on DS domain a. If subject does not enter PTA phase then use week 52 visit date from SV domain b. If subject enters PTA phase then i. Subject enters PTA on week 52 visit date then use a day prior to week 52 visit date ii. Subject enter PTA phase after week 52 then use week 52 visit date 2. Subject completes 52 weeks on core phase but permanently discontinues IAT early i.e. trt disposition reason is not equal to "COMPLETED" on DS domain and week 52 visit date is non-missing in SV domain and date of switching is missing on DS domain a. If subject does not enter PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day ii. if week 52 visit date < = treatment end date plus 27/1 day then use week 52 visit date b. If subject enters PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day

		ii. if week 52 visit date < = treatment end date plus 27/1 day then use a day prior to first dose in PTA phase 3. Subject does not complete 52 weeks on study and permanently discontinues IAT i.e. week 52 visit date is missing in SV domain and date of switching is missing on DS domain and core phase treatment disposition reason is not equal to "COMPLETED in DS domain then use min(trt disposition date, trt end date plus 27/1 day) 4. Subject switches IAT then use day prior to date of first switch on DS domain
Switched treatment period (core phase)	Date of first switch on DS domain	1. Subject completes 52 weeks on switched treatment i.e. core phase treatment disposition reason is "COMPLETED" and week 52 visit date is non-missing in SV domain a. If subject does not enter PTA phase then use week 52 visit date from SV domain b. If subject enters PTA phase then i. Subject enters PTA on week 52 visit date then use a day prior to week 52 visit date ii. Subject enter PTA phase after week 52 then use week 52 visit date 2. Subject completes 52 weeks on core phase but discontinues switched treatment early i.e. core phase trt disposition reason is not equal to "COMPLETED on DS domain a. If subject does not enter PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day ii. if week 52 visit date < = treatment end date plus 27/1 day then use week 52 visit date b. If subject enters PTA phase i. if week 52 visit date > treatment end date plus 27/1 day then use treatment end date plus 27/1 day ii. if week 52 visit date < = treatment end date plus 27/1 day then use a day prior to first dose in PTA phase 3. Subject does not complete 52 weeks on switched treatment i.e. core phase trt disposition reason is not

		equal to "COMPLETED" on DS domain and week 52 visit date is missing in SV domain then use min(treatment disposition date, treatment end date plus 1 day)

Note: DS: Disposition domain; SV:Visit domain; IAT: Initially assigned treatment

Monthly interval for efficacy endpoints (from ediary)

Monthly efficacy measurements will be calculated based on the subject's starting dose and visit schedule defined below using eDiary data collected from beginning of the baseline phase (week -4 visit) up to week 52 visit if subjects do not have safety follow up visit. For subjects with safety follow up, consider data up to the safety follow-up visit. The algorithm remains the same for initially assigned treatment and switched treatment. ediary data will be collected during core phase only and will not be collected during extension phase.

Table 2-3 Study intervals for efficacy endpoints – Erenumab and Oral prophylactics

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
Treatment Period	Week 4	Study day 1	• Week 4 visit date - 1 • Study day 1 + 27 days if Week 4 visit is missed Note: if day 1 dose is the last dose subject received, the rest of monthly rates during treatment period will be calculated based on consecutive 28-day interval beginning
	Week 8	• Week 4 visit date • Week 4 analysis visit end date + 1 day if Week 4 visit is missed	• Week 8 visit date – 1 • Week 4 analysis visit start date + 27 days if Week 8 visit is missed
	Week 12	• Week 8 visit date • Week 8 analysis visit end date + 1 day if Week 8 visit is missed	• Week 12 visit date – 1 • Week 12 analysis visit start date + 27 days if Week 12 visit is missed
	Week 16	• Week 12 visit date	• Week 16 visit date – 1

		• Week 12 analysis visit end date + 1 day if Week 12 visit is missed	• Week 16 analysis visit start date + 27 days if Week 16 visit is missed
	Week 20	• Week 16 visit date • Week 16 analysis visit end date + 1 day if Week 16 visit is missed	• Week 20 visit date – 1 • Week 20 analysis visit start date + 27 days if Week 20 visit is missed
	Week 24	• Week 20 visit date • Week 20 analysis visit end date + 1 day if Week 20 visit is missed	• Week 24 visit date – 1 • Week 24 analysis visit start date + 27 days if Week 24 visit is missed
	Week 28	• Week 24 visit date • Week 24 analysis visit end date + 1 day if Week 24 visit is missed	• Week 28 visit date – 1 • Week 28 analysis visit start date + 27 days if Week 28 visit is missed
	Week 32	• Week 28 visit date • Week 28 analysis visit end date + 1 day if Week 28 visit is missed	• Week 32 visit date – 1 • Week 32 analysis visit start date + 27 days if Week 32 visit is missed
	Week 36	• Week 32 visit date • Week 32 analysis visit end date + 1 day if Week 32 visit is missed	• Week 36 visit date – 1 • Week 36 analysis visit start date + 27 days if Week 36 visit is missed
	Week 40	• Week 36 visit date • Week 36 analysis visit end date + 1 day if Week 36 visit is missed	• Week 40 visit date – 1 • Week 40 analysis visit start date + 27 days if Week 40 visit is missed
	Week 44	• Week 40 visit date • Week 40 analysis visit end date + 1 day if Week 40 visit is missed	• Week 44 visit date – 1 • Week 44 analysis visit start date + 27 days if Week 44 visit is missed
	Week 48	• Week 44 visit date • Week 44 analysis visit end date + 1 day if Week 44 visit is missed	• Week 48 visit date – 1 • Week 48 analysis visit start date + 27 days if Week 48 visit is missed
	Week 52	• Week 48 visit date • Week 48 analysis visit end date + 1 day if Week 48 visit is missed	• MIN (Week 48 visit date + 27, EoS) MIN (Week 52 analysis visit start date + 27 days if Week 48 visit is missed , EoS)

Where EoS date is the date of the end of study visit.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure. Tabulations of demographic and baseline characteristics, disposition, and important protocol deviations (PD) will utilize FAS.

