Statistical Analysis Plan

Protocol Title:	Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments
Short Protocol Title:	Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
AMPP	American Migraine Prevalence and Prevention
ANCOVA	analysis of covariance
ASP	average sleep propensity
BMI	body mass index
CaMEO	Chronic Migraine Epidemiology and Outcomes
CGRP	calcitonin gene-related peptide
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	double-blind treatment period
DCTS	decentralized clinical trial site
DSM-IV	Diagnostic and Statistical Manual (of Mental Disorders) fourth edition
DSM-V	Diagnostic and Statistical Manual (of Mental Disorders) fifth edition
EAS	efficacy analysis set
eDiary	electronic diary
EM	episodic migraine
ESS	Epworth Sleepiness Scale
FAS	full analysis set
GAD	generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder 7-item Scale
HRU	Health Resource Utilization
ICH	International Council for Harmonisation
IP	investigational product
IRT	interactive response technology
LIBERTY	A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies
MAR	missing at random
MFIQ	Migraine Functional Impact Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
Modified MIDAS	modified Migraine Disability Assessment
MIDAS	Migraine Disability Assessment
MMD	Monthly migraine days
MNAR	missing not at random

Abbreviation or Term	Definition/Explanation
NCT	National Clinical Trials
PHQ-9	Patient Health Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
SAS	safety analysis set
SAP	statistical analysis plan
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment 3 for study 20180060, Erenumab-aooe (AMG 334) dated 31 August 2020. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared to placebo on disability in employed subjects with episodic migraine (EM) who have previously failed 1 or more migraine preventive treatments	• Sum of monthly changes from baseline in modified Migraine Disability Assessment (MIDAS) total score over the 6-month double-blind treatment period (DBTP)
Primary Estimand	
The primary estimand for the primary objective on migraine-related disability consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of investigational product (IP) and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment • The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group The primary estimand is the difference in means between erenumab and placebo of the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment.	
Secondary	
• To evaluate the effect of erenumab compared to placebo on monthly migraine days (MMD) in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Secondary (Continued)</td></tr>
<tr><td colspan="2">The estimand for the secondary objective on MMD consists of:

• The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments
• The endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP
• The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment
• The summary measure, which is the difference between the mean of the endpoint for the erenumab group and the placebo group

The estimand is the difference in means between erenumab and placebo of the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment.</td></tr>
<tr><td>• To evaluate the effect of erenumab compared to placebo on work impairment in employed subjects with EM who have previously failed 1 or more migraine preventive treatments</td><td>• Change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP, as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI): Migraine V2.0 (WPAI questions 2, 4, and 5)

Note: the monthly percent work impairment equals to the arithmetic mean of the observed weekly percent work impairment over the monthly interval.</td></tr>
<tr><td colspan="2">The estimand for the secondary objective on work impairment consists of:

• The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments
• The endpoint, which is the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP
• The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment
• The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group</td></tr>
</table>

Objectives	Endpoints
Secondary (Continued)	
The estimand is the difference in means between erenumab and placebo of the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment.	
• To evaluate the effect of erenumab compared to placebo on physical function, usual activities, and social function in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by Migraine Functional Impact Questionnaire (MFIQ) • Change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ
The estimand for the secondary objective on function (physical, usual activities, and social) consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoints include: 1) the change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 2) the change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 3) the change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of the respective MFIQ domain score, regardless of adherence to treatment • The summary measure, which is the difference in means of the respective endpoint between the erenumab group and the placebo group	

Objectives	Endpoints
Exploratory	
• To evaluate the effect of erenumab compared to placebo on work impairment in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in monthly average percent overall work impairment at each monthly assessment time point during the 6-month DBTP, as measured by the WPAI (questions 2, 4, and 5)
• To evaluate the effect of erenumab compared to placebo on MMD in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in MMD at each monthly assessment time points during the 6-month DBTP
• To evaluate the effect of erenumab compared to placebo on function and quality of life in employed subjects with EM or who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean emotional function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in mean overall impact on usual activities global item score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in MFIQ domain scores of function (physical, usual activities, social, and emotional) and overall impact on usual activities global item score at each monthly assessment time point during the 6-month DBTP • Change from baseline in depression at months 1, 3, and 6 of the 6-month DBTP, as measured by the Patient Health Questionnaire (PHQ-9) total score • Change from baseline in anxiety at months 1, 3, and 6 of the 6-month DBTP, as measured by Generalized Anxiety Disorder 7-item Scale (GAD-7) total score • Change from baseline in insomnia at months 1, 3, and 6 of the 6-month DBTP, as measured by the Pittsburgh Sleep Quality Index (PSQI) total score

Objectives	Endpoints
Exploratory (Continued)	
	• Change from baseline in excessive daytime sleepiness at months 1, 3, and 6 of the 6-month DBTP, as measured by the Epworth Sleepiness Scale (ESS) total score • Change from baseline in monthly average activity level during and between migraine days at each monthly assessment time point during the 6-month DBTP, as measured by a wearable • Change from baseline in patient satisfaction at work at months 1, 3, and 6 of the 6-month DBTP, as measured by the questions in Section 5.1.3
• To describe the effect of erenumab on migraine-related health resource utilization (HRU) in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Occurrence of at least 1 migraine-related hospitalization or outpatient HRU during the 6-month DBTP • Occurrence of at least 1 migraine-related hospitalization during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient HRU during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient emergency room visit during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient urgent care visit during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient clinic visit during the 6-month DBTP
• To evaluate the effect of erenumab compared to placebo on attention in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean reaction time at months 1, 3, and 6 of the 6-month DBTP, as measured by the Psychomotor Vigilance Test (PVT) • Change from baseline in number of lapses and errors at months 1, 3, and 6 of the 6-month DBTP, as measured by PVT

2.2 Hypotheses and/or Estimations

The primary clinical hypothesis is that preventive treatment with monthly injections of erenumab is superior to placebo in reducing disability in employed subjects with EM who have previously failed 1 or more migraine preventive treatments.

