Statistical Analysis Plan

Protocol Title:	Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine
Short Protocol Title:	Erenumab Treatment Satisfaction Study
Protocol Number:	20190389
NCT Number:	NCT04825678
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	26MAY2021	Not applicable
Amendment 1 (v2.0)	16OCT2023	• Section 1 protocol version date updated to newest one • Section 3.2 updated to add description and table 3-2 for 240 enrolled subject due to study early termination • Section 4.2 updated to including screening period • Section 5.1 updated to add treatment-related TEAE definition • Section 5.3 updated to add enrollment date as Day 1 if no IP received • Section 5.1.1 updated the definition of migraine type to account for headache days and migraine days collected during screening period • Section 5.4.2 updated to >= 156 days for week 24 windows • Section 6.3.1 deleted baseline value and at least 1 post baseline value • Section 6.3.2 deleted Global Impression Pro Analysis set • Section 7 updated to all the 240 enrolled subjects due to early termination • Section 9.2 deleted summary of IP dose adjustment due to medical necessity after week 12 as only one subject changed dose after week 12 visit; deleted subject disposition summary due to COVID-19 • Section 9.4 updated to o Prior migraine preventive medication by categories o Reasons for stopping of prior migraine preventive medication by categories o General medical history

		○ Type of SOC for dissatisfaction with SOC ○ Targeted neurological medical history • Section 9.5.1 updated to delete the request to report treatment difference with 95% CI and P-value for primary endpoint; subgroup includes screening period • Section 9.5 updated to use efficacy analysis set for secondary endpoint mGI-I; added summary of TSQM item 14 at w12, w16 and w20 • Section 9.6.1 updated to newest MeDRA version 26.0 • Section 9.6.1 new EOIs that summaries across other studies under A334 are added for s389 • Section 9.6.2 is deleted due to no lab need to be analyzed • Section 9.6.2 updated to summarize number, percentage and reason for both doses adjusted and none or partial dose • Section 9.6.3 updated to be the same as protocol language • Section 9.7 updated to NA as COID-19 control measure protocol deviations not collected • Section 13 updated to data collected for the qualitative interviewed-based sub-study is not covered by this analysis plan • Section 14 updated to add “Not applicable”

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List of Abbreviations

Abbreviation	Explanation
COA	Clinical Outcomes Assessment
COVID-19	Coronavirus Disease 2019
CM	Chronic Migraine
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic Case Report Form
eDiary	electronic Diary
EM	Episodic Migraine
EOS	End of Study
FAS	Full Analysis Set
GAD-7	General Anxiety Disorder scale
IP	Investigational Product
LSM	Least-squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MFIQ	Migraine Functional Impact Questionnaire
mGI-I	Migraine Global Impression Item
MIBS-4	Migraine Interictal Burden Scale
MMD	Monthly Migraine Days
MSSS	Migraine Symptom Severity Scale
PHQ-9	Patient Health Questionnaire
Q4W	Every 4 Weeks
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
TSQM-14	Treatment Satisfaction Questionnaire for Medication

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 2** for study 20190389, Erenumab (AMG 334) dated **18 March 2022**. The scope of this plan includes the final 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/Estimands

Objectives	**Endpoints**
Primary	
• To evaluate the effect of erenumab on medication-specific treatment satisfaction	• Change from baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM) overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4
Primary Estimand	
The estimand for the primary efficacy objective consists of: • The target population, which includes subjects with Episodic Migraine (EM) or Chronic Migraine (CM) currently on 1 standard of care migraine prevention therapy • The endpoint, which is the change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM • There are 2 intercurrent events, discontinuation of investigational product (IP) due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive least 1 dose of IP and have a baseline score and at least 1 post-baseline score on the TSQM overall satisfaction scale. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation, defined by the worst postbaseline	

<table>
<tr><td colspan="2">value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
• The treatment, which is erenumab 70 or 140 mg every 4 weeks
• The summary measure, which is the mean change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM

The primary estimand for the primary efficacy objective is the mean change from baseline in TSQM overall satisfaction scale score at week 24 in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline and at least 1 post-baseline TSQM overall satisfaction scale score, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive), while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To assess the effect of erenumab on medication-specific treatment satisfaction</td><td>• Achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4</td></tr>
<tr><td colspan="2">The estimand for the secondary efficacy objective on treatment satisfaction consists of:
• The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
• The endpoint, which is achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM</td></tr>
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- There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value for Item 14 of the TSQM. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not satisfied after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
- The treatment, which is erenumab 70 or 140 mg every 4 weeks
- The summary measure, which is the proportion of subjects who achieves overall satisfaction at week 24

The estimand for the secondary efficacy objective on treatment-related satisfaction is the proportion of subjects who achieves overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value for Item 14 of the TSQM. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not satisfied after IP discontinuation, while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
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- To assess the effect of erenumab on global impression of change in migraine (by subject, treating clinician, and key family member)
</td><td>

- Improvement in subject global impression at week 24, as defined by subject reporting of much improved or a little improved on the migraine Global Impression Item (mGI-I)
- Improvement in treating clinician's global impression at Week 24, as defined by treating clinician's reporting of much improved or a
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	little improved on the mGI-I for each individual subject • Improvement in key family member's impression at week 24, as defined by key family member's reporting of much improved or a little improved on the mGI-I for each individual subject

The estimand for the secondary efficacy objectives on impression of change in migraine consists of:

- The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
- The endpoints, which include:
  - Improvement in subject global impression at week 24, as defined by subject reporting of much improved or a little improved on the mGI-I
  - Improvement in treating clinician's global impression at week 24, as defined by the clinician's reporting of much improved or a little improved on the mGI-I for each individual subject
  - Improvement in key family member's global impression at week 24, as defined by family member's reporting of much improved or a little improved on the mGI-I for each individual subject
- There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have at least 1 post-baseline value of each respective mGI-I item. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
- The treatment, which is erenumab 70 or 140 mg every 4 weeks

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- The summary measure, which is the proportion of subjects who achieves impression of improvement at week 24.