The Safety Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

Screen failures will not be included in any analysis sets.

Please refer to appendix 5.4 for Rules of exclusion criteria of analysis sets**.**

[redacted]

2.3 Subject disposition, demographics and other baseline characteristics.

2.3.1 Subject disposition

Subject disposition will be summarized on FAS. The number and percentage (based on the number of subjects within each randomized treatment arm) of subjects who completed / discontinued the study will be displayed by initially assigned treatment and overall. The primary reason for premature study discontinuation will be displayed by initially assigned treatment and overall. The core phase completers are defined as subjects who either complete week 52 on study or complete safety follow up visit.

Treatment completion will be summarized in the same manner as subject disposition. The number and proportion of subjects, who complete the study treatment or discontinue the study treatment prematurely along with the primary reason for study drug discontinuation will be presented.

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

Screen Failures: The total number of subjects screened and the number of subjects screened, but not randomized (discontinued prior to screening or baseline phase completion) will be summarized, including the reason for screening failure. Data on screen failures will also be presented in listings.

Analysis sets: The number of subjects within each of the analysis sets used in the study will be summarized.

The impact of COVID-19 pandemic on study subjects with respect to randomization, study and treatment discontinuations, protocol deviations and dose interruptions will be assessed and summarized for pre- and during COVID-19 phases. The pandemic phase will be defined based on start date of pandemic. For Italy start date of pandemic will be used as 23Feb2020 and for rest of the world start date of pandemic will be used as 01March2020.

2.3.2 Protocol deviations

The number of subjects with PDs according to the applicable standard operating procedures (SOP-7035752 V4.0) will be presented. 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 PDs leading to data exclusion from analysis sets will be listed.

In addition to the pre-defined standard PD terms, Novartis has also defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, patient concerns, etc.) to the COVID-19 pandemic in line with “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency” (March 2020) and “Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic” (April 2020) from EMA as listed below. The following deviations related to the COVID-19 pandemic will be summarized.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Patient discontinuation due to COVID-19 situation
- Other study specific PDs

A cross-tabulation of COVID-19 related PD vs. corresponding relationship will also be produced.

2.3.3 Demographic variables and other baseline characteristics

Demographic variables and other baseline characteristics including previous migraine treatments will be summarized for each initially assigned treatment group and for all subjects (total) using FAS.

At baseline (end of the baseline period; see Section 2.1.1.4, baseline definition), the following demographic and baseline characteristics will be summarized:

- Categorical variables:
  - Age (< 65 years, >= 65 years)
  - Sex
  - Ethnicity
  - Race
  - Acute headache medication (none, migraine-specific/non migraine-specific) during baseline phase
  - Strata: Prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during screening / baseline period: 1 treatment failure (TF1) vs 2 treatment failures (TF2)
  - 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)
- Continuous variables:
  - Age
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI, kg/m2)
  - Age at onset of migraine (years)
  - Disease duration of migraine with or without aura (years)
  - Monthly migraine days during baseline phase
  - Monthly migraine attacks during baseline phase
  - Monthly headache days during baseline phase
  - Monthly acute migraine-specific medication use in days during baseline phase
  - Monthly acute headache medication use in days during baseline phase

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables for each initially assigned 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.

Summary of prior migraine prophylactic treatment and reasons for discontinuation will be presented by treatment group.

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)

The impact of COVID-19 pandemic on subject demographics will be assessed by summarizing data for subjects randomized in pre- and during- COVID-19 phases. The pandemic phase will be defined based on either start date of pandemic as a global cutoff or by region.

2.3.4 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 initially assigned treatment group and for all participants (total) using FAS. The SOCs will be presented in alphabetical order. Preferred terms will be ordered within each SOC by decreasing order of frequency in the AMG334 arm.

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. Descriptive statistics will be produced to describe the exposure to initially assigned study drugs as well as for switched drugs.

A listing of dose administration with the initially assigned study treatments along with switched drugs will be provided.

The duration of exposure since first injection/dose will be summarized descriptively by study treatment.

Additionally, the number and percentage of subjects with dose change and reason for dose change will be summarized by treatment group.

Summary of subjects switching to oral prophylactics from initially assigned study treatment with reasons for switching will be presented.

2.4.2 Prior, concomitant and post therapies

The number and percentage of participants receiving prior/concomitant medications, and significant non-drug therapy in SAF population will be summarized by Anatomic Therapeutic Chemical classification [ATC] (coded by WHO), preferred term and by treatment group. Summary of concomitant medications will be provided by initially assigned and switched drugs separately. As per B3 format there will be one record for each CMTRT variable value and the newly created CMCLS variable in SDTM.CM contains only lowest ATC class.

Use of acute headache medication during the baseline phase and the treatment period will be summarized by category of medication for each treatment group.

Use of alternative migraine therapies during the baseline phase 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 6.2.2) and given during the conduct of the study will be addressed by the currently planned outputs of the Protocol deviations.

