Statistical Analysis Plan

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| **Protocol Title:** | A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache |
| **Short Protocol Title:** | A Phase 4 Randomized Controlled Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Medication Overuse Headache |
| **Protocol Number:** | 20170703 |
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| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
|---|---|---|
| Original (v1.0) | 13JAN2020 | NA |
| Amendment 1 (v2.0) | 10DEC2022 | • Section 4.2 updated to<br>o Include an additional subgroup analysis by prior history of depression<br>o Clarify the medication categories of migraine preventive medications<br>• Section 5.1 updated to<br>o Include ditans as acute migraine-specific medications and acute headache medication<br>o Include the definition of concomitant migraine preventive medication<br>o Clarify the exclusion of gepant-based medication in the derivation of MOH<br>o Remove the definition of information day<br>o Clarify the table of prorations of monthly frequency variable in days<br>o Include the definition of treatment-related treatment-emergent adverse events<br>o Clarify the calculation of a headache last for multiple days and multiple qualified headaches within the same day<br>o Clarify the definition of complete response of MPFID<br>• Section 5.2 updated to include the definition of primary completion date<br>• Section 5.3 updated to<br>o Clarify the handling of measurements with multiple individual items<br>o Include the definition of pre-OLTP<br>o Clarify the definition of study day 1 in Section 5.3<br>• Table 5-1 updated to clarify the definition of the start date of Week 44 and baseline period<br>• Table 5.6 updated to clarify the analysis visit window of HRU<br>• Section 6.2 updated the definition of efficacy analysis set to include all endpoints<br>• Section 7 updated to describe database disposition<br>• Section 8.3 updated to clarify missing HRU dates imputation, missing items in eCOA, |

| Version Number | Date (DDMMMYYYY) | Summary of Changes, including rationale for changes |
|---|---|---|
| | | and missing endpoints evaluations at postbaseline during OLTP<br>• Section 8.7 updated to clarify TFLs will be produced and validated in accordance with SOP-430399<br>• Section 9.1 updated to include descriptive summary of primary, secondary and change from baseline in mean monthly opioid/opioid-containing medication days for the 'observed' opioid-treated cohort as sensitivity analyses<br>• Section 9.2 and 9.3 included summary of protocol deviations related to COVID-19 measures<br>• Section 9.4 updated to include additional summary of baseline characteristics<br>• Table 9-1, Table 9-2, and Section 9.5 updated to include additional sensitivity analyses to examine the derived values of concomitant oral migraine preventive medications with respect to the primary and secondary endpoints<br>• Section 9.5 updated to include breslow-test for the analysis of dichotomized endpoints, ANCOVA for continuous endpoints collected at one or two timepoints postbaseline, and the analysis of BDI-II and PGIC<br>• Section 9.6 updated to include exposure-adjusted subject incidence for the DBTP, serious TEAE occuring on or after the COVID infection, device-related AEs and the EOI COVID-19 SMQ (Narrow)<br>• Section 10 updated to specify the addition of ditans in the list of acute headache medication and changes in definition of efficacy analysis set<br>• Section 12 updated to clarify the scope of this Statistical Analysis Plan will not include the data for biomarker development and optional interview-based substudy<br>• Editorial/changes were made throughout the document to improve overall clarity |

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## List of Tables

## List of Abbreviations and Definition of Terms

| Abbreviation or Term | Definition/Explanation |
|---|---|
| AHMD | Acute headache medication day |
| ALT | Alanine aminotransferase |
| **ANCOVA** | **Analysis of covariance** |
| ASC | Allodynia symptom checklist |
| BDI-II | Beck Depression Inventory - II |
| BMI | Body mass index |
| CM | Chronic migraine |
| CM-MOH | Chronic migraine subjects who met thresholds for medication overuse headache |
| CMH | Cochran-Mantel-Haenszel |
| COA | Clinical outcomes assessment |
| CRF | Case Report Form |
| **CTCAE** | **Common Terminology Criteria for Adverse Events** |
| DBTP | Double-blind treatment period |
| EAS | Efficacy analysis set |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eDiary | Electronic diary |
| EM | Episodic Migraine |
| Enrollment | When the investigator decides that the subject has met Part 1 and Part 2 eligibility criteria, and follows procedures for subject randomization, and a randomization number has been assigned |
| ET | Early termination |
| EU | European Union |
| FAS | Full analysis set |
| GAD-7 | Generalized Anxiety Disorder 7-item scale |
| HIT-6 | Headache Impact Test-6 |
| HRU | Health resource utilization |
| ICH | International Council for Harmonisation |
| ICHD-3 | International Classification of Headache Disorders, 3rd Edition |
| Interactive Voice Response System (IVRS) | telecommunication technology that is linked to a central computer in real time as an interface to collect and process information |
| **IP** | **Investigational Product** |
| LSM | Least squares mean |
| MFIQ | Migraine Functional Impact Questionnaire |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| MHD | Monthly headache days |
| MIDAS | Migraine Disability Assessment |
| MMD | Monthly migraine days |
| MO | Medication overuse |
| MOH | Medication overuse headache |
| MPFID | Migraine Physical Function Impact Diary |
| NCT | National Clinical Trials |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OLTP | Open-label treatment period |
| PFS | Prefilled syringe |
| PGIC | Patient's Global Impression of Change |
| QM | every 4 weeks |
| Randomization | A subject is randomized to a treatment assignment |
| SAS | Safety analysis set |
| **SAP** | **Statistical analysis plan** |
| **Study month** | **Generally 4 weeks** |