The estimand for the secondary efficacy objective on impression of change in migraine is the proportion of subjects who achieves global impression of migraine improvement at week 24 as defined by subject, treating clinician, or family member reporting of much improved or a little improved on the mGI-I, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have at least 1 post-baseline value of the respective mGI-I, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation, while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
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- To assess the effect of erenumab on subject functional impairment
</td><td>

- Change from baseline in physical function domain score at week 24, as measured by the Migraine Functional Impact Questionnaire (MFIQ)
- Change from baseline in usual activities domain score at week 24 as measured by MFIQ
- Change from baseline in emotional function domain score at week 24 as measured by MFIQ
- Change from baseline in social function domain score at week 24 as measured by MFIQ
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The estimand for the secondary efficacy objective on subject functional impairment consists of:

- The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
- The endpoints, which include:
  - Change from baseline in MFIQ physical function domain score at week 24
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- Change from baseline in MFIQ usual activities domain score at week 24
- Change from baseline in MFIQ emotional function domain score at week 24
- Change from baseline in MFIQ social function domain score at week 24

- There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects 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 scores. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
- The treatment, which is erenumab 70 or 140 mg every 4 weeks
- The summary measure, which is change from baseline in each MFIQ domain score at week 24

The estimand for the secondary efficacy objective on subject functional impairment is the change from baseline at week 24 in each MFIQ domain score, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value in each MFIQ domain score, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive), while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.

Exploratory	
• To explore the effect of erenumab on the change from baseline in monthly	• Change from baseline in TSQM overall satisfaction scale score at weeks 12, 16, and 20 and mean over weeks 16, 20, and 24

medication-specific treatment satisfaction	• Change from baseline in TSQM sub-scale domain scores at weeks 12, 16, 20 and 24 and mean over weeks 16, 20, and 24: – effectiveness – side effects – convenience
• To explore the effect of erenumab on monthly global impression of improvement in migraine	• Improvement in subject global impression at weeks 12, 16, and 20, as defined by subject reporting of much improved or a little improved on the mGI-I • Improvement in treating clinician's global impression at weeks 12, 16, and 20, as defined by treating clinician's reporting of much improved or a little improved on the mGI-I • Improvement in key family member's global impression at weeks 12, 16, and 20, as defined by key family member's reporting of much improved or a little improved on the mGI-I
• To explore the effect of erenumab on the change from baseline in monthly functional impairment	• Change from baseline in MFIQ functional impairment domain scores, at weeks 12, 16, and 20, and mean over weeks 16, 20, and 24: – Impact on physical function – Impact on usual activities – Impact on emotional function – Impact on social function
• To explore the effect of erenumab on the change from baseline in the burden of migraine	• Change from baseline in the Migraine Symptom Severity Scale (MSSS) total score at weeks 12, 16, 20, and 24 and mean over weeks 16, 20, and 24

	• Change from baseline in the Migraine Interictal Burden Scale (MIBS-4) total score at weeks 12, 16, 20, and 24 and mean over weeks 16, 20, and 24
• To explore the effect of erenumab on the change from baseline in number of monthly migraine days (MMD)	• Change from baseline in mean MMD over weeks 16, 20, and 24 • Change from baseline in MMD at weeks 16, 20, and 24 • Achievement of at least a 50% reduction from baseline in mean MMD over weeks 16, 20, and 24 • Achievement of at least a 50% reduction from baseline in MMD at weeks 16, 20, and 24
• To explore the effect of erenumab on the change from baseline in acute migraine-specific medication use	• Change from baseline in mean monthly acute migraine-specific medication days over weeks 16, 20, and 24 • Change from baseline in monthly acute migraine-specific medication days at weeks 16, 20, and 24
• To explore the effect of erenumab on the change from baseline in anxiety and depression	• Change from baseline in General Anxiety Disorder scale (GAD-7) total score at weeks 12 and 24 • Change from baseline in Patient Health Questionnaire (PHQ-9) total score at weeks 12 and 24

2.2 Hypotheses and/or Estimations

The study is descriptive in nature without a comparator arm, and as such no formal statistical hypothesis is defined.

3. Study Overview

3.1 Study Design

Study 20190389 is a phase 4 open-label study that will enroll subjects with EM or CM in an approximately 1:1 ratio. The study will comprise the following periods:

- A combined screening/baseline period consisting of the following:

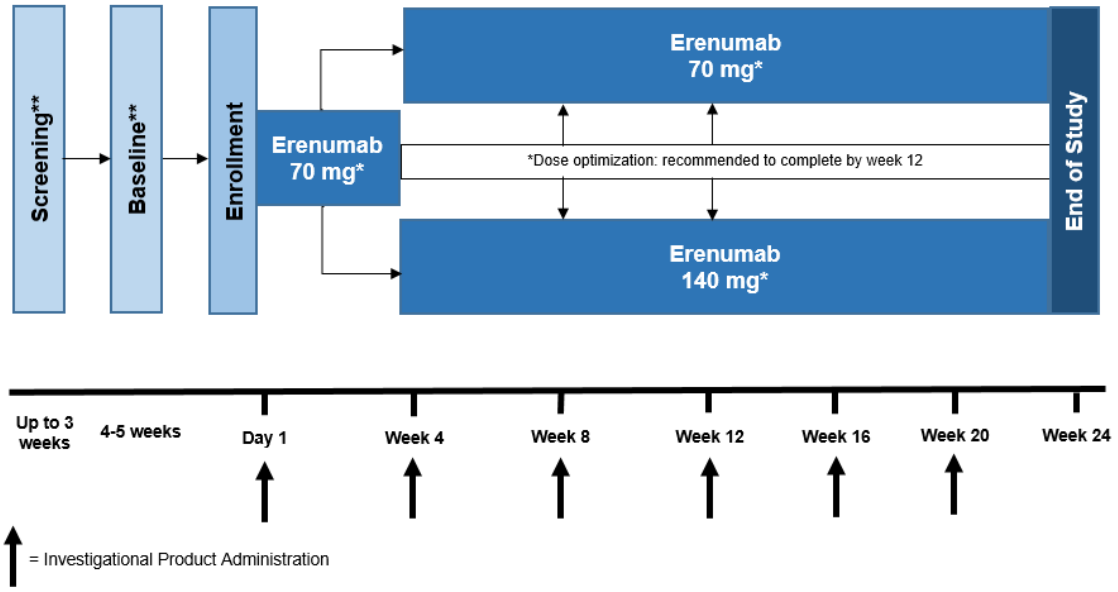
  - A screening visit (which may coincide with the first day of the baseline period) for the assessment of eligibility criteria