3. Study Overview

3.1 Study Design

Study 20180060 is a phase 4, 24-week, prospective, double-blind, randomized, placebo-controlled, multicenter study in the United States (US), evaluating the effect of erenumab on disability and work productivity in employed patients with EM who have previously failed 1 or more migraine preventive treatments. Subjects will enter initial screening (up to 21 days) to determine if they meet Eligibility Criteria Part 1. If Part 1 eligibility criteria are met, subjects will enter baseline (28 days). After subjects complete baseline and are found eligible based on Eligibility Criteria Part 2, they will be enrolled and randomized in a 1:1 ratio to either erenumab 140 mg or placebo. Randomization will be performed separately within traditional sites and decentralized clinical trial site (DCTS). Subjects will then enter a 24-week DBTP which will conclude with an end-of-study visit at week 24.

3.2 Sample Size

The total sample size of 240 subjects (120 subjects per treatment group) enrolled from traditional sites will provide at least a 94% power for the primary efficacy hypothesis. The statistical power for secondary efficacy hypotheses ranges from 88% to 99%. This sample size is not inflated for dropouts since subjects who drop out early during the 6-month DBTP are likely to have at least 1 post-baseline measurement and therefore will still be included in the analysis based on the primary estimand utilizing a repeated measures linear mixed model approach. Table 3-1 provides sample size assumptions and resulting statistical power for each hypothesis.

Table 3-1. Sample Size Assumptions and Statistical Power for Traditional Sites

Hypothesis	Assumed Treatment Effect (Erenumab – Placebo)	Assumed Common Standard Deviation	Power for Sample Size of 240 Subjects
Primary: modified MIDAS total score	-20	43	94%
Secondary:			
• MMD	-2.0	3.4	> 99%
• Work impairment (WPAI)	-10.0	23.1	91%
• MFIQ physical function	-7.6	16.2	95%
• MFIQ usual activities	-6.1	14.9	88%
• MFIQ social function	-6.8	15.6	91%

MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MMD = monthly migraine days; WPAI = Work Productivity and Activity Impairment.

Note: All power calculations are based on a 2-sided significance level of 0.05 and not adjusted to reflect the sequential testing procedure. The assumed treatment effects and common standard deviations for modified MIDAS, MMD, and MFIQ hypotheses are derived from a subset of subjects in erenumab Study 20120296 satisfying the key entry criteria of the current study. The assumed treatment effect and common standard deviation for the work impairment hypothesis is derived from the LIBERTY study.

In addition, a total sample size of 100 subjects (50 per treatment group) will be enrolled as part of the DCTS for pilot purposes.

4. Covariates and Subgroups

4.1 Planned Covariates

All model-adjusted analyses of efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed.

4.2 Subgroups

The primary and secondary endpoints will be summarized in the subgroups defined by number of prior treatment failures (1, 2, and 3 or more treatment failures) for the traditional sites only.

The subgroups will be re-examined for appropriateness and may be re-categorized (due to small sample size, for example, if there are < 10% of subjects within a subgroup) before unblinding.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints Based on Daily Data Collection

The eDiary collects headache events (including start and stop time, pain features, symptoms, and severity), aura events (including start and stop time), and acute headache medications (including taken time) in 3 independent modules. The eDiary design includes optional any-time diaries and a mandatory evening diary from 5:00:00 pm to 11:59:59 pm (local time) each day for data collection.

Acute Headache Medication (AHM)

Acute headache medications include following categories collected in the eDiary:

- Triptan-based migraine medications
- Ergotamine-based migraine medications
- Non-opioid acute headache medications
- Non-opioid butalbital containing medications
- Opioid-containing acute headache medications
- Opioid-containing butalbital containing medications

Acute Migraine-specific Medication (AMSM)

A subset of acute headache medication consisting of triptan-based migraine medications and ergotamine-based migraine medications

Qualified Headache

A qualified headache is defined as

- A headache of duration ≥ 30 minutes
- A headache with acute headache medications (migraine-specific or not) taken during the headache (start time and end time inclusive) with any length of duration
- Acute migraine-specific medications taken during an aura (start and end time inclusive)

Headache Day

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified headache

Headache Pain Intensity

Worst or peak pain intensity collected on a headache ranges from 0 (no pain) to 10 with a higher score indicating more severe pain. Pain intensity are categorized into mild (1 to 3), moderate (4 to 6), and severe (7 to 10).