## 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 for study 20170703 dated **27 May 2020**. The scope of this plan includes the primary analysis and the final analysis **that are 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 with placebo on achieving medication overuse headache (MOH) remission during the double-blind treatment period (DBTP) | • Absence of MOH at month 6 as defined by mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported |
| **Primary Estimand** | |
| The estimand for the primary efficacy endpoint consists of:<br>• The target population, which includes subjects diagnosed with **chronic migraine** (CM) and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month<br>• The endpoint, which is the absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment<br>• The summary measure, which is the odds ratio of absence of MOH between each erenumab dose group (ie, 70 mg or 140 mg) and the placebo group | |
| **Secondary** | |
| • To evaluate the effect of erenumab compared with placebo in reducing AHMD during the DBTP | • Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |

| Objectives | Endpoints |
|---|---|
| The estimand for the secondary objective on AHMD consists of:<br>• The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month<br>• The endpoint, which is the change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP) and have at least 1 change from baseline in MHD, regardless of adherence to treatment<br>• The summary measure, which is the difference in mean of the endpoint between each erenumab dose group (ie, 70 mg and 140 mg) and the placebo group | |
| • To evaluate the effect of erenumab compared with placebo on sustaining MOH remission during the DBTP | • Sustained MOH remission during DBTP, as defined by absence of MOH at months 3 **(week 12)** and 6 **(week 12)** of the DBTP and "absence of MOH" is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period |
| The estimand for the secondary objective on sustained absence of MOH consists of:<br>• The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month<br>• The endpoint, which is the sustained MOH remission during DBTP, as defined by absence of MOH over months 1, 2, and 3 **(week 1 through week 12)** AND over months 4, 5, and 6 of the DBTP **(week 13 through 24**). Absence of MOH is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period<br>• The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment<br>• The summary measure, which is the odds ratio of sustained MOH remission between each erenumab dose group (ie, 70 mg and 140 mg) and the placebo group | |
| • To evaluate the effect of erenumab compared with placebo on reducing the impact of migraines on physical impairment and everyday activities as measured by the Migraine Physical Function Impact Diary (MPFID) during the DBTP[a] | • Change from baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• Change from baseline in mean monthly average impact on everyday activities |

| Objectives | Endpoints |
|---|---|
| | domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| The estimand for the secondary objective on MPFID consists of:<br>• The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month<br>• The endpoints, which include (1) the change from baseline in mean monthly average physical impairment domain scores and (2) the change from baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of IP and have at least 1 change from baseline in the respective domain score, regardless of adherence to treatment<br>• The summary measure, which is the difference in mean of the endpoint between each erenumab dose group (ie, 70 mg and 140 mg) and the placebo group | |
| • To evaluate the effect of erenumab compared to placebo on change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6)[a] | • Change from baseline in mean HIT-6 score over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| The estimand for the secondary objective on HIT-6 consists of:<br>• The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month<br>• The endpoint, which is the change from baseline in mean HIT-6 total score over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP) and have at least 1 change from baseline in HIT-6 total score, regardless of adherence to treatment<br>• The summary measure, which is the difference in mean of the endpoint between each erenumab dose group (ie, 70 mg and 140 mg) and the placebo group | |
| **Safety** | |
| • To evaluate the safety and tolerability of erenumab in subjects with CM-MOH | • Adverse events<br>• **Vital** signs |

[a] In the EU region **including UK**, HIT-6 will replace MPFID as a secondary endpoint and MPFID will be evaluated as an exploratory endpoint. In non-EU regions, MPFID will remain as a secondary endpoint while HIT-6 will be evaluated as an exploratory endpoint.

| Objectives | Endpoints |
|---|---|
| **Exploratory (Double-blind treatment period)** | |
| • To explore the effect of erenumab compared with placebo in promoting conversion to EM | • Achievement of conversion to episodic migraine (EM) at month 3 defined as mean MHD < 14 days over months 1, 2, and 3 **(week 1 through 12)** of the DBTP<br>• Achievement of conversion to EM at month 6, defined as mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• Achievement of conversion to EM over 6 months, defined as mean MHD < 14 days over months 1 through 6 **(week 1 through 24)** of the DBTP |
| • To explore the effect of erenumab compared with placebo on the change of **at least** moderate **pain intensity** MHD from baseline to the DBTP | • Change from baseline in MHD **of at least moderate pain intensity** at monthly assessment time points<br>• Change from baseline in mean **at least moderate pain intensity** MHD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• Achievement of at least 30%, 50%, and 75% reductions from baseline in **at least moderate pain intensity** MHD at monthly assessment time points<br>• Achievement of at least 30%, 50%, and 75% reduction from baseline in mean **at least moderate pain intensity** MHD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| • To explore the effect of erenumab compared with placebo on the change from baseline in monthly migraine days (MMD) during the DBTP | • Change from baseline in MMD at monthly assessment time points<br>• Change from baseline in mean MMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br>• Achievement of at least a 30%, 50%, and 75% reductions from baseline in MMD at monthly assessment time points<br>• Achievement of at least 30%, 50%, and 75% reductions from baseline in MMD mean over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| • To explore the effect of erenumab compared with placebo on the change from baseline in average headache pain severity during the DBTP | • Change from baseline in the monthly average pain severity score of qualified headache days at monthly assessment time points |

| Objectives | Endpoints |
|---|---|
| | • Change from baseline in the mean monthly average pain severity score of qualified headache days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| • To explore the effect of erenumab compared with placebo on the change from baseline in migraine-free days during the DBTP | • Change from baseline in monthly migraine-free days at monthly assessment time points of the DBTP<br>• Change from baseline in mean monthly migraine-free days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP |
| • To explore migraine-related disability metrics as measured by the migraine functional impact questionnaire (MFIQ) | • Change from baseline in MFIQ domain scores and overall impact on usual activities global item score at assessment time points |
| • To explore migraine-related disability and productivity as measured by the Migraine Disability Assessment (MIDAS) Questionnaire | • Change from baseline in MIDAS total score, absenteeism score and presenteeism score at assessment time points during DBTP<br>• Cumulative (sum of) changes from baseline in MIDAS total score, absenteeism score and presenteeism score over 6 months during DBTP |
| • To explore the effect of erenumab compared with placebo on the change from baseline in health resource utilization (HRU) | • Occurrence of at least 1 headache-related hospitalization or outpatient HRU during the DBTP<br>• Occurrence of at least 1 headache-related hospitalization during the DBTP<br>• Occurrence of at least 1 headache-related outpatient HRU during the DBTP<br>• Occurrence of at least 1 headache-related outpatient emergency room visit during the DBTP<br>• Occurrence of at least 1 headache-related outpatient urgent care visit during the DBTP<br>• Occurrence of at least 1 headache-related outpatient clinic visit during the DBTP |
| • To explore the effect of erenumab compared with placebo on the change | • Change from baseline in Generalized Anxiety Disorder 7-item scale (GAD-7) score at assessment time points |