No separate outputs will be produced related to prohibited medications.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary aim of the study is to evaluate the effect of AMG334 vs oral cycling on the net benefit, a measure of sustained long-term benefit in these two treatment paradigms of migraine prophylactic agents.

The primary endpoint of the study is the proportion of subjects achieving net benefit, defined as completion of one year on the initially assigned treatment and achieving at least a 50% reduction from baseline in monthly migraine days in the last month (week 52).

Subjects who complete one year on the initially assigned treatment and achive at least a 50% reduction from baseline in monthly migraine days in the last month (week 52) are considered as responders for the purpose of primary endpoint.

A subject will be considered as a non-responder if

- a subject does not complete one year on the initially assigned treatment or

- a subject does not achieve at least 50% reduction from baseline in monthly migraine days or

- does not satisfy both of the above conditions

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

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analyses will compare the proportion of subjects in FAS who achieve a net benefit (defined in previous section) between AMG334 vs oral cycling.

Below is the hypothesis to be tested for primary analysis:

Null hypothesis: In subjects with episodic migraine, the AMG334 treatment group has the same effect as oral prophylactics group, in terms of the net benefit i.e. net benefit odds ratio =1.

Alternative hypothesis: In subjects with episodic migraine, the AMG334 treatment group is different from oral prophylactics group, in terms of the net benefit i.e. net benefit odds ratio ≠ 1.

Randomization will be stratified by prior prophylactic migraine medication treatment failure (due to insufficient efficacy or poor tolerability) reported during screening / baseline period: 1 treatment failure (TF1) vs 2 treatment failures (TF2).

A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) will be used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment. The p-value of the test, and the estimated odds ratio between AMG334 and active comparator, as well as its 95% confidence interval, will also be reported.

2.5.3 Handling of missing values/censoring/discontinuations

Subjects with missing monthly migraine day data at week 52 of treatment, and subjects that discontinue initially assigned treatment prior to the week 52 visit will be imputed as non-responders (not achieving a net benefit).

2.5.4 Sensitivity / Supplementary analyses

For the primary endpoint sensitivity analyses under missing at random (MAR) assumption will be performed. Multiple imputation (MI) techniques applying MAR approach will be used to assess the impact of missing values on the interpretation of the results from primary analysis.

Since primary endpoint is composite, missing data imputation can be used only when subject completes 52 weeks on initially assigned treatment and has missing MMD value at week 52. To assess impact of these missing values on interpretation of results will be analyzed using below given sensitivity analyses:

1.1 Sensitivity analysis I: This data will be multiply imputed using the MAR assumption. The analysis method remains same as primary endpoint analysis. The multiple imputation model will be based on similar subjects in the same treatment arm.

Points to note:

- Due to composite primary endpoint off-treatment data cannot be used for primary analysis.

If MMD data is available say up to week 36 then data will be imputed from week 40 till week 52.

Table 2-4 Summary of primary endpoint and analysis methods

Endpoint	Analysis	Imputation
The proportion of subjects achieving net benefit, defined as completion of one year on the initially assigned treatment and achieving at least a 50% reduction from baseline in monthly migraine days in the last month (week 52)	Primary analysis: A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) will be used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment.	No imputation.
	Sensitivity analysis: A Cochran-Mantel-Haenszel (CMH) test stratified by number of previous treatment failures (1 vs. 2) will be used under a 2-sided significance level of 0.05 to evaluate the association between the net benefit rate and the treatment.	Missing MMD data will be imputed using multiple imputation under MAR assumption. The multiple imputation model will be build based on similar subjects in the same treatment arm.

Supplementary analysis to assess impact of COVID-19 pandemic:

The primary endpoint is composite and one component is the completion of intially assigned treatment for 52 weeks. The impact of COVID-19 pandemic will be assessed by following analysis:

a) The summary of discontinuations for initially assigned treatment and last available switched treatment will be provided by due to COVID-19 and non-COVID-19 reasons.

b) In light of COVID-19 pandemic and its potential impact on treatment effect, an important scientific question of interest to address is to estimate the treatment effect had COVID-19 pandemic not occurred.

- The target population is defined by all subjects in the study who received at least one dose of study treatment.
- The variable of interest is reduction in MMD from baseline to week 52 on initially assigned treatment.
- The intercurrent event describes how events that may occur after randomization are considered when assessing the treatment effect

- Discontinuation of initially assigned treatment due to non COVID-19 related reason: Subjects who discontinue due to non COVID-19 related reasons prior to week 52 will be considered as non-responders.
- Discontinuation of initially assigned treatment due to COVID-19 related reason (hypothetical strategy): All MMD data up to discontinuation of initially assigned treatment will be used. Ignore all the MMD data after treatment discontinuation and impute MMD data till week 52 using missing at random approach (MAR). The discontinuation reason due to COVID-19 pandemic will be identified from the defined COVID-19 protocol deviations.

- The summary measure is the odds ratio between two treatment arms. It will be obtained by CMH test similar to primary endpoint analysis. A subject will be responder if subject has at least 50% reduction in MMD from baseline at week 52 and completed initially assigned treatment for one year; otherwise subject will be a non-responder.

c) Summary statistics will be provided for change from baseline in MMD for subjects with COVID-19 infection separatele for before and after COVID-19 infection period. The information about whether subject has COVID-19 infection is collected on AE CRF.