Qualified Migraine Headache

A qualified migraine headache should meet at least one of the following criteria:

- A headache of duration ≥ 30 minutes, and meeting ≥ 1 of the following criteria (a and/or b):
  a) ≥ 2 of the following pain features:
    - Unilateral
    - Throbbing
    - Moderate to severe (ie, headache pain intensity ≥ 4)
    - Exacerbated with exercise/physical activity
  b) ≥ 1 of the following associated symptoms:
    - Nausea
    - Vomiting
    - Photophobia and phonophobia
- A headache with acute migraine-specific medications taken during the headache (start time and end time inclusively) regardless of the headache duration, pain features, and associated symptoms
- Acute migraine-specific medications taken during aura

Migraine Day

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified migraine headache.

Diary Day

A calendar day (00:00 to 23:59) with complete headache, aura, and acute headache medication data recorded in the eDiary device.

Information Day

A calendar day (00:00 to 23:59) which is either a diary day or a headache day that can be derived based on available information.

Monthly Migraine Days (MMD)

Number of migraine days during one monthly interval as defined below**.**

Number of Diary Days in a Monthly Interval	Monthly Migraine Days
• ≥ 14 days	Prorate to 28-day equivalent without rounding as follows: $\frac{Number\ of\ observed\ migraine\ days\ within\ each\ monthly\ interval}{Number\ of\ diray\ days\ within\ each\ monthly\ interval}\ x\ 28$
• < 14 days	Set to missing

Monthly Headache Days (MHD)

Number of headache days during one monthly interval as defined below**.**

Number of Diary Days in a Monthly Interval	Monthly Headache Days
• ≥ 14 days	Prorate to 28-day equivalent without rounding as follows: $\frac{Number\ of\ observed\ headache\ days\ within\ each\ monthly\ interval}{Number\ of\ information\ days\ within\ each\ monthly\ interval}\ x\ 28$
• < 14 days	Set to missing

5.1.2 Efficacy Endpoints Based on Weekly Collection

Work Productivity and Activity Impairment (WPAI) Questionnaire

In the WPAI-Migraine questionnaire, subjects are asked 6 questions about work and activity impairment due to their migraine, including hours worked and hours missed in the last 7 days. The questionnaire will be collected weekly during baseline and post-baseline.

The weekly percent work impairment score is calculated based on questions 2, 4 and 5. Higher score indicates worse outcome.

The monthly percent work impairment equals to the arithmetic mean of the observed weekly percent work impairment scores over the monthly interval, if the number of weekly scores during baseline period or each of the monthly interval during post-baseline is ≥ 2. Otherwise, monthly measurement will be set to missing.

5.1.3 Efficacy Endpoints Based on Monthly Collection

Modified Migraine Disability Assessment (Modified MIDAS)

The modified MIDAS Questionnaire is a 5-item self-administered questionnaire that assesses in the past month the number of productive days lost in 2 settings (workplace and home) and disability in family, social, and leisure activities. Absenteeism score is

the response from question 1, and presenteeism score is the response from question 2. The total score ranging from 0 to 93 is the sum of the responses to all 5 items. Higher scores indicate worse outcome. The modified MIDAS will be collected monthly during baseline and post-baseline.

Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ version 2.0 is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including 4 domains: Impact on Physical Functioning (5 items), Impact on Usual Activities (10 items), Impact on Social Functioning (5 items), and Impact on Emotional Functioning (5 items). In addition, there is 1 stand-alone global item assessing the overall impact on usual activities. Subjects respond to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period is the past 7 days and will be collected monthly during baseline and post-baseline.

5.1.4 Efficacy Endpoints Collected at Specific Visits

Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ) is a 9-question, self-administered instrument for screening, diagnosing, monitoring, and measuring the severity of depression. Each item has response as “0” (not at all) to “3” (nearly every day). The score is calculated as the sum of the 9 item responses, ranging from 0 to 27 with higher score representing severer depression. PHQ-9 will be collected at baseline and at months 1, 3 and 6 post-baseline.

Generalized Anxiety Disorder 7-item Scale Questionnaire (GAD-7)

The GAD-7 is a self-administered 7-item instrument to identify probable cases of GAD along with measuring anxiety symptom severity. Responders are asked to rate the frequency of anxiety symptoms in the last 2 weeks on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). Items are summed to provide a total score, ranging from 0 to 21 with higher score indicating severer symptoms. GAD-7 will be collected at baseline and at months 1, 3 and 6 post-baseline.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-reported questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce 1 global score. Each component scored 0 (better) to 3 (worse). The global score is the sum of each component score, ranging from 0 to 21 with higher score indicating worse sleep quality. PSQI will be collected at baseline and at months 1, 3 and 6 post-baseline.

Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions designed to assess daytime sleepiness. Respondents are asked to rate, on a 4-point scale (0 to 3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The ESS score (the sum of 8 item scores, 0 to 3) can range from 0 to 24 with higher ESS scores indicating higher average sleep propensity (ASP) in daily life, or "daytime sleepiness". ESS will be collected at baseline and at months 1, 3 and 6 post-baseline.

Patient Satisfaction at Work

To better understand impact of depression, anxiety, sleepiness, and inability to concentrate on work productivity, subjects will be asked to complete the following questions on a 10-point scale with higher score representing severer impacts:

- How much does your depressed mood, as a result of your migraines, impact your ability to function at work? **Scale,** 0 = no impact to 10 = severely impacts
- How much does your anxiety, as a result of your migraines, impact your ability to function at work? **Scale,** 0 = no impact to 10 = severely impacts
- How much does your sleepiness, as a result of your migraines, impact your ability to function at work? **Scale,** 0 = no impact to 10 = severely impacts
- How much does your inability to concentrate, as a result of your migraines, impact your ability to function at work? **Scale,** 0 = no impact to 10 = severely impacts
- How would you rate your overall satisfaction with your productivity at work? **Scale,** 0 = as dissatisfied as you can imagine to 10 = as satisfied as you can imagine

These questions are not part of a validated questionnaire and will be scored individually. The recall period is the past month. Patient satisfaction at work will be collected at baseline and at months 1, 3 and 6 post-baseline.