  - A baseline period of approximately 4 weeks (no less than 28 days; up to 35 days) to collect data on migraine headaches and acute headache medication use using electronic diary (eDiary) and to assess compliance in eDiary usage

- A 24-week open-label treatment period

Eligible subjects may enter the baseline period at the same visit or may delay baseline procedures up to 3 weeks after the screening visit. At completion of the baseline period, those who meet eligibility criteria and choose to proceed will be enrolled and will enter the open-label treatment period to receive erenumab 70 or 140 mg once every 4 weeks (Q4W) by subcutaneous (SC). All subjects will be started on a 70 mg dose of erenumab at day 1 with provider discretion for dose optimization (either 70 mg or 140 mg), which is recommended to be completed by week 12. All subjects will be required to enter the study on 1 standard of care preventive medication for their migraine, whose dose then can be adjusted by the investigator's discretion and must be stable by week 12. The treating clinician and a key family member (if available) for each participating subject will be invited to complete an mGI-I at weeks 12, 16, 20, and 24/End of Study (EOS) for the mGI-I endpoints.

Figure 1 1. Study Schema



* All subjects will be started on a 70 mg dose of erenumab at day 1 with provider discretion for dose optimization. Dose optimization will allow patients to remain on 70 mg, increase the dose from 70 mg to 140 mg, and if needed decrease the dose back down from 140 mg to 70 mg. It is highly recommended that all erenumab dose adjustments be completed by week 12, after which all subjects should remain on the week 12 erenumab dose for the rest of the study. Additional dose adjustments after week 12 are not recommended and must only be made if deemed medically necessary by the investigator.

** Baseline may begin on the same day as screening

3.2 Sample Size

The total sample size of approximately 322 subjects (effective sample size of 289, assuming 10% dropout at week 24) is driven by the precision of the proportion estimates for the binary secondary endpoints, which targets a half-width of 95% confidence intervals (CIs) around 5%. The half-width of the 95% CI will be the widest when the estimated percentage is 50%, given a fixed sample size, and will become narrower if the percentage moves further away from 50% (see Table 3-1).

Table 3-1. Half-width of 95% CI for Various Estimated Percentages With Effective Sample Size of 289 Subjects

Percentage Estimate	Half-width of 95% CI With Effective Sample Size = 289
50%	5.8%
60%	5.6%
70%	5.3%
80%	4.6%

Given the evolving landscape of migraine preventive trials and treatment paradigm, the exploratory design of this trial, and the descriptive nature of the study objectives and endpoints, it had been understood that prolonging screening and enrollment efforts beyond this point would be of little additional value, thus, it has been decided to terminate study 20190389 early to enroll only 240 subjects. Table 3-2 is the updated half-width of 95% CI based on the sample size of 240 subjects (effective sample size of 216, assuming 10% dropout at week 24).

Table 3-2. Half-width of 95% CI for Various Estimated Percentages With Effective Sample Size of 216 Subjects

Percentage Estimate	**Half-width of 95% CI With Effective Sample Size = 216**
50%	**6.7%**
60%	**6.5%**
70%	**6.1%**
80%	**5.3%**

3.3 Adaptive Design

The adaptive design is not applicable for this study.

4. Covariates and Subgroups

4.1 Planned Covariates

All model-adjusted analyses of primary and secondary efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed **if applicable,** visit, the prevailing erenumab dose from week 12 onwards, and baseline MMD in the model.

4.2 Subgroups

The primary and secondary endpoints will be analyzed in the following subgroups:

- Whether remained on standard of care migraine preventive treatment throughout the study (yes vs no)
- Migraine type (EM vs CM) based **on both CRF data collected on form "Headache and Migraine Frequency Medical History" during screening and eDiary collection during baseline**

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 final analysis.

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints Based on Monthly Collection

The daily eDiary collection will occur during the baseline period and months 4, 5, and 6.

Subjects' daily headache information will be collected through the following questions. Possible outcomes on migraine-related endpoints are summarized below:

Table 5-1. Definitions of Migraine Day, Headache Day, and Acute Migraine-specific Medication Day

	Scenarios									
	1	2	3	4	5	6	7	8	9	10
eDiary data collection										
Headache (Y/N)	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
If Y, (a) Pain intensity (1 to 10)	1 to 10	1 to 10	1 to 10	1 to 10	1 to 10	1 to 10	NA	NA	NA	NA
(b) Migraine (Y/N)	Yes	Yes	Yes	No	No	No	NA	NA	NA	NA
(c) Acute medication for headache (Y/N)	Yes	Yes	No	Yes	Yes	No	NA	NA	NA	NA
If Y, Triptan (Y/N)	Yes	No	NA	Yes	No	NA	NA	NA	NA	NA
If N, Aura (Y/N)	NA	NA	NA	NA	NA	NA	Yes	Yes	Yes	No
If Y, acute medication for aura (Y/N)	NA	NA	NA	NA	NA	NA	Yes	Yes	No	NA
If Y, Triptan (Y/N)	NA	NA	NA	NA	NA	NA	Yes	No	NA	NA
Endpoint definition										
Headache Day	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Migraine Day	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Acute Migraine-specific Medication Day	Yes	No	No	Yes	No	No	Yes	No	No	No

Migraine Type

CM is defined as subjects with ≥ 15 headache days per month of which ≥ 8 headache days meet criteria as migraine on either CRF data collected on form "Headache and Migraine Frequency Medical History" during screening or eDiary collection during baseline; EM is defined as subjects who does not fulfill criteria for CM.