| Objectives | Endpoints |
|---|---|
| from baseline in depression and anxiety symptoms | • Change from baseline in Beck Depression Inventory-II (BDI-II) score at assessment time points |
| • To explore the effect of erenumab compared with placebo on the change from baseline in measures of sleep quality | • Change from baseline in each of the sleep questionnaire domain scores at assessment time points |
| • To explore the effect of erenumab compared with placebo on the subject's assessment of the change in clinical status since the start of treatment | • Change in clinical status as measured by the Patient's Global Impression of Change (PGIC) as assessed by the subject at month 6 of the DBTP |
| • To explore the effect of erenumab compared to placebo on the change from baseline in allodynia symptoms | • Change from baseline in Allodynia Symptoms Checklist-12 (ASC-12) score at assessment time points |
| **Exploratory (Open-label treatment period)** | |
| • To explore the rate of MOH relapse in the end of **open-label treatment period (**OLTP**)** | • MOH relapse at year 1, defined as both mean monthly AHMD ≥ 10 days over months 11, 12, and 13 **(week 41 through 52)** AND mean MHD ≥ 14 days over months 11, 12, and 13 **(week 41 through 52)** in subjects who achieved MOH remission at month 6 of the DBTP<br>**Note: This endpoint will be analyzed among subjects who were treated with erenumab throughout the entire study** |
| • To explore absence of MOH at end of OLTP | • Absence of MOH at end of study as defined by mean monthly AHMD < 10 days over months 11, 12, and 13 **(week 41 through 52)** OR mean MHD < 14 days over months 11, 12, and 13 **(week 41 through 52)** |
| • To explore sustainability of MOH remission during OLTP | • Sustained absence of MOH over 1 year as defined by absence of MOH over the DBTP (months 1, 2, and 3 **[week 1 through 12]**, OR months 4, 5, and 6 **[week 13 through 24]**) AND OLTP (months 11, 12, and 13) **[week 41 through 52]**.<br>**Note:** "Absence of MOH" is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period<br>**This endpoint will be analyzed among subjects who were treated** |

| Objectives | Endpoints |
|---|---|
| | **with erenumab throughout the entire study** |
| • To explore change in AHMD, MMD, **and** MHD **of at least moderate pain intensity** | • Change from baseline in mean AHMD, MMD and **MHD of at least moderate pain intensity** at assessment time points<br>• Change from week 24 (OLTP baseline) in mean AHMD, MMD, and MHD **of at least moderate pain intensity** at assessment time points during OLTP |
| • To explore everyday activities as measured by the MPFID | • Change from baseline in monthly average impact on everyday activities score as measured by the MPFID at assessment time points<br>• Change from week 24 (OLTP baseline) in monthly average impact on everyday activities score as measured by the MPFID at assessment time points during OLTP |
| • To explore physical impairment as measured by the MPFID | • Change from baseline in monthly average physical impairment score as measured by the MPFID at assessment time points<br>• Change from week 24 (OLTP baseline) in monthly average physical impairment score as measured by the MPFID at assessment time points during OLTP |
| • To explore the daily activity impact of headache as measured by the HIT-6 | • Change from baseline in HIT-6 total score at week 52<br>• Change from week 24 (OLTP baseline) in HIT-6 total score at week 52 |
| • To explore migraine-related disability metrics as measured by MFIQ | • Change from baseline in MFIQ domain scores and overall impact on usual activities global item score at week 52<br>• Change from week 24 (OLTP baseline) in MFIQ domain scores and overall impact on usual activities global item score at week 52 |
| • To explore migraine-related disability and productivity as measured by the MIDAS Questionnaire | • Change from baseline in MIDAS total score, absenteeism score and presenteeism score at week 52<br>• Change from week 24 (OLTP baseline) in MIDAS total score, absenteeism score, and presenteeism score at week 52 |
| **Exploratory (Opioid-treated Cohort Only)[a]** | |

| Objectives | Endpoints |
|---|---|
| • To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during DBTP | • Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during DBTP<br>• **Change from baseline in mean monthly opioid/opioid-containing medication days over months 4, 5 and 6 (week 13 through 24) of the DBTP** |
| • To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during OLTP | • Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during OLTP |

[a] In addition to these objectives/endpoints, all primary, secondary, and exploratory objectives/endpoints will be evaluated for the opioid-treated cohort.

### 2.2 Hypotheses and/or Estimations

The primary clinical hypothesis of Study 20170703 is that preventive treatment with monthly injections of erenumab is superior to placebo in achieving MOH remission for subjects with CM-MOH in the nonopioid-treated cohort who have a history of at least 1 preventive treatment failure as measured by the absence of the MOH status based on the mean over months 4, 5, and 6 **(week 13 through 24)** of the DBTP.

The secondary clinical hypotheses of Study 20170703 are that preventive treatment with monthly injections of erenumab is superior to placebo in reducing AHMDs over months 4 to 6 **(week 13 through 24)** of the DBTP; sustaining MOH remission during the entire DBTP; reducing migraine-related impact on physical functioning and everyday activities as measured by Migraine Physical Function Impact Diary (MPFID) physical function and everyday activities domains (non-EU) or migraine-related impact on physical functioning as measured by the Headache Impact Test 6 (HIT-6) (EU only).