Psychomotor Vigilance Task (PVT)

Psychomotor Vigilance Task is a sustained-attention, reaction-timed task that measures the speed with which a subject responds to a visual stimulus. Mean reaction time in millisecond, number of lapses and errors will be calculated from the individual elapsed time recordings during the 10-minute session. PVT will be collected at baseline and at months 1, 3 and 6 post-baseline.

Subjects enrolled as part of the DCTS will not complete this assessment.

Health Resource Utilization (HRU) Questionnaire

The questionnaire is designed to collect data on HRU. Specifically, the aim is to capture frequency of migraine-related hospitalizations and outpatient visits including emergency department visits, urgent care visits, and other clinical visits. The recall period for the HRU questionnaire is 24 weeks, and the HRU questionnaire will be administered on day 1, and week 24 of the DBTP. The questionnaire assessed at the early termination visit before week 24 should only include HRU recalled since the previous assessment at day 1 to avoid collecting duplicate information. HRU will be collected at baseline and at month 6 post-baseline.

5.1.5 Efficacy Endpoints Based on Wearable Device Collection

Physical activity will be measured continuously by a wearable device (accelerometer) from baseline through the end of study except when recharging. Analysis of physical activity endpoints will only include activity data collected while subjects are wearing the device and are awake (not sleeping), ie, during wear and awake time.

Valid Day

A valid day is defined when there are at least 10 hours (600 minutes) of wear and awake time per calendar day (00:00 to 23:59). Analysis of physical activity endpoints will only include activity data collected during wear and awake time on valid days.

Physical Activity Category

Physical activity level can be defined in the following 6 categories:

- Sedentary
- Light
- Lifestyle

- Moderate
- Vigorous
- Very vigorous

Note: The raw data will include total minutes of wear and awake time corresponding to each physical activity category per calendar day.

Total Minutes of Wear and Awake Time in a Valid Day

Sum of total minutes of wear and awake time for each of the 6 physical activity categories in a valid day

Daily Proportion of Time Spent in Each Physical Activity Category per Valid Day

$$\frac{Total\ minutes\ of\ wear\ and\ awake\ time\ spent\ in\ each\ physical\ activity\ category\ in\ a\ valid\ day}{Total\ minutes\ of\ wear\ and\ awake\ time\ in\ a\ valid\ day}$$

Note: Since total minutes of wear and awake time vary daily, daily proportion is meant to normalize the *daily* physical activity level before calculating the *monthly* average.

Monthly Average of Daily Proportion of Time Spent in Each Physical Activity Category on Valid Days

Number of Valid Days in a Monthly Interval	Monthly average of daily proportion of time spent in each physical activity category
• ≥ 14 days	$\frac{Sum\ of\ (daily\ proportion\ of\ time\ spent\ in\ each\ physical\ activity\ category)}{Total\ number\ of\ valid\ days\ in\ a\ month}$
• < 14 days	Set to missing

Sleep Period

A sleep period is defined to be at least 160 minutes long that starts when 5 consecutive minutes marked as “sleep” and ends once there are 10 consecutive minutes marked as “awake”.

Sleep Efficiency

Sleep efficiency is the total number of minutes marked as sleep during the total length of the sleep period in minutes.

$$\frac{sleep\ time\ in\ minutes}{Total\ minutes\ of\ sleep\ period\ (sleep\ minutes + awake\ minutes)}$$

5.1.6 Safety Endpoints

Serious Adverse Event (SAE)

An event categorized as “Adverse Event” with the indicator flag “Serious” equal to “Yes” on the Events eCRF starting on or after signing of the informed consent and up to the End of Study date

Treatment-Emergent Adverse Event (TEAE)

An event categorized as “Adverse Event” on the Events eCRF starting on or after first dose of investigational product, as determined by “Did event start before first dose of investigational product” equal to “No” or missing, and up to the End of Study date.

Serious Treatment-emergent Adverse Event

A treatment-emergent adverse event with the indicator flag “Serious” equal to “Yes” on the Events eCRF

Treatment-emergent Adverse Device Effect

A treatment-emergent adverse event with the indicator flag “Is there a reasonable possibility that the event may have been caused by the investigational device” equal to “Yes” on the Events eCRF

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

Date of Device Ready for Entry

The date on which an eDiary device is ready for entry after completion of initial screening.

Randomization (Enrollment) Date

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

First IP Dose Date

First IP Dose Date is the date on which a subject is administered the first dose of IP following randomization as recorded on the IP Administration eCRF. The first IP dose may be the same day or after the randomization date.

Last IP Dose Date

Last IP Dose Date is the date on which a subject is administered the last dose of IP as recorded on the IP Administration eCRF.

End of Study (EOS) Date

End of study (EOS) date is defined as the last date on which the subject participates in the study as recorded on the End of Study eCRF.