Diary Day

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

Headache Day

A calendar day (00:00 to 23:59) in which the subject reports a headache (ie, Scenarios 1 to 7 in Table 5-1)

Migraine Day

A calendar day (00:00 to 23:59) in which the subject reports a migraine (ie, Scenarios 1 to 4 in Table 5-1) or takes a migraine-specific medication (ie, Scenario 7 in Table 5-1)

Acute Migraine-specific Medication Day

A calendar day (00:00 to 23:59) in which the subject takes a migraine-specific medication (ie, Scenarios 1, 4, and 7 in Table 5-1).

Monthly Frequency Variable in Days

Number of days of interest during one monthly interval as defined in Table 5-2. Monthly frequency variables include

- Monthly Migraine Days (MMD)
- Monthly Acute Migraine-specific Medication Days

The following proration rule will be applied to all monthly frequency variables for each monthly interval.

Within Each Monthly Interval	Monthly Frequency Variable
≥ 14 diary days	Prorate to 28-day equivalent without rounding $\frac{Number\ of\ frequency\ days\ within\ each\ monthly\ interval}{Number\ of\ diary\ days\ within\ each\ monthly\ interval} * 28$
< 14 diary days	Set to missing

5.1.2 Efficacy Endpoints Based on Clinical Outcome Assessments

- **Treatment Satisfaction Questionnaire for Medication (TSQM)**

The Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 is a 14-item instrument designed to measure important dimensions of patients' experiences with their medication. It has 4 domains: effectiveness, side effects, convenience, and global satisfaction. Scores range from 0 to 100, with higher scores indicating greater satisfaction. The recall period is the last two to three weeks, or since the medication was last used.

Scoring Algorithm: TSQM Scale scores range from 0 to 100 and no computed score should be lower or higher than these limits.

Effectiveness: Effectiveness domain contains Item 1 to Item 3

$$Effectiveness = \frac{[(Item\ 1 + Item\ 2 + Item\ 3) - 3]}{18} \times 100$$

Side Effects: Side effects domain contains Item 5 to Item 8

$$Side\ Effects = \frac{[(Item\ 5 + Item\ 6 + Item\ 7 + Item\ 8) - 4]}{16} \times 100$$

Convenience: Convenience contains Item 9 to Item 11

$$Convenience = \frac{[(Item\ 9 + Item\ 10 + Item\ 11) - 3]}{18} \times 100$$

Overall satisfaction: Overall satisfaction domain contains Item 12 to Item 14

First recode Item14, recode Item 14 = (Item14 − 1) × 5/6

Then

$$Overall\ satisfaction\ = \frac{[(Item\ 12 + Item\ 13 + Item\ 14) - 3]}{12} \times 100$$

- **Migraine Global Impression Item (mGI-I)**

The mGI-I is a single item instrument designed to measure improvement/worsening in migraine. The 3 versions of the instrument include the perspective of study subjects, key family members, and treating clinicians measured on the following scale: much improved; a little improved; no change; a little worse; or much worse. The recall period is the past 7 days.

- **Migraine Functional Impact Questionnaire (MFIQ)**

The Migraine Functional Impact Questionnaire (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 (items 1 to 5), Impact on Usual Activities (items 6 to 15), Impact on Social Functioning (items 17 to 21), and Impact on Emotional Functioning (items 22 to 26). In addition, there is 1 stand-alone global item (item 16) assessing the overall impact on usual activities. Subjects respond to each item 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 (ie, raw score) and rescaled to a 0-100 scale according to the formula below, with higher scores representing greater burden. No total score is created for the MFIQ. The recall period is the past 7 days.

$$Domain\ Score = \frac{(Raw\ score - Lowest\ possible\ raw\ score)}{(Highest\ possible\ raw\ score - Lowest\ possible\ raw\ score)} * 100$$

For the purposes of domain scoring, “does not apply” will be imputed with the mean of other items in the domain.

- **Migraine Symptom Severity Scale (MSSS)**

The Migraine Symptom Severity Scale (MSSS) is a 7-item questionnaire that assesses frequency of pain and other symptoms associated with migraines. Responses are as follows: “never”, “rarely”, “less than half the time”, “half the time or more”, and “all or nearly all of the time”. The responses are given a value from 1 to 3 as follows: Never = 0, Rarely = 1, Less Than Half the Time = 2, Half the Time or More = 3, and All or Nearly All of the time = 3. The MSSS score is the sum of the 7 items, and has a range from 0 to 21.

- **Migraine Interictal Burden Scale (MIBS-4)**

The Migraine Interictal Burden Scale (MIBS-4) measures interictal migraine-related burden with 4 questions that assess impairment in work or school, impairment in family

and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress. Each of the 4 questions is responded to using 1 of 6 response categories: “Don’t know/NA” (Score = 0), “Never” (Score = 0), “Rarely” (Score = 1), “Some of the time” (Score = 2), “Much of the time” (Score = 3) or “Most or all of the time” (Score = 3). Each question is multiplied with its score and summed up to produce total score ranges from 0 to 12. The MIBS-4 total scores are categorized into 4 level of interictal burden: None (0), Mild (1 to 2), Moderate (3 to 4) and Severe (5 or higher).

Total Score = {[(Number of responses for ‘Don't Know’ for Item 1 to Item 4)* 0] +

[(Number of responses for ‘Never’ for Item 1 to Item 4)* 0] +

[(Number of responses for ‘Rarely’ for Item 1 to Item 4)* 1] +

[(Number of responses for ‘Some of the time’ for Item 1 to Item 4)* 2] +

[(Number of responses for ‘Much of the time’ for Item 1 to Item 4)* 3] +

[(Number of responses for ‘Most or all of the time’ for Item 1 to Item 4)* 3]}

- **Generalized Anxiety Disorder Scale (GAD-7)**

The Generalized Anxiety Disorder Scale (GAD-7) is a self-administered 7-item instrument that uses some of the Diagnostic and Statistical Manual (of Mental Disorders) fifth edition (DSM-V) criteria for general anxiety disorder (GAD) 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. Score interpretation is as follows: 1 to 4 minimal symptoms, 5 to 9 mild symptoms, 10 to 14 moderate symptoms, and 15 to 21 severe symptoms. Changes of 5 points or more are clinically meaningful.