2.5.5 Sensitivity analyses with corrected stratification factor

The sensitivity analyses will be performed by deriving the correct stratification factor for subjects who have been mis-stratified. Such subjects can be identified by PD criteria as specified below:

- For subjects with a INCL06 PD = 0 treatment failure (TF) (These subjects should be excluded from analysis as not in strata 1 or 2)
- For Subjects with a EXCL04 PD = 3 (or greater) TF (These subjects should be excluded from analysis as not in strata 1 or 2)
- For subjects with assigned (IRT) strata of TF1 (but have a TRT07 PD present), correct strata = TF2
- For subjects with assigned (IRT) strata of TF2 (but have a TRT07 PD present), correct strata = TF1

Analysis for primary endpoint will be repeated using corrected strata.

2.5.6 Sensitivity analyses excluding subjects taking non-approved medications or prohibited medications or polytherapy

Subjects who have taken non-approved medications or prohibited medications or polytherapy (data is identified using protocol deviations) during initially assigned treatment are excluded from sensitivity analysis for primary endpoint. The analysis for primary endpoint will be repeated after excluding these subjects.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary efficacy variables are as listed below and respective definitions of responders / non-responders are added in subsequent sections:

- Proportion of subjects completing the study at Month 12 on the initially assigned treatment
- Cumulative average change from baseline in monthly migraine days during the treatment period week 4 to week 52 (Months 1-12)
- Proportion of responders as measured by PGIC at month 12 on the initially assigned treatment

2.7.2 Statistical hypothesis, model, and method of analysis

Analysis of above mentioned secondary endpoint will utilize the FAS.

- Proportion of subjects completing the study at Month 12 on the initially assigned treatment

The responders and non-responders for this endpoint are defined as given below:

Subjects who complete one year on the initially assigned treatment are considered as responders.

A subject will be considered as a non-responder if a subject do not complete one year on the initially assigned treatment. This includes (a) subjects who discontinue initially assigned treatment permanently (b) subjects who switched to oral prophylactics other than initially assigned treatment.

In subjects with episodic migraine, the proportion of subjects completing 12 months on initially assigned treatment will be compared between the AMG334 treatment group and oral prophylactics group, in terms of odds ratio. Thus, below hypothesis will be tested between initially assigned treatment groups:

Null hypothesis: Odds ratio =1 vs Alternative hypothesis: Odds ratio $\neq$ 1.

A Cochran-Mantel-Haenszel (CMH) test stratified by number of prior prophylactic migraine medication failures (1 vs. 2) will be used under a 2-sided significance level of 0.05. The p-value of the test, and the estimated odds ratio between AMG334 and active comparator, as well as its 95% confidence interval, will also be reported.

- Cumulative average change from baseline on the monthly migraine days during the treatment period week 4 to week 52 (Months 1-12)

The average of monthly migraine days will be obtained cumulatively every 4 weeks across 52 weeks (e.g. at week 8 the average will be based on data from week 1 to week 8; at week 12 the average will be based on week 1 to week 12 and so on). The cumulative average change from baseline in monthly migraine days will be derived using difference between cumulative average of each month and baseline monthly migraine days.

The change from baseline will be analyzed using a linear mixed effects repeated measures model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit. If applicable, in the repeated statement,

an unstructured covariance structure is assumed. Least squares means (LSMs) for each treatment group and its associated 95% confidence intervals, difference of LSMs compared to SoC treatment group and the associated 95% confidence interval of the differences, as well as the nominal two-sided p-values, will be tabulated by visit and treatment.

- Proportion of responders as measured by PGIC at month 12 on the initially assigned treatment

The Patients' Global Impression of Change (PGIC) is a global assessment by the subject of the change in clinical status since the start of treatment. The PGIC is assessed periodically through the treatment period and at the end of the treatment period. The PGIC ratings are as follows:

1 = No change (or condition is worse)

2 = Almost the same, hardly any change at all

3 = A little better, but no noticeable change

4 = Somewhat better, but the change has not made any real difference

5 = Moderately better, and a slight noticeable change

6 = Better, and a definite improvement that has made a real and worthwhile difference

7 = A great deal better, and a considerable difference that has made all the difference

Subject will be considered as responder if PGIC score is 5, 6, or 7 at month 12 on initially assigned treatment. Subject will be considered as non-responder if subject does not complete 12 months on initially assigned treatment or if subject does not have score 5, 6 or 7 at month 12.

Proportion of responders based on PGIC score at month 12 will be analyzed same as that of the primary endpoint.

2.7.3 Handling of missing values/censoring/discontinuations

Subjects with missing PGIC score data at week 52 of treatment, and subjects that discontinue initially assigned treatment prior to week 52 will be imputed as non-responders (not achieving a net benefit).

For MMD values there will not be any missing data imputation.

2.7.4 Sensitivity / Supplementary analyses

Sensitivity analysis for secondary endpoint:

To assess impact of missing values on interpretation of results sensitivity analyses will be performed for secondary endpoint “Cumulative average change from baseline on the monthly migraine days during the treatment period week 4 to week 52 (Months 1-12)”. Missing MMD data will be imputed using multiple imputation under MAR assumption. The multiple imputation model will be build based on similar subjects in the same treatment arm.

Supplementary analysis for secondary endpoint:

The supplementary analysis for secondary endpoint “Cumulative average change from baseline on the monthly migraine days during the treatment period week 4 to week 52

(Months 1-12)" is defined considering hypothetical strategy for subjects who are discontinuing early or switching initially assigned treatment.