5.3 Study Points of Reference

Baseline Assessment

Baseline assessment for the endpoint of the interest is defined as the last non-missing measurement taken or the monthly interval assessed (for endpoints derived from daily and weekly eDiary collection) before the first dose of investigational product. In cases where baseline measurements are taken on the same day as IP, it will be assumed that these measurements are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline of the study is defined as the last non-missing measurement prior to or on the date of randomization.

Study Day 1

Study Day 1 is defined as the first 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

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.

5.4 Study Time Intervals

5.4.1 Monthly Intervals for Efficacy Endpoints Derived From Daily, Weekly, or Wearable Data Collection

The (4-week) monthly intervals for efficacy endpoints derived from daily eDiary collection, weekly collection for WPAI, or wearable device (physical activity data only) will be determined based on each subject's monthly IP dosing dates. When an IP is

missed, discontinued, or no longer required, a 28-day monthly interval will be used. Any eDiary or wearable data occurring after EOS date will not be included in the analysis.

Applicable efficacy endpoints utilizing the monthly intervals in Table 5-1 include:

- Monthly migraine days (MMD)
- Monthly headache days (MHD)
- Monthly percent work impairment as measured by WPAI
- Monthly average daily proportion of time spent in each physical activity category: sedentary, light, lifestyle, moderate, vigorous, and very vigorous

Table 5-1. Monthly Intervals for Efficacy Endpoints Derived From Daily, Weekly, or Physical Activity Wearable Data Collection

Study Period	Assessment Timepoint	Monthly Interval	
		Start Date (Day) [a]	End Date (Day) [b]
Baseline Period	Baseline	Date of device ready for entry [c]	Day prior to study day 1
Double-blind Treatment Period	Week 4 (Month 1)	Study Day 1	Week 4 dose date – 1
	Week 8 (Month 2)	Week 4 dose date	Week 8 dose date – 1
	Week 12 (Month 3)	Week 8 dose date	Week 12 dose date – 1
	Week 16 (Month 4)	Week 12 dose date	Week 16 dose date – 1
	Week 20 (Month 5)	Week 16 dose date	Week 20 dose date – 1
	Week 24 (Month 6)	Week 20 dose date	Week 20 dose date + 27

[a] Start Date (Day) = End date (day) of previous monthly interval + 1 if IP dose date is not available
[b] End Date (Day) = Start date (day) of current monthly interval + 27 if IP dose date is not available
[c] For physical activity wearable data, Baseline Start Date (day) is defined as Max (Earliest valid activity date, week -4 visit date)

Sleep associated endpoints from each sleep period will utilize the monthly invervals defined in Table 5-2 based on the sleep start date/time.

Table 5-2. Monthly Intervals for Sleep Associated Endpoints

Study Period	Assessment Timepoint	Monthly Interval	
		Start Date/Time [a]	End Date/Time [b]
Baseline Period	Baseline	Max (Earliest recorded sleep start date, week -4 visit date)	Day 1 dose date/time
Double-blind Treatment Period	Week 4 (Month 1)	Day 1 dose date/time	Week 4 dose date/time
	Week 8 (Month 2)	Week 4 dose date/time	Week 8 dose date/time
	Week 12 (Month 3)	Week 8 dose date/time	Week 12 dose date/time
	Week 16 (Month 4)	Week 12 dose date/time	Week 16 dose date/time
	Week 20 (Month 5)	Week 16 dose date/time	Week 20 dose date/time
	Week 24 (Month 6)	Week 20 dose date/time	≤ Week 24 visit date

[a] Start Date/Time = End date/time of previous monthly interval if IP dose date is not available
[b] End Date/Time = Start date/time of current monthly interval + 27 if IP dose date is not available

5.4.2 Analysis Visits for Endpoints Based on Monthly Collection

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to the analysis visit as in Table 5-3, Table 5-4, and Table 5-5. Any data occurred after EOS date will not be included in the analysis.

For by-visit summaries, if more than one visit with non-missing measurement (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') fall within the same visit window, the following rules will be applied according to the order described below for selecting one visit per visit window for summary:

1. 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 visit window.
2. The visit closest to the target day among visits of the same type (all scheduled visits or all unscheduled visits) will be considered for analysis.
3. If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis.

Table 5-3. Modified MIDAS and MFIQ Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
	Week 4 (Month 1)	29	16 to 43
	Week 8 (Month 2)	57	44 to 71
	Week 12 (Month 3)	85	72 to 99
	Week 16 (Month 4)	113	100 to 127
	Week 20 (Month 5)	141	128 to 155
	Week 24 (Month 6)	169	156 to 183

Table 5-4. PHQ-9, GAD-7, PSQI, ESS, Patient Satisfaction at Work and PVT Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
	Week 4 (Month 1)	29	16 to 43
	Week 12 (Month 3)	85	72 to 99
	Week 24 (Month 6)	169	156 to 183

Table 5-5. HRU Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Double-blind Treatment Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
	Week 24 (Month 6)	169	156 to 183

5.5 Subject Disposition

Randomized

Individuals are considered randomized if they have been assigned a randomization number. Randomized individuals are referred to as “subjects”.

Exposed to Investigational Product

Subjects are defined as exposed if they receive at least one dose of investigational product.

Completing Investigational Product

Subjects are defined as completing investigational product if the primary reason for ending IP on End of IP eCRF is “Completed”.