- **Patient Health Questionnaire (PHQ-9)**

The Patient Health Questionnaire (PHQ-9) is a self-administered questionnaire, widely used for diagnosis and severity assessment of depression in primary care settings. The Patient Health Questionnaire (PHQ) is a 9-question, self-administered instrument for screening, diagnosing, monitoring, and measuring the severity of depression. It incorporates Diagnostic and Statistical Manual (of Mental Disorders) fourth edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. The tool rates the frequency of the symptoms which factors into the scoring severity index. PHQ-9 scores each of the 9 DSM-IV criteria as “0” (not

at all) to “3” (nearly every day). The score is calculated as the sum of the item responses and corresponds to one of the 5 severity categories: Minimal or None = 0 to 4, Mild = 5 to 9, Moderate = 10 to 14, Moderately Severe = 15 to 19, and Severe = 20 to 27. Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.

5.1.3 Safety Analysis

Serious Adverse Event (SAE)

An event categorized as “Adverse Event” with the indicator flag “Serious” equal to “Yes” on the Events Case Report Form (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 Events

A TEAE with the indicator flag “Serious” equal to “Yes” on the Events eCRF.

Treatment-emergent Adverse Device Effect

A TEAE 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.

Treatment-related Treatment-emergent Adverse Event

A treatment-emergent adverse event with the indicator flag “Is there a reasonable possibility that the event may have been caused by Investigational Medicinal Product” 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 data entry after completion of the eDiary training module.

Enrollment Date

Enrollment Date is the day a subject has met all eligibility criteria and is enrolled.

First IP Dose Date

First Dose Date is the date on which a subject is administered the first dose of IP following completion of the Baseline period as recorded on the IP Administration eCRF.

End of IP Administration Date

The end of IP admin date for each subject is defined as the date the decision was made to end IP as recorded on the End of IP 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 eDiary collection during baseline period) 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.

Study Day 1

Study Day 1 is defined as the first IP dose date **or enrollment date if no IP received.**

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.

Treatment Discontinuation Visit

Treatment discontinuation visit is defined as the earliest visit on or after the date when the decision to discontinue treatment is made.

5.4 Study Time Intervals

5.4.1 Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

The (4-week) monthly intervals for efficacy endpoints derived from eDiary collection 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.

Applicable efficacy endpoints utilizing the monthly intervals in Table 5-2 includes:

- Monthly Migraine Days (MMD)
- Monthly Acute Migraine-specific Medication Days

Table 5-2. Monthly Intervals for Efficacy Endpoints Derived From Daily Diary 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	Day prior to study day 1
Open-label Treatment Period	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 24 visit date – 1

[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, unless stated otherwise

5.4.2 Analysis Visits for Endpoints Derived Based on Monthly Data 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, Table 5-5, and Table 5-6.

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. MFIQ, MSSS, and MIBS-4 Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
Open-label Treatment Period	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**

Table 5-4. mGI-I Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Open-label Treatment Period	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**

Table 5-5. GAD-7 and PHQ-9 Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
Open-label Treatment Period	Week 12 (Month 3)	85	72 to 99
	Week 24 (Month 6)	169	**≥ 156**

Table 5-6. TSQM Version 1.4 Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	**Day 1 (Baseline)**	**1**	**Last measurement ≤ Day 1**
Open-label Treatment Period [a]	**Week 12 (Month 3)**	**85**	**79 to 106**
	Week 16 (Month 4)	**113**	**107 to 134**
	Week 20 (Month 5)	**141**	**135 to 162**
	Week 24 (Month 6)	**169**	**≥ 163**

[a] The recall period for TSQM Version 1.4 is the last 2 to 3 weeks.

5.4.3 Subject Disposition

Exposed to Investigational Product

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

Completing the 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 **are enrolled and** have not yet completed their EOS visit.

5.5 Arithmetic Calculations

Duration of IP Exposure (Days)

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.

Percent Change From Baseline

The change from baseline divided by baseline and multiplied by 100:

$$Percent\ Change\ From\ Baseline = \frac{(Postbaseline - Baseline)}{Baseline} \times 100$$

If the baseline value is 0 and the postbaseline value is also 0, the percent change from baseline is set to 0. If the baseline value is 0 and the postbaseline value is non-zero, the percent change from baseline is set to missing.

Mean Monthly Change From Baseline Over Multiple Months

Arithmetic Mean monthly change from baseline is the arithmetic mean of the observed monthly change from baseline values for the months with non-missing change from baseline values.

5.6 Disease Characteristics

Treatment Failure of Prior Migraine Preventive Medications

Treatment failure of prior migraine preventive medications is determined by the medications marked as “Prior Migraine Prophylactic” with “Reason for Stopping” being “Lack of Efficacy” or “Adverse reaction” or “Intolerance” on the Prior Migraine Prophylactic And Ongoing Migraine Prophylactic eCRF.

6. Analysis Sets

The following analysis sets are defined for this study.

6.1 Full Analysis Set

The full analysis set (FAS) consists of all subjects enrolled in the study. Analysis of disposition, demographic and baseline characteristics, important protocol deviations, and protocol deviations related to COVID-19 control measures will utilize the FAS.

6.2 Efficacy Analysis Set

The efficacy analysis set consists of a subset of subjects from FAS who receive at least 1 dose of investigational product. Analysis of efficacy endpoints will utilize the efficacy analysis set.

6.3 Safety Analysis Set

The safety analysis set (SAS) will consist of a subset of subjects from FAS who received at least 1 dose of investigational product. Analysis of safety endpoints and summary of investigational product administration will utilize the safety analysis set.

7. Planned Analyses

There is only one milestone analysis to be conducted for this study once **all the 240** enrolled subjects have completed the week 24/EOS visit. The data will be cleaned, and the database will be locked for the final analysis.

7.1 Final Analysis

The final analysis will be conducted when **all** enrolled subjects have completed the week 24/EOS visit.