For subjects with CM-MOH allocated to the opioid-treated cohort, an additional exploratory clinical hypothesis of Study 20170703 is that preventive treatment with monthly injections of erenumab could help reduce opioid use as measured by the mean change in monthly opioid medication days from baseline over months 4, 5, and 6 **(week 13 through 24)** of the DBTP. Formal statistical testing does not apply to this exploratory clinical hypothesis.

# 3. Study Overview

## 3.1 Study Design

Study 20170703 is a phase 4, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study to evaluate the safety and efficacy of erenumab against placebo in a CM population with MOH and prior history of treatment failure. Subjects will be enrolled based on fulfillment of the International Classification of Headache Disorders, 3rd Edition (ICHD-3) CM and MOH criteria and will not be advised to early discontinue acute medication. During randomization, subjects will be separated into 2 distinct cohorts based on their opioid medication use at baseline. Subjects with an opioid medication use $>$ 4 days per month during the baseline period will be allocated to the opioid-treated cohort. Subjects with an opioid medication use of $\leq$ 4 days per month during the baseline period will be allocated to the nonopioid-treated cohort. The randomization process on the nonopioid-treated cohort will be balanced based on the following stratum:

- Concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No).

Subjects allocated to the opioid treated cohort will be analyzed separately as an exploratory cohort.

During the DBTP, subjects will be randomized in a 1:1:1 fashion to either placebo, erenumab 70 mg SC every 4 weeks, or erenumab 140 mg SC every 4 weeks. Subjects who successfully complete the 24-week DBTP of the study will be offered an opportunity to continue in an OLTP of 28-weeks duration. Subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose during the OLTP. Subjects who received placebo during the DBTP will be allocated in a 1:1 ratio to receive either erenumab 70 mg or 140 mg SC QM during the OLTP. All subjects will remain blinded to their original DBTP treatment assignment.

## 3.2 Sample Size

The sample size calculation has been performed based on the primary endpoint (absence of MOH at month 6) for the nonopioid-treated cohort.

Based on a subgroup analysis of subjects who failed preventive migraine medication**,** overused acute headache medication, and had at least 14 MHD at baseline in the erenumab CM pivotal Study 20120295, 33.1%, 50.5%, and 64.1% of subjects in placebo, erenumab 70 mg and erenumab 140 mg treatment group, respectively,

achieved absence of MOH at month 3. Assuming similar response rates over month 4, 5 and 6 and a conservative scenario that includes a dropout rate of 20% during the 6-month DBTP, the planned sample size of 183 subjects per group will provide 85% power for 70 mg versus placebo and > 99% power for 140 mg versus placebo using a 2-sample chi-squared test with a 2-sided significance level of 0.05.

In addition, up to 138 opioid-treated cohort subjects will be randomized to receive erenumab or placebo (46 on placebo, 46 on 70 mg, and 46 on 140 mg).

### 3.3 Adaptive Design

Not applicable.

## 4. Covariates and Subgroups

### 4.1 Planned Covariates

All model-adjusted analyses of efficacy endpoints in nonopioid-treated cohort will include the following covariates:

- Concomitant oral migraine preventive treatment initiated before screening AND taken during baseline (Yes or No)
- Corresponding baseline value for the endpoint being analyzed (for continuous endpoints only)

### 4.2 Subgroups

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

- concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No)
- **g**eographic region (North America vs. Other)
- BMI (< median vs. ≥ median)
- prior history of treatment with onabotulinumtoxinA (Yes or No)
- total number of prior treatment failures (1 vs. 2 or more)
- total number of prior treatment failures (1 vs. 2 vs. 3 or more)
- **prior history of depression (Yes or No)**
- acute headache medication overuse category
    - overuse of triptan (Yes or No)
    - overuse of simple analgesics/NSAIDs (Yes or No)
    - overuse of combination analgesics (Yes or No)
    - overuse of combination therapies (Yes or No)

**Summary of prior and concomitant migraine preventive medication use is based on the following 9 categories: topiramate, other antiepileptics, beta blockers, tricyclic antidepressants, other antidepressants, calcium channel blockers/calcium antagonists, angiotensin receptor blockers/angiotensin-converting enzyme (ACE) inhibitors, botulinum toxin, and other drugs used for migraine prevention.**

## 5. Definitions

### 5.1 Definition of Terms Included in Study Endpoints

#### 5.1.1 Efficacy Endpoints Based on Daily eDiary Collection

**Acute Headache Medication (AHM)**

Acute headache medications include

- Triptan-based migraine medications
- Ergotamine-based migraine medications
- **Ditan-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**,** ergotamine-based migraine medications, **and ditan-based migraine medications**.

**Medication Overuse (MO)**

Monthly acute **headache** medication **use** meeting at least one of the following criteria:

- ≥ 10 days of a combination of ergotamines, triptans, opiates or opioid-containing meds or opioid combination-analgesic, non-opioid combination-analgesic medications or simple analgesics/NSAIDs **whilst not satisfying medication overuse criteria in any of the below individual medication categories alone**
- ≥ 10 days of opiates or opioid-containing medications or opioid combination-analgesics
- ≥ 10 days of triptans or triptan-containing medications
- ≥ 10 days of ergotamines or ergotamine-containing medications
- ≥ 10 days of non-opioid combination-analgesics

- ≥ 15 days of simple analgesics/NSAIDs **if subjects use simple analgesics/NSAIDs ONLY during the monthly interval**

**Monthly acute headache medication days for each medication category will be calculated using the same proration approach as monthly acute headache medication days.**

**Concomitant migraine preventive medication**

**Migraine preventive medication that were reported in concomitant medication CRF, belonged to medication category defined in Section 4.2 and had start date < study day 1 AND (end date > day 1 OR missing end date).**

**Overuse of Combination Analgesics**

Monthly acute **headache** medication days meeting at least one of the following criteria:

- ≥ 10 days of opioid-containing combination-analgesics
- ≥ 10 days of non-opioid combination-analgesics