Completing Study

Subjects are defined as completing study if they complete the entire 24 weeks of study evaluation**.** It will be derived from the End of Study eCRF with “Completed” as the primary reason for ending study.

On-study

Subjects are considered on-study if they have been randomized and have not yet had their EOS visit.

5.6 Arithmetic Calculations

Duration of Migraine

The number of years from the diagnosis date (DXDT) of migraine (migraine with aura or migraine without aura, whichever is earlier) to the date informed consent is signed.

Observed Portion	Missing Portion	Duration of Migraine (Years)
Year, Month, Day	NA	(Informed Consent Date – DXDT) / 365.25
Year, Month	Day	[Year(Informed Consent Date) – Year(DXDT)] + [Month(Informed Consent Date) – Month(DXDT)] / 12 [a]
Year	Month, Day	[Year(Informed Consent Date) – Year(DXDT)] [a]

[a] If it equals 0, add 1/12 years (ie, 1 month) to avoid a disease duration of 0.

Duration of IP Exposure

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

Change From Baseline

Postbaseline monthly value – Baseline, as defined in Section 5.4.

If the baseline or postbaseline value is missing, the change from baseline value will be set to missing.

Mean Monthly Change From Baseline Over Multiple Months

Mean monthly change from baseline is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there is at least one observed monthly value.

Sum of Monthly Changes From Baseline Over the 6-month DBTP

Sum of monthly changes from baseline over the 6-month DBTP is calculated as the arithmetic mean of the monthly change from baseline over the same 6-month period times 6.
Note: This prorated value will be used to provide summary statsitics of the primary efficacy endpoint.

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 enter that period (ie, number of at-risk subjects). For subjects with multiple occurrences of the same event in a given period, the event will only be counted once per subject in that period.

5.7 Disease Characteristics

Treatment Failure of Prior Migraine Preventive Medications

Treatment failure of prior migraine preventive medications is determined by “Reason for Stopping” as “Lack of efficacy” or “Adverse reaction” or “Intolerance” on the Prior Migraine Prophylactic Medication eCRF.

6. Analysis Sets

6.1 Full Analysis Set

The respective full analysis set (FAS) consists of all subjects who were randomized in the study through traditional study sites or DCTS. Analysis of disposition, demographic

and baseline characteristics, and important protocol deviations will utilize the respective FAS.

6.2 Efficacy Analysis Set

The respective efficacy analysis set (EAS) consists of a subset of subjects from traditional study sites or DCTS who receive at least 1 dose of IP and have a baseline value and at least 1 post baseline value for the endpoint of interest. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Primary analysis of the efficacy endpoints will utilize the respective EAS.

6.3 Safety Analysis Set

The respective safety analysis set (SAS) will consist of all randomized subjects from traditional study sites or DCTS who received at least 1 dose of IP. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect randomized treatment during the entire DBTP. Analysis for safety endpoints and summary of IP administration will utilize the respective SAS.

7. Planned Analyses

The primary analysis (or final analysis since there is only one milestone analysis for this study) will occur after all subjects have completed their week 24 visit (or discontinued from the study). The DBTP treatment assignment will be unblinded and all efficacy and safety analyses will be conducted and reported by the DBTP treatment group. The primary analysis at the end of the study will be based on cleaned, locked data.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database. The database will be subjected to edit check outlined in the Data Management Plan (DMP). eDiary data, physical activity and sleep data collected through wearable, pharmacogenetic, and biomarkers data is outside of RAVE database. All the datasets to be used for planned analyses will be received from GSO-DM department. Additional details will be provided in the DMP and Data Transfer Plan (DTP).

8.3 Handling of Missing and Incomplete Data

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 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 monthly interval. The general procedures outlined below describe what will be done when a data point is missing.

Missing daily data in the calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following proration method, also described in Section 5.1.1.

- For each monthly interval with ≥ 14 days of eDiary use:
  - Monthly frequency measurements will be prorated to 28-day equivalents. Prorated result does not need to be rounded.
  - Monthly average scores will be calculated as the average of observed scores.
- For monthly intervals with < 14 days of eDiary use, all monthly measurements will be set as missing.

Missing monthly efficacy measurements will not be imputed in the primary analysis method utilizing a generalized linear mixed model to handle missing data under MAR assumption. In the sensitivity analysis on primary and secondary efficacy endpoints, missing data in monthly values will be handled using multiple imputation (MI) with assumption of missing not at random (MNAR) (with control-based pattern imputation).

For the descriptive summary the mean monthly value over months 4, 5, and 6 is calculated using the arithmetic mean of observed monthly values from each of months 4, 5, and 6 of the DBTP. Therefore, a subject with at least one monthly value at months 4, 5, and 6 will contribute to the summary statistics.

For the descriptive summary the primary endpoint, sum of monthly changes from baseline in MIDAS total score over the 6-month DBTP, will be prorated as follows for subjects with missing data in monthly changes from baseline:

$$\frac{Sum\ of\ observed\ monthly\ changes\ from\ baseline\ in\ MIDAS\ score\ \ within\ 6\ month\ DBTP}{Number\ of\ months\ with\ observed\ monthly\ values\ within\ 6\ month\ DBTP}\ x\ 6$$

Missing safety endpoints will not be imputed. Missing or incomplete dates will be listed as reported, except for incomplete start date of an adverse event or concomitant medication, which will be imputed as follows:

Missing	Imputation	Exception on adverse event start date
Day	01	Default to study day 1 if an adverse event started the same year and month as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month	01 JAN	Default to study day 1 if an adverse event started the same year as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month/Year	None	-

8.4 Detection of Bias

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

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

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated. If necessary, the incidence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR.