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 electronic Clinical Outcome Assessments (eCOAs) data including eDiary, GAD-7, MFIQ, mGI-I, MIBS-4, MSSS, PHQ-9, TSQM version 1.4 questionnaires data will be stored outside of RAVE database. The database is subject to edit check outlined in the Data Management Plan (DMP).

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, inability to evaluate an endpoint at a particular point in time, and treatment discontinuation due to lack of efficacy, adverse event, or non-response. The efficacy endpoints will be collected via daily eDiary and monthly eCOA assessments device. Subjects could miss entering several days of daily migraine data or an eCOA assessment in each monthly interval.

The general procedures outlined below describe how missing data will be handled.

For the eDiary data collected daily, if at least 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements (eg, headache days, migraine days or acute migraine-specific medications days [AMSMD]) will be prorated based on the number of days with available information. If less than 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements will be set to missing (Table 8-1). For the descriptive summary of the mean monthly value calculated using the monthly value from each of months 4, 5, and 6, if a subject has at least one monthly value at months 4, 5, and 6, then the subject contributes to the summary statistics.

For the endpoints derived from the daily diary data, please refer to proration approach specified in Section 5.1.1. On handling missing daily diary data. Missing monthly measurement after proration will be handled by statistical analysis approaches listed in Section 9.5.

Table 8-1. Handling of Missing and Incomplete eDiary Data

Monthly Frequency Endpoint	**Condition**	**Proration Method (Without Rounding)**
Monthly frequency measurements (migraine days and acute migraine-specific medication days)	A diary day is a day with all headache-related questions completed in eDiary. If diary days in baseline or each post-baseline interval ≥ 14, apply proration for that monthly interval; Else monthly frequency measurement is set to missing	Number of event days of interest in a monthly interval* 28/ Number of diary days in the monthly interval Note: Event days of interest is referred to migraine days and acute migraine-specific medication days

Missing or incomplete dates will be listed as reported, except for incomplete start date of an adverse event or concomitant medication (Table 8-2).

Table 8-2. Imputation for Incomplete Start Date of an Adverse Event or Concomitant Medication

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	—

eCRF = electronic case report form

Missing data will not be imputed for safety endpoints.

8.4 Detection of Bias

The below mentioned factors that may bias the results of the study:

- Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- Investigational product dosing non-compliance
- The timing of and reasons for early withdrawal from study treatment and from study

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

The reasons for early withdrawal from study 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 will be queried 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 presented in this statistical analysis plan unless there is sufficient justification to exclude them. 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.

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

Summary statistics will be computed at each timepoint of interest. For continuous endpoints, the following descriptive statistics will be computed: number of observations, means, standard deviations, standard errors, medians, first and third quartiles, minimums and maximums. For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

Due to lack of a control arm, all analyses should be considered as descriptive in nature. If a subject discontinued treatment due to lack of efficacy or adverse event, data on primary and secondary efficacy endpoints collected after treatment discontinuation will be defined based on the worst post-baseline value observed (for continuous endpoints) up to IP discontinuation (inclusive) or non-response (for binary endpoints) using a composite strategy. If a subject discontinued treatment due to other reasons, data collected after treatment discontinuation visit will be censored based on a hypothetical strategy and not be used in efficacy analyses as described in Section 9.5.

Analysis for primary and secondary endpoints will be using observed data with intercurrent event handling; analysis for exploratory endpoints will be using observed data without intercurrent event handling. **A sensitivity analysis using observed data without any intercurrent event handling will also be performed for primary endpoint.**

9.2 Subject Accountability

The disposition of all enrolled subjects will be tabulated based on two migraine types (EM vs CM) separately and overall population using FAS.

The number and percentage of subjects who were enrolled, received investigational product, completed investigational product, discontinued investigational product and reasons for discontinuing, completed study, discontinued study and reasons for discontinuing will be summarized by the two migraine types (EM vs CM) separately, and the overall population. Summary of subjects who discontinue investigational product/study due to COVID-19 control measures will be included.

In addition, the descriptive summaries listed below will be done by the two migraine types (EM vs CM) separately and overall population using safety analysis set.

- At week 12, the number and percentage of subjects who remained on 70 mg and did not receive any 140 mg dose, who increased the dose to 140 mg, and who received 70 mg at week 12 and have received at least one dose of 140 mg previously.
- At week 12, the number and percentage of subjects who continued or discontinued SOC

The summary of the study reporting phase including a description of key dates such as the first subject enrolled, last subject enrolled, last subject's end of investigational product, last subject's end of study will also be provided using FAS by the two migraine types (EM vs CM) separately and overall population.

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 course of the study. Eligibility deviations are defined in the protocol.

The final IPD list will be used to produce the Summary of IPDs table and the list of subjects with IPDs using the FAS.

Protocol deviations related to COVID-19 control measures will be summarized separately.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline disease characteristics will be summarized using descriptive statistics separately for the two migraine types and overall study population using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple race.

The following demographics and baseline disease characteristics will be summarized:

- Age
- Sex
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI, kg/m^2)
- Overall Migraine
- **Prior migraine preventive medication by categories**
- **Reasons for stopping of the prior migraine preventive medication by categories**
- **General medical history**
- **Type of SOC for dissatisfaction with SOC**
- Summary of prior migraine preventive medication and reasons for discontinuation
- **PRO (TSQM 1.4, MFIQ, MSSS, MIBS-4, GAD-7, PHQ-9, and ETS) at baseline**
- **Targeted neurological medical history**
- Disease duration of migraine
- Age at onset of migraine
- Monthly headache days during baseline period
- Monthly migraine days during baseline period
- Monthly acute migraine-specific medication days during baseline period

9.5 Efficacy Analyses

The final analysis of primary, secondary and exploratory endpoints will utilize the efficacy analysis set.

The primary and secondary endpoints will be analyzed in the following subgroups:

- Whether remained on standard of care migraine preventive treatment throughout the study (yes vs no)
- Migraine type (EM vs CM)

Detailed analysis methods and covariates included in the models are summarized in the table below. The value for the covariate "prevailing dose from week 12 onwards" will be the prevailing dose if all three planned doses are administered, or the last dose if two or fewer doses are administered from week 12 to week **20 or last observed dose prior to week 12 if none of three doses are administered**.