This analysis will evaluate what if subject would have continued initially assigned treatment for 52 weeks

- if subject discontinues initially assigned treatment and does not switch to other SoC then missing data after discontinuation will be imputed using MAR. This is because we are considering what if subject would have continued initially assigned treatment.

- if subject switched to other SoC drug then for switched period until week 52 data will be considered as missing and such missing data will be imputed using MAR.

Points to note:

- The off-treatment MMD data and MMD data from switched drug cannot be used for analysis since it will not represent MMD values under initially assigned treatment.
- If MMD data is available say up to week 36 then data will be imputed from week 40 till week 52.

Table 2-5 Summary of secondary efficacy endpoints and analysis methods

Endpoint	Analysis	Imputation
Proportion of subjects completing the study at Month 12 on the initially assigned treatment	A Cochran-Mantel-Haenszel (CMH) test stratified by number of prior prophylactic migraine medication failures (1 vs. 2) will be used under a 2-sided significance level of 0.05.	No imputation.
Cumulative average change from baseline on the monthly migraine days during the treatment period week 4 to week 52 (Months 1-12)	The change from baseline will be analyzed using a linear mixed effects repeated measures model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit.	No imputation.
	Sensitivity analysis: The change from baseline will be analyzed using a linear mixed effects repeated measures model including treatment group, baseline	Missing MMD data will be imputed using multiple imputation under MAR assumption. The multiple imputation model will be

	value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit.	build based on similar subjects in the same treatment arm.
	Supplementary analysis: The change from baseline will be analyzed using a linear mixed effects repeated measures model including treatment group, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment group with scheduled visit. This analysis will be performed considering hypothetical strategy for subjects who are discontinuing early or switching initially assigned treatment.	Intermittant missing MMD data will be imputed using multiple imputation under MAR assumption. To get imputed data for entire treatment period: - if subject discontinues initially assigned treatment and does not switch to other SoC then missing data after discontinuation will be imputed using MAR. - if subject switched to other SoC drug then for switched period until week 52 data will be considered as missing and such missing data will be imputed using MAR.
Proportion of responders as measured by PGIC at month 12 on the initially assigned treatment	A Cochran-Mantel-Haenszel (CMH) test stratified by number of prior prophylactic migraine medication failures (1 vs. 2) will be used under a 2-sided significance level of 0.05.	No imputation.

2.8 Safety analyses

For safety endpoints, all randomized subjects who received at least one dose of study treatment will be analyzed based on the actual treatment received (defined as the randomized treatment unless a subject has received the incorrect treatment during the treatment period).

Unless otherwise specified, all safety summaries and listings will be provided by initially assigned treatment group.

Missing data will not be imputed for safety endpoints.

2.8.1 Adverse events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT All adverse event tables will be summarized by treatment group.

For all AEs tables presented by SOC and PT (and grade), the SOCs will be presented in alphabetical order and PTs will be ordered within the SOC by decreasing order of frequency in the AMG334 treatment group. AE tables by preferred term only will be sorted in descending order of frequency in the AMG334 treatment group. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Separate summaries by initially assigned treatment will be provided for study medication related adverse events, death, serious adverse events, adverse events leading to discontinuation and adverse events leading to dose adjustment.

All AEs, deaths, serious adverse events (SAE) and AEs leading to permanant study treatment discontinuation will be listed seperately.

Summary of all AEs by SOC, PT and severity will also be provided by switched treatment. A separate listing of all AEs by initially assigned treatment and switched treatment will be provided.

Summary of treatment emergent AEs will be provided for COVID-19 and hypertension data by SMQ levels.

Summary of treatment emergent AEs will be provided for constipation by CMQ and corresponding preferred term.

Summary of exposure adjusted subject incidence rates for treatment emergent AEs and SAEs will be provided by primary system organ class and preferred terms.

2.8.1.1 Clinical trial safety disclosure (CTSD) reports

For clinicaltrials.gov and EuDRACT, two required tables on treatment emergent adverse events (TEAE) which are not SAEs with an incidence greater than a certain threshold based on the final database and on treatment emergent serious adverse events and SAEs suspected to be related to study drug will be provided by system organ class and PT on the safety set population.

If for a same subject, several consecutive AEs (irrespective of study drug causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

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

2.8.3 Laboratory data

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

Subject incidence of liver enzyme abnormalities (including AST, ALT, Total Bilirubin (TBL) and Alkaline Phosphatase (ALP)) will also be summarized by treatment group.

Shift from baseline for some liver enzyme level categories (specified in the Tables, Figures and Listings (TFL) shells; for e.g. ALP<=1 x ULN) will also be provided by initially assigned treatment group.

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

Parameters measured in the urine at screening including urine drug tests will be listed.

Table 2-6 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 AMG334 exposure are listed.

2.8.4 Other safety data

2.8.4.1 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 2-7) will be summarized by treatment group and by visit for initially assigned treatment.

ECG measurements with abnoramlities will be listed by treatment.

However, since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, these data are not expected to be useful for meta-analysis with data from other trials.

Table 2-7 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 (%)		

2.8.4.2 Vital signs

The vital signs data is collected prior to dosing. 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 initially assigned treatment.

The number and percentage of subjects with clinically relevant abnormality (see Table 2-8) at any post-baseline visit will be presented for initially assigned treatment. This vital sign data will also be listed.

Table 2-8 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

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

The number and percentage of subjects reporting any suicidal ideation or any suicidal behavior at baseline and any time post-baseline will be summarized descriptively by treatment group and all subjects. Refer to section 5.9 for details on scores.