The reasons for early withdrawal from treatment and from study will be tabulated and/or listed.

8.5 Outliers

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

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

8.6 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, appropriate transformations or the non-parametric alternatives will be used, such as Quade test (Quade D, 1966) may additionally be considered.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

All analyses will be conducted separately for subjects enrolled from traditional sites and subjects from DCTS. Formal statistical hypothesis testing for the primary and secondary endpoints will be performed for subjects enrolled from traditional sites only. Subject characteristics for both traditional sites and DCTS will be summarized descriptively.

Summary statistics by each treatment group will be tabulated at each assessment time point if applicable. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% CIs of the means (CIs will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

The primary analysis method utilizing a repeated measures linear mixed effects model will include all observed data regardless of treatment adherence.

A sequential testing procedure will be used to maintain the family-wise type 1 error $\alpha = 0.05$ between the primary and secondary endpoints following the order of modified MIDAS total score, MMD, WPAI, MFIQ physical function, MFIQ usual activity, and MFIQ social function endpoints. An endpoint will only be tested if the endpoint tested in the previous step is statistically significant at 2-sided significance level of 0.05.

9.2 Subject Accountability

The disposition of all randomized (enrolled) subjects will be tabulated by randomized treatment group. The summary will include the number of subjects who are randomized, the number and percent of subjects who receive/never receive IP, who complete IP, discontinue IP and reasons for discontinuing, who complete the study, and who withdraw prematurely from the study and their reasons for withdrawal.

A footnote on the subject disposition tables will include the number of subjects screened.

A summary of the study reporting period including a description of key dates will also be provided, including dates of the first and last subject enrolled and the last subject's end of study date.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the study. Eligibility deviations are defined in the protocol. In addition, protocol deviations related to COVID-19 control measures will be summarized and listed.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by randomized treatment group and overall study population using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple races.

At baseline, the following demographic and baseline characteristics will be summarized:

- Age
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m^2)
- Targeted neurological disease diagnosis at baseline

- Disease duration of migraine with or without aura (years)
- Age at onset of migraine
- Number of prior migraine preventive treatment failure categories
- Summary of prior migraine preventive medication and reasons for discontinuation
- Summary of current migraine preventive treatment at baseline
- Acute headache medication used during baseline period:
    a) Migraine-specific
    b) Non-migraine-specific
- Monthly migraine days during baseline period
- Monthly headache days during baseline period
- Monthly acute migraine-specific medication days during baseline period
- Monthly acute migraine-specific medication days during baseline period among baseline users
- Monthly acute headache medication days during baseline period
- Monthly acute headache medication days during baseline period among baseline users
- Modified MIDAS total score, absenteeism score, and presenteeism score
- Monthly percent work impairment as measured by WPAI during baseline period
- MFIQ domain scores of function (physical, usual activities, social, and emotional) and overall impact on usual activities global item score

9.5 Efficacy Analyses

The primary analysis of efficacy endpoints will utilize the EAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

For primary analysis, the continuous change from baseline efficacy endpoints calculated by the method as specified in Section 5.6 will be analyzed using generalized linear mixed effect models including treatment group, scheduled visit, the interaction between treatment group and scheduled visit and the baseline value on observed data.

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

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Sum of monthly changes from baseline in modified MIDAS total score over the 6-month double-blind treatment period (DBTP) (Note: Results from individual time point during the DBTP will also be generated in the same generalized linear mixed effect model.)	1. Summary statistics by visit using observed data at each visit and the calculated sum of each monthly change from baseline value over 6 months 2. Least squares means from a generalized linear mixed effect model including treatment group, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data 3. Test treatment difference (AMG 334 – Placebo) using a contrast from the model in #2.	MI with assumption of MNAR (control-based pattern imputation)

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in mean MMD over months 4, 5, and 6; Change from baseline in mean monthly percent work impairment as measured by WPAI over months 4, 5, and 6; Change from baseline in MFIQ domain scores of function (physical function, usual activities, and social function) over months 4, 5, and 6 (Note: Results from individual time point during the DBTP as exploratory endpoints will also be generated in the same generalized linear mixed effect model.)	1. Summary statistics by visit using observed data at each visit, and the calculated mean monthly migraine days or mean domain scores over months 4, 5, and 6 2. Least squares means from a generalized linear mixed effect model including treatment group, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data 3. Test treatment difference (AMG 334 – Placebo) using a contrast from the model in #2.	MI with assumption of MNAR (control-based pattern imputation)

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in mean emotional function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ [a] (Note: Results from individual time point during the DBTP will also be generated in the same generalized linear mixed effect model.)	1. Summary statistics by visit using observed data at each visit, and the calculated mean domain score over months 4, 5, and 6 2. Least squares means from a generalized linear mixed effect model including treatment group, scheduled visit, interaction of treatment group and scheduled visit and baseline value using observed data 3. Test treatment difference (AMG 334 – Placebo) using a contrast from the model in #2.	
Endpoints defined as change from baseline at months 1, 3, and 6 [b]	1. Summary statistics by visit using observed data 2. Least squares means from a generalized linear mixed effect model including treatment group, scheduled visit, interaction of treatment group and scheduled visit and baseline value using observed data 3. Test treatment difference (AMG 334 – Placebo) from the model in #2.	