Table 9-1. Primary Efficacy Endpoint and analysis Summary Table

Endpoint	Primary Summary and Analysis Method
Change from baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM) overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4 (Note: Results from individual time point and mean over time points will also be generated in the same repeated measures mixed effects model.)	1. Summary statistics using observed data **(after intercurrent event handling)** 2. The change from baseline in the TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4 will be analyzed using a repeated measures mixed effects model, including baseline TSQM overall satisfaction scale score, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data**. The mean change from baseline in TSQM overall satisfaction scale score at week 24 will be estimated from the least-squares mean (LSM) of the mixed effects model, and the corresponding 95% CI will be provided. The nominal p-value will be reported by comparing the mean change

Endpoint	Primary Summary and Analysis Method
	from baseline in TSQM overall satisfaction scale score at week 24 to zero with a two-sided 5% significance level. 3. The efficacy analysis set will be used for this endpoint analysis.

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4	1. Summary statistics using observed data **(after intercurrent event handling)**; 2. The achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4 will be analyzed using a generalized linear mixed effects model with the logit link function. The model will include baseline achievement of overall satisfaction, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data**. The proportions and the corresponding 95% CI at week 24 will be estimated from the LSM (with inverse link function) of the mixed effects model. 3. The efficacy analysis set will be used for this endpoint analysis.
Improvement in subject global impression at **week 24**, as defined by subject reporting of much improved or a little improved on the mGI-I Improvement in treating clinician's global impression at **week 24**, as	1. Summary statistics using observed data **(after intercurrent event handling)**; 2. The Improvement in global impression at week 24, as defined by subject's, clinician's, and key family member's reporting of much improved or a little

Endpoint	Primary Summary and Analysis Method
defined by treating clinician's reporting of much improved or a little improved on the mGI-I Improvement in key family member's global impression at **week 24**, as defined by key family member's reporting of much improved or a little improved on the mGI-I	improved on the migraine Global Impression Item (mGI-I) will be analyzed separately using a generalized linear mixed effects model with the logit link function. The model will include the visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data**. The proportions and the corresponding 95% CI at week 24 will be estimated from the LSM (with inverse link function) of the mixed effects model. 3. The **efficacy analysis set** will be used for this endpoint analysis.
Change from baseline in subject functional impairment domain score at week 24, as measured by the Migraine Functional Impact Questionnaire (MFIQ) – Physical function domain score – Usual activities domain score – Emotional function domain score – Social function domain score	1. Summary statistics using observed data **(after intercurrent event handling)**; 2. The change from baseline in subject functional impairment domain score at week 24, as measured by the MFIQ will be analyzed using a generalized linear mixed effects model with the identity link function. The model will include baseline subject functional impairment domain score, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data.** The mean change from baseline in subject functional impairment domain score at week 24 with the corresponding 95% CI will be estimated from the LSM of the mixed effects model, and p-values comparing with zero at a two-sided 5% significance level will be reported.

Endpoint	Primary Summary and Analysis Method
	3. The efficacy analysis set will be used for this endpoint analysis. 4. This endpoint will be analyzed separately for each functional domain.

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Change from baseline in TSQM overall satisfaction scale score at weeks 12, 16, and 20 and mean over weeks 16, 20, and 24	This endpoint will be analyzed same as primary efficacy endpoint.
Achievement of overall satisfaction as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on item 14 of the TSQM version 1.4 at weeks 12, 16, and 20.	**This endpoint will be analyzed same as primary efficacy endpoint.**
Change from baseline in TSQM sub-scale domain scores at weeks 12, 16, 20 and 24 and mean over weeks 16, 20, and 24: – effectiveness – side effects – convenience	This endpoint will be analyzed same as primary efficacy endpoint. Note: Use baseline value covariate as a "Baseline TSQM sub-scale domain score"
Improvement in subject global impression at weeks 12, 16, and 20, as defined by subject reporting of much improved or a little improved on the mGI-I Improvement in treating clinician's global impression at weeks 12, 16, and 20, as defined by treating	This endpoint will be analyzed same as above mentioned mGI-I endpoint.

Endpoint	Primary Summary and Analysis Method
clinician's reporting of much improved or a little improved on the mGI-I Improvement in key family member's global impression at weeks 12, 16, and 20, as defined by key family member's reporting of much improved or a little improved on the mGI-I	
Change from baseline in MFIQ functional impairment domain scores, at weeks 12, 16, and 20, and mean over weeks 16, 20, and 24: – Impact on physical function – Impact on usual activities – Impact on emotional function – Impact on social function	1. Summary statistics by visit using observed data at each visit, and the calculated mean MFIQ physical function impairment domain score over weeks 16, 20, and 24. 2. The change from baseline in physical function impairment domain score at weeks 12, 16, and 20, and mean over weeks 16, 20, and 24, as measured by the MFIQ will be analyzed using a generalized linear mixed effects model with the identity link function. The model will include baseline MFIQ physical function domain score, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data**. The mean change from baseline in physical function impairment domain score at weeks 12, 16, and 20, and mean over weeks 16, 20, and 24 with the corresponding 95% CI will be estimated from the LSM of the mixed effects model. 3. The efficacy analysis set will be used for this endpoint analysis.

Endpoint	Primary Summary and Analysis Method
Achievement of at least a 50% reduction from baseline in mean MMD over weeks 16, 20, and 24	1. Summary statistics by visit using observed data at each visit, and at least a 50% reduction from baseline in mean MMD over weeks 16, 20, and 24. 2. The achievement of at least a 50% reduction from baseline in mean MMD over weeks 16, 20, and 24 will be analyzed using a generalized linear mixed effects model with the logit link function. The model will include the prevailing erenumab dose from Week 12 onwards, and baseline MMD. The probabilities and the corresponding 95% CI for 50% reduction from baseline MMD in mean MMD over months 4 to 6 will be estimated using the mixed effects model. 3. The efficacy analysis set will be used for this endpoint analysis.
Achievement of at least a 50% reduction from baseline in MMD at weeks 16, 20, and 24	○ Summary statistics by visit using observed data at each visit, and at least a 50% reduction from baseline in MMD at weeks 16, 20, and 24. ○ The change from Achievement of at least a 50% reduction from baseline in MMD at weeks 16, 20, and 24 will be analyzed using a generalized linear mixed effects model with the logit link function. The model will include achievement of at least a 50% reduction from baseline in MMD, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD.