**Medication Overuse Headache (MOH; Over 3 Months)**

Mean monthly AHMD ≥ 10 days AND mean MHD ≥ 14 days over 3 consecutive study months**, excluding gepant-based medication in the derivation.**

**Absence of MOH (Over 3 Months)**

Mean monthly AHMD < 10 days OR mean MHD < 14 days over 3 consecutive study months**, excluding gepant-based medication in the derivation.**

**Sustained MOH Remission (Over 6 Months During DBTP)**

Mean monthly AHMD < 10 days OR mean MHD < 14 days over 3 consecutive study months **at both time points** (months 1, 2, and 3 **[week 1 to week 12]**, AND months 4, 5, and 6 **[week 13 through 24]**)**, excluding gepant-based medication in the derivation.**

**Absence of MOH at End of Study**

Mean monthly AHMD < 10 days OR mean MHD < 14 days over months 11, 12 and 13 **(week 41 through 52), excluding gepant-based medication in the derivation.**

**Sustained Absence of MOH (Sustained MOH Remission) Over 1 Year**

Absence of MOH over the DBTP (months 1, 2, and 3 **[week 1 through 12]**, OR months 4, 5, and 6 **[week 13 through 24]**) AND OLTP (months 11,12 and 13 **[week 41 through 52]**)**, excluding gepant-based medication in the derivation.**

**Conversion to Episodic Migraine (EM) (Over 3 Months)**

Mean MHD < 14 days over 3 consecutive study months

**Achievement of Conversion to Episodic Migraine (EM) (Over 6 Months During DBTP)**

Mean MHD <14 days over **months 1 through 6 (week 1 through 24) of the DBTP.**

**Qualified Headache**

A qualified headache is defined as

- A headache of duration ≥ 4 hours, or
- A headache of duration < 4 hours during which an acute headache medication is administered

**Headache Day**

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified headache or takes ≥ 1 acute migraine-specific medication (ie, triptan**,** ergotamine**, ditan**) during aura

**Qualified Migraine Headache**

A qualified migraine headache is defined as

- A headache lasting for ≥ 4 hours, 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 during which an acute migraine-specific medication (ie, triptan**,** ergotamine, **ditan**) is administered regardless of the headache duration, pain features, and associated symptoms

**Migraine Day**

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified migraine **headache** or takes ≥ 1 acute migraine-specific medication (ie, triptan, ergotamine**, ditan**) during aura.

**Migraine-free Day**

A calendar day (00:00 to 23:59) **of a diary day** in which the subject does not experience any headache pain or any symptoms including aura, nausea, vomiting, phonophobia, and photophobia, and does not take any acute headache medication.

**Acute Headache Medication Day**

A calendar day (00:00 to 23:59) in which the subject takes ≥ 1 acute headache medication.

**Opioid Medication Day**

A calendar day (00:00 to 23:59) in which an opioid/opioid containing medication was administered**.**

**Headache Pain Intensity**

Worst or peak pain intensity collected on a headache ranges from 1 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).

**Headache Day of at Least Moderate Pain Intensity**

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified headache with the worse or peak pain intensity of ≥ 4**.**

**Diary Day**

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

**Monthly Frequency Variable in Days**

Number of days of interest during one monthly interval as defined in Table 5-1. Monthly frequency variables include:

- Monthly migraine days (MMD)
- Monthly headache days (MHD)
- Monthly migraine-free days
- Monthly opioid/opioid-containing medication days
- Monthly acute headache medication days (AHMD)
- Monthly headache days with at least moderate pain intensity
- Monthly acute migraine-specific medication days

The following proration rule will be applied to all monthly frequency variables for analysis. If a subject misses diary on a day when a headache is ongoing, that day will still be included in MHD calculation as only headache duration is required to identify a

headache day. For other endpoints which are derived using headache symptoms and medication information, days without diary completion will not be included in the proration.

| **Within Each Monthly Interval** | **Monthly Frequency Variable** |
|---|---|
| ≥ 14 diary days | **For monthly headache days with at least moderate pain intensity, prorate to 28-day equivalent without rounding**<br>$\frac{\textbf{Number of observed headache days with at least moderate pain within each monthly interval}}{\textbf{Number of diary days or days with headache pain intensity collected within each monthly interval}} \textbf{ x 28}$ |
| | **For monthly migraine-free days, prorate to 28-day equivalent without rounding**<br>$\frac{\textbf{Number of frequency days within each monthly interval}}{\textbf{Number of diary days or headache days or acute headache medication days within each monthly interval}} \textbf{ x 28}$ |
| | **For monthly acute migraine-specific medication days and monthly opioid/opioid-containing medication days, prorate to 28-day equivalent without rounding**<br>$\frac{\textbf{Number of frequency days within each monthly interval}}{\textbf{Number of diary days or acute headache medication days within each monthly interval}} \textbf{ x 28}$ |
| | For other frequency variables, prorate to 28-day equivalent without rounding<br>$\frac{\textit{Number of frequency days within each monthly interval}}{\textit{Number of diary days } \textbf{or frequency days} \textit{ within each monthly interval}} \textit{ x } 28$<br><br>Note: diary days with complete headache, aura, and acute headache medication data is required to derive endpoints related to symptoms, pain intensity and acute medication use. |
| < 14 diary days | Set to missing |

**Monthly Average Variable Based on Qualified Headaches**

Monthly average **headache pain intensity** based on qualified headache **will be calculated as below:**

| Within Each Monthly Interval | Monthly Average Variable |
|---|---|
| ≥ 14 diary days | Sum of the **headache pain intensity** values from all qualified headaches during a monthly interval as defined in Table 5-1 divided by the total number of qualified headaches in that monthly interval |
| | Set to 0 if no qualified headache reported |
| < 14 diary days | Set to missing |

**A headache lasts for multiple days will be separated to multiple qualified headaches by midnight. Multiple qualified headaches within the same day will be calculated as separate qualified headaches.**

**Monthly Average Variable Based on Daily PRO Scores**

Monthly average variables derived from daily MPFID assessment include

- Monthly average physical impairment domain score
- Monthly average impact on everyday activities domain score

| Days With Complete Response Within Each Monthly Interval | Monthly Average Variable |
|---|---|
| ≥ 14 days | Sum of values from daily assessment during a monthly interval as defined in Table 5-1 divided by the number of days with complete response. |
| < 14 days | Set to missing |

**Complete response is defined as the completion of a MPFID questionnaire with all questions answered. The latest record of the duplicate MPFIDs will be used for the calculation of monthly MPFIDs.**

**Migraine Physical Function Impact Domains and Everyday Activities**

The MPFID is a self-administered 13-item instrument measuring physical functioning. It has 2 domains, Impact on Everyday Activities (7 items) and Physical Impairment (5 items), and 1 stand-alone global question which provides an assessment of overall impact on everyday activities.