2.9 Pharmacokinetic endpoints

Not Applicable.

2.10 PD and PK/PD analyses

Not Applicable.

2.11 Patient-reported outcomes (PRO)

PRO based on PGIC score is a secondary endpoint and it is detailed in section 2.7. [redacted]

2.12 Biomarkers

Not Applicable.

[redacted]

2.14 Interim analysis

Not Applicable.

3 Sample size calculation

The sample size calculation is based on the primary variable, rate of net benefit. The details of hypothesis testing are described in section 2.5.2.

A 2-sided test with significance level 0.05, and a 2:1 randomization ratio are considered. A sample size of 591 (394 erenumab arm; 197 control arm) is required to achieve 90% power to reject the odds ratio of 1 set by the null hypothesis when the odds ratio is actually 2, and success rate in control arm is 0.18.

An odds ratio of 2 and control rate of 0.18 is based on more conservative assumptions for rate of net benefit than observed previously (for erenumab in studies NCT02456740, NCT01952574, and oral cycling in Hepp et al 2017, Shei et al 2015), resulting in a rate difference of 12%. Sample size calculations were done using PASS 11 and Cochran-Mantel-Haenszel test was used.

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 AE / 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:

Table 5-1 Imputation of AE/Concomitant dates

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to Study Day 1 if an adverse event starts the same year and month as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month	01Jan	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF

	Day/Month/Year	No imputation	

5.1.2 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.

5.1.3 Post therapies date imputation

NA.

5.1.4 Other imputations

5.1.4.1 eDiary data

The eDiary includes the following clinical outcome assessments:

• Incidence of headache (ie, migraine with or without aura or non-migraine headache)

• Time of onset of headache

• Time of resolution of headache

• Pain severity per headache

• Symptoms (eg, nausea, vomiting, photophobia, phonophobia)

• Presence of aura

• Use of acute medication during aura or to treat headache

as well as, patient-reported outcomes (PROs) measures.

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

1. For monthly intervals with ≥ 14 days of eDiary days (including retrospective eDiary days) in each interval**:**

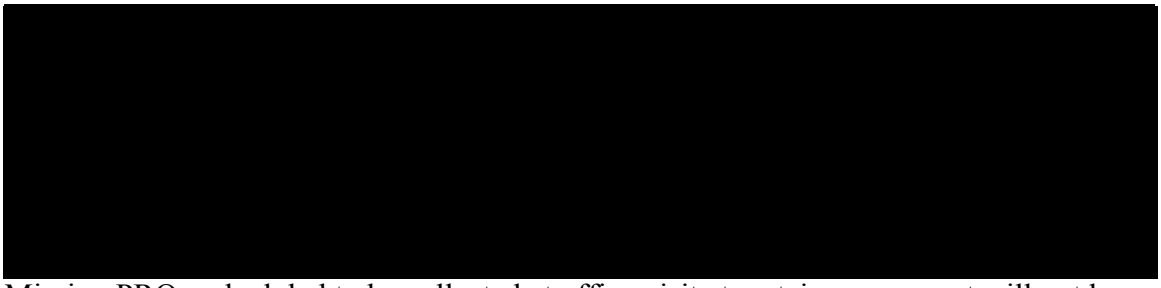
a) Monthly frequency measurements (including migraine days, headache days, migraine attacks, [redacted]) will be prorated to 28-day equivalents**.** Prorated result does not need to be rounded.

[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.

Table 5-2 Rules for handling missing and incomplete eDiary data

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



Missing PROs scheduled to be collected at office visit at certain assessment will not be imputed.

5.1.4.2 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.

5.1.4.3 Missing Post-baseline Evaluation

Primary analysis will be conducted using the stratified CMH test on observed data without imputation (see Section 5.5.1).

In the sensitivity analysis on primary and secondary efficacy endpoints, missing continuous efficacy endpoints will be handled using multiple imputation (MI) with assumption of missing at random (MAR). See below for more details.

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 52) or if substantial 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 ssumptions, will be performed as deemed appropriate and necessary.

5.1.4.3.1 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.

5.1.4.3.2 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, stratification factor, sex, race group, age group, BMI group (subjid trt01pn mmstratn sexn race agemedn bmimedn) from ADBS, ADSL.
- Obtain number of prior migraine prophylactic treatment failed, baseline disease duration group (prophfln durmedn) from ADBS.
- Obtain avisitn paramcd param aval avalc base chg dtype from ADATTACK
- Perform minor data manipulation, as required, to reinstate the missing data, eg if dtype="LOCF" then aval=., avalc=” “ and chg=.

- Ensure the baseline values are included in the chg variables before data transformation, eg if avisitn=2000 is baseline then chg=base;
- Transpose all the data so you have one observation per subject and each visit becomes a variable within its own right, eg rows where avisitn=2004, 2008, 2012 etc become the column week4, week8, week 12 etc.
- Impute the missing data for MAR according to the methods in next steps

MAR multiple imputations steps:

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

- FCS logistic is used for dichotomous variables (mmstratn sexn agemedn bmimedn prophgrp durmedn); discrim is used for categorical variables with more than 2 categories (race); regpmm is used for continuous variables (wk0, wk4, wk8,... wk52).
- wk4, wk8 , ... and wk52 represent the chg variable for each of the visits respectively, and wk0 is baseline.