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Footnotes defined on last page of the table

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Endpoints defined as change from baseline at each monthly assessment time point [c]	1. Summary statistics by visit using observed data 2. Least squares means from a generalized linear mixed effect model including treatment group, scheduled visit, interaction of treatment group and scheduled visit and baseline value using observed data 3. Test treatment difference (AMG 334 – Placebo) from the model in #2.	
Occurrence of at least 1 migraine-related hospitalization or outpatient HRU during the 6-month DBTP [d]	1. Summary statistics using observed data at month 6	

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[a] The same analysis methods will be applied to the endpoints:
Change from baseline in mean overall impact on usual activities global item score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ.

[b] The same analysis methods will be applied to the following endpoints at months 1, 3, and 6:
PHQ-9 total score,
GAD-7 total score,
PSQI total score,
ESS total score,
Patient satisfaction at work,
Mean reaction time, number of lapses, and number of errors as measured by PVT.

[c] The same analysis methods will be applied to the following endpoints at all 6 months:
Change from baseline in monthly average daily proportion of time spent in each physical activity category: sedentary, light, lifestyle, moderate, vigorous, and very vigorous,
Change from baseline in monthly average sleep efficiency.

[d] The same analysis method will be applied to all HRU endpoints.

9.5.1 Analyses of Primary and Secondary Efficacy Endpoints

The primary analysis of the primary and secondary endpoints will be performed using a generalized linear mixed model based on observed monthly data with appropriate contrasts for treatment comparison relative to placebo for the corresponding efficacy endpoints: sum of monthly changes from baseline value over the 6-month DBTP, and change from baseline in mean monthly values or mean domain scores over months 4, 5 and 6. The model will include treatment, scheduled visit, treatment-by-visit interaction, and baseline value as covariates. If applicable, the first-order autoregressive covariance structure is assumed. Least squares means (LSMs) for each treatment group, standard errors, associated 95% confidence intervals, difference of LSMs compared to placebo group, associated 95% confidence intervals and nominal two-sided p-values will be tabulated by visit, as well as for the mean monthly values over months 4, 5, and 6 of the DBTP.

Sensitivity analysis described below will be performed for the primary and secondary endpoints:

1. MI with assumption of MNAR (control-based pattern imputation).
2. Primary summary and analysis by the subgroup of treatment failure of prior migraine prophylactic medications (Section 4.2)

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Analysis within each interested subgroup will be performed using the same primary analysis method for the same endpoint. The treatment difference with associated 95% confidence interval and p-value will be reported within each subgroup.

The heterogeneity of the treatment effect across the subgroups will be evaluated by examining the treatment-by-subgroup interaction p-value obtained from the primary analysis model with the addition of treatment-by-subgroup interaction.

9.5.2 Analyses of Exploratory Efficacy Endpoints

The primary analysis of the exploratory efficacy endpoints will be conducted in the same way as that for the primary and secondary endpoints as outlined in Table 9-3. No sensitivity analyses will be performed for the exploratory efficacy endpoints.

9.6 Safety Analyses

9.6.1 Analyses of Safety Endpoint(s)

For safety endpoints, all randomized subjects who received at least one dose of IP (ie, Safety Analysis Set) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose during the entire study.

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

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later will be used to code all adverse events (AEs) to a system organ class (SOC) and a preferred term (PT). All AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AE summary tables described below will be summarized by treatment group using subject incidence.

The subject incidence of AEs will be summarized for all treatment-emergent adverse events (TEAEs), serious AEs, AEs leading to withdrawal of investigational product, fatal AEs, and adverse events of interest (EOI) including

- Ischaemic Central Nervous System Vascular Conditions SMQ (Narrow)
- Ischaemic Heart Disease SMQ (Narrow and Broad)
- Peripheral Arterial Disease AMQ (Narrow)
- Hypertension SMQ (Narrow and Broad)
- Constipation AMQ (Narrow and Broad)
- Alopecias AMQ (Broad)

Subject incidence of all TEAEs, SAEs, AEs leading to withdrawal of investigational product, fatal AEs, and device related AEs will be tabulated by SOC in alphabetical order and PT in descending order of frequency.

Subject incidence of EOI (standardized MedDRA queries [SMQ] and/or Amgen medical queries [AMQ]) will also be summarized according to their categories and PT in descending order of frequency.

In addition, summarizes of all TEAEs and SAEs occurring in at least 3% of the subjects by PT in any treatment arm will be provided in descending order of frequency. Summaries of all TEAEs and SAEs will be tabulated by SOC, PT, and grade.

9.6.3 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group. The number and percentage of subjects with dose change, reason for dose change and duration of exposure to IP in days will be summarized by treatment group. Missed doses due to COVID-19 control measures will also be summarized.

9.6.4 Exposure to Concomitant Medication

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

10. Changes From Protocol-specified Analyses

In addition to modified MIDAS total score, absenteeism score and presenteeism score will also be analyzed as exploratory endpoints.

11. Literature Citations / References

Quade, D. (1966), Rank analysis of covariance, University of North Carolina, Institute of Statistics Mimeo Series. No. 483

12. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following data points.

- Data from pharmacogenetic substudy
- Data for biomarker development

13. Appendices

NA