Subjects respond to items using a 5-point scale, with difficulty items ranging from "Without any difficulty" to "Unable to do" and frequency items ranging from "None of the time" to "All of the time". These are assigned scores from 1 to 5, with 5 representing the greatest burden. For each domain, the scores 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 impact of migraine (ie, higher burden). There will be a score for

each of the 2 domains and a third score for the stand-alone item. The recall period is the past 24 hours. Subjects will complete the MPFID daily using the eDiary.

### 5.1.2 Efficacy Endpoints Based on Monthly Collection

**Headache Impact Test (HIT-6)**

The scoring of the HIT-6 total score will be performed using the Optum Scoring Software. The HIT-6 total scores ranging from 36 to 78 can be categorized into 4 grades, representing little or no impact (49 or less), some impact (50 to 55), substantial impact (56 to 59), and severe impact (60 to 78) due to headache. Subjects will complete the HIT-6 using the eDiary.

**Migraine Functional Impact Questionnaire (MFIQ)**

The MFIQ 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 scores 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. Subjects will complete the MFIQ using the eDiary.

**Allodynia Symptoms Checklist 12 items (ASC-12)**

The ASC-12 is a subject reported outcome measure used to assess the frequency of allodynia symptoms. The checklist will ask subjects to assess how often they experience increased pain or an unpleasant sensation on their skin during their most severe type of headache while engaging in each of the following: combing their hair, pulling their hair back (eg, ponytail), shaving their face, wearing eyeglasses, wearing contact lenses, wearing earrings, wearing a necklace, wearing tight clothing, taking a shower (when the shower water hits their face), resting their face or head on a pillow, exposure to heat (eg, cooking, washing their face with hot water), and exposure to cold (eg, using an ice pack, washing their face with cold water).

The subject answers each question using the following categories: “Does not apply to me”, “Never”, “Rarely”, “Less than half of the time”, “Half the time or more”. Responses to each question are assigned a score. A positive response to answer options 1 to 3 is scored as 0, a positive response to answer option 4 is scored as a 1, and a positive

response to answer option 5 is scored a 2. The final grading is based on the sum of the 12 items. Subjects will complete the ASC-12 using the eDiary.

**Migraine Disability Assessment Questionnaire (MIDAS)**

The MIDAS Questionnaire is a 5-item self-administered questionnaire that sums the number of productive days lost over the past 3 months in 2 settings: the workplace and the home. The MIDAS also assesses disability in family, social, and leisure activities. The MIDAS score is the sum of missed days due to a headache from paid work, housework, and nonwork (family, social, leisure) activities; and days at paid work or housework where productivity was reduced by at least half. The recall period is 3 months.

The score is categorized into 4 severity grades: grade I = 0 to 5 (defined as minimal or infrequent disability), grade II = 6 to 10 (mild or infrequent disability), grade III = 11 to 20 (moderate disability), and grade IV = 21 and over (severe disability). Two other questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain severity. Subjects will complete the MIDAS using the eDiary.

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

The GAD-7 is a self-administered 7-item instrument that uses some of the 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. Subjects will complete the GAD-7 using the eDiary.

**Patient Global Impression of Change (PGIC)**

The PGIC is a subject-reported outcome that evaluates general aspects of a subject’s health and assesses if there has been an improvement or decline in clinical status. The PGIC employs a 7-point Likert scale that ranges from (1) ‘Very much improved’ to (7) ‘Very much worse’. Subjects will complete the PGIC using the eDiary.

**American Registry for Migraine Research (ARMR) Sleep Questionnaire**

The ARMR sleep questionnaire is a novel self-administered 10-item patient-reported outcome that measures parameters of sleep quantity, sleep quality and daytime sleepiness and their relationship with migraine symptomatology and treatment over a 3-month recall period. Items 1 to 3 of the questionnaire evaluate parameters of sleep quantity as a discrete time variable. Items 4-6 and 8-10 evaluate several behaviors that denote poor sleep quality and excessive daytime sleepiness using a five-level Likert scale that ranges from 'strongly disagree' to 'strongly agree'. For each question, 'not applicable' options are also provided and are not scored. Each item may be scored separately or in combination within the same domain. Item 7 refers to lifetime sleep disorders history and will only be collected at day 1 post randomization visit. Subjects will complete the ARMR sleep questionnaire using the eDiary.

**Beck Depression Inventory (BDI)-II**

The Beck Depression Inventory (BDI)-II is a 21-item questionnaire that assesses severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: minimal depression (0 – 13), mild depression (14 – 19), moderate depression (20 – 28), and severe depression (29 – 63).

**Sites will be able to activate baseline period BDI-II on the eDiary at the end of the subject's baseline period, after at least 28 full calendar days have passed (inclusive of the day the subject was set-up on the eDiary device).**

### 5.1.3 Safety Endpoints

**Serious Adverse Event (SAE)**

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

**Treatment-emergent Adverse Event**

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**.**

**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 setup and ready for entry

**Randomization (Enrollment) Date in DBTP**

Randomization (Enrollment) Date in DBTP is the date on which a subject is assigned to one of the treatments through the Interactive Voice Response System (IVRS) in the DBTP.