Endpoint	Primary Summary and Analysis Method
	The probabilities and the corresponding 95% CI for at least 50% reduction from baseline MMD at weeks 16, 20, and 24 will be estimated using the mixed effects model. o The efficacy analysis set will be used for this endpoint analysis.

The same analysis methods will be applied to the below exploratory endpoints:

Change from baseline in the Migraine Symptom Severity Scale (MSSS) total score at weeks 12, 16, 20, and 24 and mean over weeks 16, 20, and 24

Change from baseline in the Migraine Interictal Burden Scale (MIBS-4) total score at weeks 12, 16, 20, and 24 and mean over weeks 16, 20, and 24

Change from baseline in mean MMD over weeks 16, 20, and 24

Change from baseline in MMD at weeks 16, 20, and 24

Change from baseline in mean monthly acute migraine-specific medication days over weeks 16, 20, and 24

Change from baseline in monthly acute migraine-specific medication days at weeks 16, 20, and 24

Change from baseline in General Anxiety Disorder scale (GAD-7) total score at weeks 12 and 24

Change from baseline in Patient Health Questionnaire (PHQ-9) total score at weeks 12 and 24

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The primary endpoint, the change from baseline in the TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4 will be analyzed using a repeated measures mixed effects model, including baseline TSQM overall satisfaction scale score, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD **based on observed data**.

The mean change from baseline in TSQM overall satisfaction scale score at week 24 will be estimated from the least-squares mean (LSM) of the mixed effects model, and the corresponding 95% CI will be provided. The nominal p-value will be reported by comparing the mean change from baseline in TSQM overall satisfaction scale score at week 24 to zero with a two-sided 5% significance level.

This endpoint will be analyzed using the following subgroups **respectively**:

- Whether remained on standard of care migraine preventive throughout the study (yes vs. no)
- Migraine type (EM vs. CM)

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 final analysis.

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses will be performed using the same method as primary analysis method but within level of each subgroup of interest.

The efficacy analysis set will be used for this endpoint analysis.

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints calculated by the methods as specified detailed in Table 9-2. Secondary Efficacy Endpoint Summary Table, column Primary Summary and Analysis Method.

For continuous secondary endpoints, a generalized linear mixed effects model with the identity link function will be used. The model will include the corresponding baseline value for the endpoint being analyzed, visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD. The corresponding 95% CI will be estimated from the LSM of the mixed effects model, and p-values comparing with zero at a two-sided 5% significance level will be reported.

For binary secondary endpoints, a generalized linear mixed effects model with the logit link function will be used. The model will include the corresponding baseline value for the endpoint being analyzed (except for the global impression endpoints), visit, the prevailing erenumab dose from Week 12 onwards, and baseline MMD. The proportions and the corresponding 95% CI will be estimated from the LSM (with inverse link function) of the mixed effects model and will be reported.

The secondary endpoints will be analyzed in the following subgroups:

- Whether remained on standard of care migraine preventive treatment throughout the study (yes vs. no)
- Migraine type (EM vs. CM)

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 final analysis.

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses will be performed using the same method as primary analysis method but within level of each subgroup of interest.

The efficacy analysis set will be used for this endpoints analyses.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints calculated by the method as specified in Table 9-3. All the exploratory endpoints will be analyzed the same way as that for the primary and secondary endpoints **without any intercurrent event handling**.

The subgroup analysis is not applicable for exploratory endpoints.

The efficacy analysis set will be used for all the exploratory endpoint analyses.

9.6 Safety Analyses

All safety analyses will be performed based on all subjects in the Safety Analysis Set, both overall and separately by migraine prevention therapy standard of care status (continuation vs discontinuation).
The safety analysis will includes the adverse events, serious adverse events, and adverse device effects.

No formal hypothesis testing will be performed for this study.

9.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version **26.0** or later will be used to code all adverse events.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class (SOC) and preferred term (PT). Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or other protocol-required therapies, 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)**
- **COVID-19 SMQ (Narrow)**

Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

In addition, summaries of treatment-emergent and serious adverse events will be tabulated by SOC, PT, and grade.

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

9.6.2 Laboratory Test Results

Not applicable.

9.6.3 Exposure to Investigational Product

The number and percentage of subjects with dose change, reason for dose change for **both dose adjustment and none or partial dose**, and duration of exposure to investigational product in days will be summarized over time.

Descriptive statistics will be produced to describe the exposure to investigational product by migraine types (EM/CM) separately and overall population.

9.6.4 Exposure to Concomitant Medication

Number and proportion of subjects receiving migraine preventive medications will be summarized by medication category. Number and proportion of subjects who discontinue standard of care migraine prevention therapy will also be summarized.

9.7 Other Analyses

Not applicable.

10. Changes From Protocol-specified Analyses

Frequency of headache and migraine days collected on CRF "Headache and Migraine Frequency Medical History" at screening period will be included to derive migraine type, in addition to eDiary at baseline.

The definition of efficacy analysis set stated in the protocol is not applicable to all efficacy endpoints and has been corrected in Section 6.3 to what was intended. These changes will also be documented in the clinical study report.

11. Literature Citations / References

NA

12. Prioritization of Analyses

Prioritization of analyses has not been identified at this time.

13. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following substudy outcome variables.

- Migraine impact
- Treatment efficacy
- Migraine experience

Qualitative data on changes resulting from treatment received in the open-label treatment period will be collected via telephone interview.

Data will be analyzed to achieve the study objectives, using qualitative data analysis software (ie, ATLAS.ti).

14. Appendices

Not applicable.