MAR modeling step:

- For the primary endpoint, first, define 50% Responders based on imputed MMD data under the assumption of MAR.Then, use the same method as for primary variable - the stratified CMH test to get estimates for numbers of responders in each treatment group and odds ratio at week 52 for each dataset.
- For change from baseline in MMD it is used a linear mixed effects model on imputing data under the assumption of MAR. 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=2052/week52 data.

MAR 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 as shown below:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

5.3 Laboratory parameters derivations

NA.

5.4 Rule of exclusion criteria of analysis sets

The protocol deviations during screening, baseline and treatment periods are defined below (Table 5-3). The deviation ID, deviation code and it's corresponding text description are explained in Table 5-3. Subjects exclusion based on protocol deviations and non- protocol deviations criteria are in Table 5-4.

Table 5-3 Deviation Codes Description

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

Table 5-4 Patient 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*	Not randomized; No study drug taken

5.5 Statistical models

5.5.1 Primary analysis

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

H0: $\theta 1 \leq 1$ vs H1: $\theta 1 > 1$

where $\theta 1$ is the odds ratio of AMG334 over standard of care oral prophylactics.

After the missing data are imputed as non-response a Cochran-Mantel-Haenszel (CMH) test stratified by prior treatment failure=1 versus prior treatment failures=2 will be used under a significance level of 0.025, one-sided (0.05, two-sided) to evaluate the association between the 50% responder rate at month 12 and the treatment. The estimated common odds ratio, 95% confidence intervals and two-sided p-values will be reported.

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

The test can be implimented using SAS, PROC FREQ with options CMH, RELRISK, RISKDIFF under TABLE statement.

5.5.2 Secondary analysis

Follow same instructions as Section 5.5.1 for secondary analysis using CMH test.

Linear mixed models using repeated measurements:

The secondary endpoint of the study cumulative average change from baseline on MMD will be tested for AMG334 compared to standard of care oral prophylactics, respectively.

- Null Hypothesis: In subject with episodic migraine, the AMG334 treatment group is the same as SoC, in terms of the reduction from baseline in cumulative mean monthly migraine days in month 12
- Alternative Hypothesis : In subject with episodic migraine, the AMG334 treatment group is different as SoC, in terms of the reduction from baseline in cumulative mean monthly migraine days in month 12

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

The test can be implemented using SAS, PROC MIXED procedure.

5.6 Important derivations

- 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.

- Duration of exposure of study treatment

  For AMG334 calculation of exposure, dose date refers to receiving dose > 0, but can include partial doses. The duration of exposure for AMG334 is computed as of last injection of study drug + 27 days - date of first injection of study drug +1.

  For oral prophylactics arm calculation of exposure, dose date refers to receiving dose > 0. The duration of exposure for initially assigned treatment is computed as last dose date – First Dose Date + 1.

- Compliance with the eDiary

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

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

- 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.

- 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 5.7. A qualified migraine headache (IHS, 2013) is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria:

  1. ≥ 2 of the following pain features:
     - Unilateral
     - Throbbing
     - Moderate to severe
     - Exacerbated with exercise/physical activity
  2. ≥ 1 of the following associated symptoms:
     - Nausea and/or vomiting
     - Photophobia and phonophobia

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

- Monthly Migraine Days

  Number of migraine days between each analysis visit 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 5.1.4 (The same proration method will be applied for other efficacy endpoints thereafter).

- Duration of Migraine

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

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

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

- Achievement of at least a 50% reduction from baseline in monthly migraine days at month 12

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

- Migraine Attack

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

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

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

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

- Monthly Migraine Attacks

  Number of migraine attacks between each analysis visit. Monthly migraine attacks at baseline are the number of migraine attacks in baseline period. Days without eDiary data are handled by proration according to Section 5.1.4.

- Headache Day

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

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

- Monthly Headache Days

Number of headache days between each analysis visit. Monthly headache days at baseline are the number of headache days in baseline period. Days without eDiary data in each monthly interval are handled by proration according to Section 5.1.4.

[redacted]

- Response

  At least 50% [redacted] reduction from baseline in monthly migraine days.

- Cumulative Monthly Migraine Days

  Cumulative monthly migraine days during treatment period is the sum of qualified monthly migraine headache days during the entire treatment period normalized into the 28-day period. If eDiary compliance>=50% (definition in Section 5.6) then the cumulative monthly migraine days are calculated according to the formula:

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

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

- Change from baseline

When change from baseline is of interest, the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value; and

Percent change from baseline = change from baseline *100/ baseline value

The change from baseline in monthly efficacy measurement is the monthly efficacy measurement in the monthly interval prior to the given time point minus the baseline monthly efficacy measurement. Please, refer to the monthly intervals for efficacy endpoints defined in Table 2-3. For example, change from baseline in monthly migraine days in the last month (month 52) of the treatment period will be calculated based on the following:

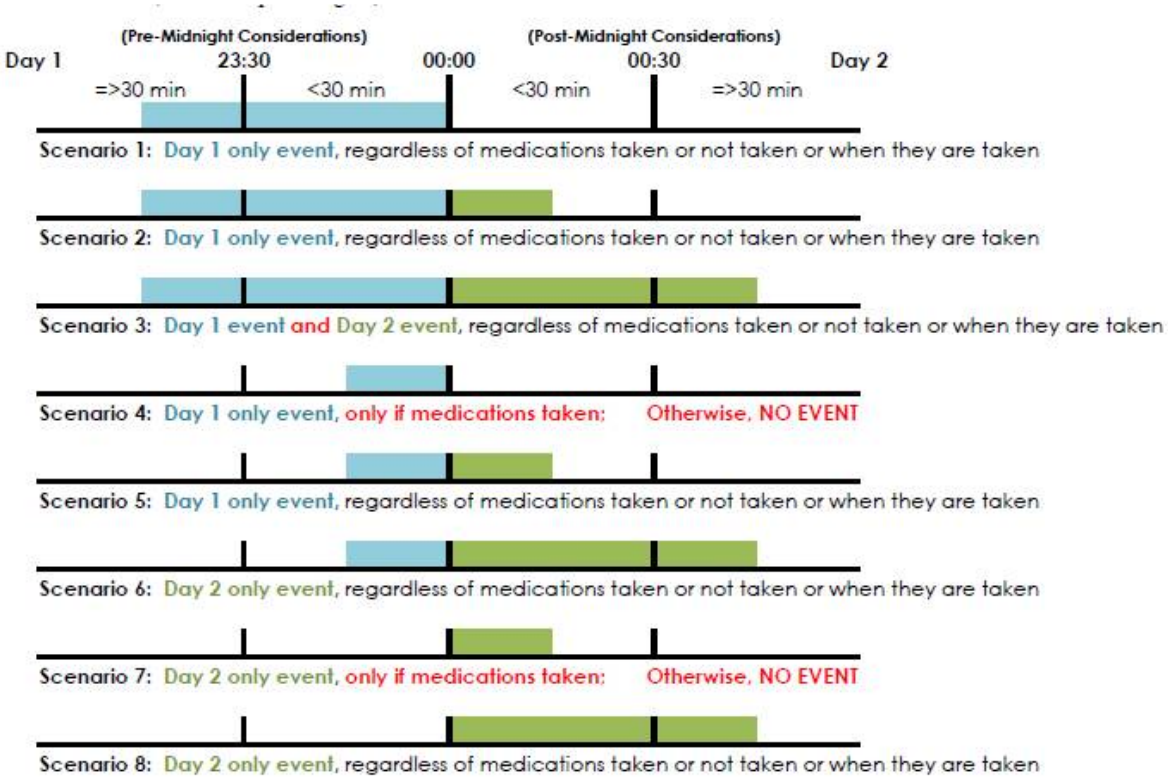
(Monthly migraine days in the last month of the treatment period) – (monthly migraine days during the baseline phase)

If baseline or post-baseline values are missing, then the change from baseline will be missing.

5.7 MMD derivation, exceptions

5.7.1 Assigning Headache and Migraine Days to Events Spanning Midnight

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

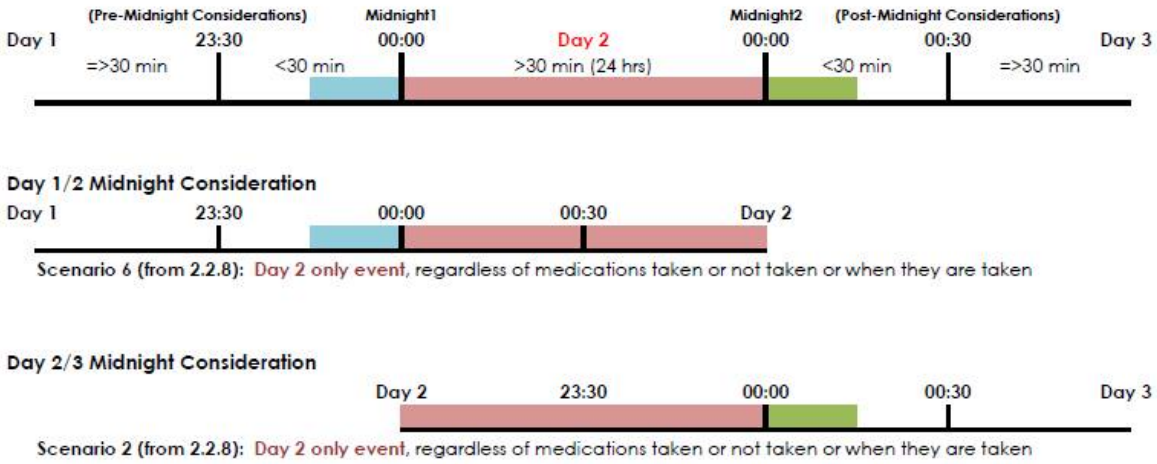


5.7.2 Spanning Midnight Rules for Multi-Day Events Longer Than Two Days

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

Example

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



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

5.8 Patient Global Impression Change (PGIC)

PGIC

Since beginning study drug (Erenumab or Oral Prophylactics), how would you describe the change (if any) in Activity Limitations, Symptoms, Emotions and overall Quality of Life, related to your painful condition?

Please select your response on the following screen.

- ☐ 1 = No change (or condition is worse)
- ☐ 2 = Almost the same, hardly any change at all
- ☐ 3 = A little better, but no noticeable change
- ☐ 4 = Somewhat better, but the change has not made any real difference
- ☐ 5 = Moderately better, and a slight noticeable change
- ☐ 6 = Better, and a definite improvement that has made a real and worthwhile difference
- ☐ 7 = A great deal better, and a considerable difference that has made all the difference

5.9 The Columbia-Suicide Severity Rating Scale (C-SSRS)

Category number	C-SSRS category
Suicidal Ideation	

1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal behavior	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Completed suicide
Self-injurious behavior, without suicidal intent	
11	Non-suicidal self-injurious behavior

6 Reference

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EMA Guidance: “Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic” (April 2020)