**First (DBTP) IP Dose Date**

The first (DBTP) IP dose date is the date on which a subject is administered the first dose of IP during the DBTP following randomization as recorded on the IP Administration eCRF. The first IP dose date may be the same day or after the randomization date.

**Last DBTP IP Dose Date**

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

**First OLTP IP Dose Date**

The first OLTP IP Dose Date is the date on which a subject is administered the first dose of IP in the OLTP following completion of the DBTP as recorded on the IP Administration eCRF.

**Last OLTP IP Dose Date**

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

**Last IP Dose Date**

Last IP Dose Date is the date on which a subject is administered the last dose of IP, which can be during the DBTP or OLTP, 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**.**

**Primary Completion Date**

**The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.**

**For this study, the primary completion date is the date when the last subject in the nonopioid-treated cohort has completed the assessments for week 24 (month 6) or discontinues study.**

## 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) 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**.**

**For measurements with multiple individual items, such as MFIQ and ARMR, all individual items from the same set of measurement will be used for analysis.**

**Pre-OLTP Baseline**

**Pre-OLTP baseline is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of OLTP IP. In cases where the**

**measurements are taken on the same day as the first dose of OLTP IP, it will be assumed that these measurements are taken prior to IP being administered. For endpoints derived based on daily eDiary data, the pre-OLTP baseline is the last non-missing monthly measurement before the first dose of OLTP IP.**

**Study Day 1**

Study day 1 is defined as the first IP dose date **regardless on or after randomization date**. For subjects who are randomized but **never received any dose**, 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 Study Periods

The following data will be categorized into treatment periods. Any data occurred after EOS date will not be included in the analysis.

**Efficacy Assessments at Scheduled Visits, Vitals**

- DBTP: Study Day 1 to minimum (first OL dose date, EOS date)
- OLTP: (First OL dose date + 1) to EOS date

**Adverse Events, Concomitant Medications**

- DBTP: Study Day 1 to minimum (first OL dose date – 1, EOS date)
- OLTP: First OL dose date to EOS date

### 5.4.2 Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

The (4-week) monthly intervals for efficacy endpoints derived from daily 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. Any eDiary 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 migraine-free days
- Monthly opioid/opioid-containing medication days
- Monthly acute headache medication days (AHMD)
- Monthly headache days with at least moderate pain intensity
- Monthly acute migraine-specific medication days
- Monthly average headache pain intensity
- Monthly average MPFID physical impairment domain score
- Monthly average MPFID impact on everyday activities domain score

**Table 5-1. Monthly Interval for Efficacy Endpoints Derived From Daily Diary Collection**

| Study Period | Assessment Timepoint | Monthly Interval | |
|---|---|---|---|
| | | **Start Date (Day)** | **End Date (Day)** |
| Baseline Period | Baseline | Device ready for entry date [d] | Day prior to study day 1 |
| Double-blind Treatment Period | Week 4 (Month 1) | Study Day 1 | Week 4 dose date – 1 [b] |
| | Week 8 (Month 2) | Week 4 dose date [a] | Week 8 dose date – 1 [b] |
| | Week 12 (Month 3) | Week 8 dose date [a] | Week 12 dose date – 1 [b] |
| | Week 16 (Month 4) | Week 12 dose date [a] | Week 16 dose date – 1 [b] |
| | Week 20 (Month 5) | Week 16 dose date [a] | Week 20 dose date – 1 [b] |
| | Week 24 (Month 6) | Week 20 dose date [a] | Week 24 dose date – 1 [b] |
| Open-label Treatment Period | Week 44 (Month 11) | Week 40 visit date [c] | Week 44 dose date – 1 [b] |
| | Week 48 (Month 12) | Week 44 dose date [a] | Week 48 dose date – 1 [b] |
| | Week 52 (Month 13) | Week 48 dose date [a] | Start date (day) + 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] eDiary will be re-activated at the week-40 visit **during OLTP** irrespective of IP dose status. **Week 40 visit date will be determined by week 40 dose date. If week 40 dose date is missing, week 40 clinic visit date will be used instead. If dose date or clinic visit date of the week was missing, the target date of the week would be used to determine the start date or end date.**
[d] **Start Date of baseline period= the first eDiary date If device ready for entry date is not available**

### 5.4.3 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 5-2 to Table 5-7.

By-visit data collected on or before the first OLTP dose date belong to DBTP. Data collected after the first OLTP dose date, not including the safety follow-up visit, belong to OLTP. Any data occurred after EOS date will not be included in the analysis except antibody data.

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 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 5-2. HIT-6 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 prior or on 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 Week 24 dose date, if available, else to 183 |
| Open-label Treatment Period | Week 52 (Month 13) | 365 | 352 to 379 |

**Table 5-3. MIDAS 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 12 (Month 3) | 85 | 72 to 99 |
| | Week 24 (Month 6) | 169 | 156 to Week 24 dose date, if available, else to 183 |
| Open-label Treatment Period | Week 52 (Month 13) | 365 | 352 to 379 |

**Table 5-4. ASC-12/GAD-7/BDI-II/Sleep Questionnaire 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 12 (Month 3) | 85 | 72 to 99 |
| | Week 24 (Month 6) | 169 | 156 to Week 24 dose date, if available, else to 183 |

**Table 5-5. PGIC Analysis Visit Windows**

| Study Period | Analysis Visit | Target Day | Visit Window (Study Day) |
|---|---|---|---|
| Double-blind Treatment Period | Week 24 (Month 6) | 169 | 156 to Week 24 dose date, if available, else to 183 |

**Table 5-6. HRU Questionnaire 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) | - | **2** to Week 24/**ET visit** date, if available, else to 183 |

**Table 5-7. Vital Signs 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 Week 24 dose date, if available, else to 183 |
| Open-label Treatment Period | Week 40 (Month 10) | 281 | 268 to 295 |
| | Week 52 (Month 13) | 365 | 352 to 379 |

## 5.5 Subject Disposition

**Randomized**

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

**On-study**

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

**Exposed to Investigational Product**

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

**Completing the Double-blind Investigational Product**

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

**Completing the Double-blind Treatment Period**

Subjects are defined as completing the DBTP if they complete week-24 assessment. It will be derived from the End of Double-Blind eCRF page with “Completed” as the primary reason for ending study period.

**Completing the Open-label Investigational Product**

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

**Completing the Open-label Treatment Period**

Subjects are defined as completing the OLTP if they complete the week-52 assessment. It will be derived from the End of Open-Label eCRF page with "Completed" as the primary reason for ending study period.

**Completing Study**

Subjects are defined as completing study if they complete the entire 52 weeks of study evaluation**.** It will be derived from the End of Study **e**CRF page with "Completed" as the primary reason for ending study.

## 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 DB IP Exposure**

If subject enters into OL treatment period,

Duration = Minimum (Last DB Dose Date + 27, First OL Dose Date - 1) – First DB Dose Date + 1

Otherwise,

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

**Duration of OL IP Exposure**

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

(Postbaseline – Baseline) * 100 / Baseline

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 of the observed monthly change from baseline values for the months with non-missing change from baseline values

**Subject Incidence**

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered that period (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.

**Exposure-adjusted Incidence Rate**

The exposure-adjusted incidence rate for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event in a given period divided by total exposure time of all subjects who are at risk for the event. For subjects with a given event, only the time until the onset of each subject's first event contributes to the exposure time. For subjects without a given event, the exposure time is the entire duration of the period. This incidence rate will be presented as number of subjects per 100 subject-years.

### 5.7 Disease Characteristics

**Treatment Failure of Prior Migraine Preventive Medications**

Treatment failure of prior preventative medications is determined by "Reason for stopping" as "Lack of Efficacy", "Adverse Reaction" or "Intolerance" on the Prior Migraine Prophylactic Medication eCRF.

## 6. Analysis Sets

Each analysis set will be defined separately for the non-opioid-treated cohort and the opioid-treated cohort.

### 6.1 Full Analysis Set

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

### 6.2 Efficacy Analysis Set

The efficacy analysis set (EAS) for **all** efficacy endpoints during DBTP is a subset of FAS consisting of subjects who receive at least 1 dose of investigational product during DBTP. The respective EAS will be used to perform the analyses for the efficacy endpoints of interest during DBTP. Subjects will be analyzed according to their randomized treatment in DBTP, regardless of the treatment received.

### 6.3 Safety Analysis

The safety analysis set (SAS) will consist of all randomized subjects who received at least 1 dose of investigational product. Subjects will be analyzed according to the randomized treatment unless a subject receives the incorrect dose during the entire DBTP. Analysis for safety endpoints and summary of investigational product administration will utilize this analysis set.

### 6.4 Open-label Treatment Period Analysis Set

The open-label analysis set (OLAS) will consist of all subjects who receive at least 1 dose of erenumab in the OLTP. This analysis set will be used to summarize data collected during the OLTP.

## 7. Planned Analyses

**Data will be subject to ongoing checks for integrity, completeness and accuracy in accordance with the Data Management Plan with the expectation that outstanding data issues are resolved ahead of the lock to the extent possible for the primary analysis and all outstanding data issues are resolved ahead of the final lock. The data supporting the primary analysis will be locked to prevent further changes.**

### 7.1 Primary Analysis

The primary analysis will be performed when all randomized subjects in the nonopioid-treated cohort have completed the week 24/ET assessments during the DBTP, and all data are collected for the primary endpoint. All available data up to and including the data cutoff date will be cleaned and locked. At **the** time **of primary**

**analysis**, the DBTP treatment assignment for this cohort will be unblinded to selected staff of the sponsor conducting the analysis. If data collection for all subjects in the opioid-treated cohort for the DBTP is also complete, the DBTP treatment assignment for this cohort will also be unblinded. Study subjects, investigators, and remaining sponsor staff will remain blinded to original DBTP treatment assignment until study completion. All efficacy analyses and safety analyses will be conducted for the DBTP. Safety data collected during the OLTP before the data cutoff date for the primary analysis will also be summarized.

### 7.2 Final Analysis

The final analysis will be performed after all subjects (nonopioid-treated and opioid-treated) have completed the **study through** the week-52/EOS visit. The final analysis will be performed based on the final cleaned and 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 as well as eDiary data outside of RAVE database.

### 8.3 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of reasons. In general, data could be missing due to a subject's early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, efficacy endpoints are clinical outcome assessments (COAs) collected via daily eDiary or monthly assessments at the office visits. Missing COAs with respect to quality-of-life questionnaires (MPFID, HIT-6, MFIQ, MIDAS, Sleep questionnaire, Allodynia symptom checklist, BDI-II, GAD-7 and PGIC) will not be imputed. **Missing items in each eCOA questionnaire will be handled based on the scoring algorithm for each COA.**

Subjects could miss entering several days of data in eDiary within each monthly interval. The calculation of monthly measurements about subjects' migraine and non-migraine headaches will be handled using the following 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 safety endpoints will not be imputed **except for partial AE start dates**. Missing or incomplete dates will be listed as reported, except for incomplete start date of an AE 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 | — |

**Similarly, incomplete dates of HRU will be imputed using the same imputation rule as above.**

### 8.3.1 Missing Baseline Evaluation

Missing baseline evaluations will not be imputed.

All subjects included in the efficacy analysis set will have baseline monthly rate or monthly average of migraine and non-migraine headaches related measurements after applying proration rule defined in Section 5.1.1 since only subject with ≥ 80% compliance of eDiary use during baseline will be eligible for randomization.

### 8.3.2 Missing Post-baseline Evaluation in Double-blind Treatment Period

Primary analysis of dichotomous efficacy endpoints during the DBTP will be conducted using Cochran-Mantel-Haenszel test (CMH) after the missing data are imputed as nonresponse. Primary analysis of continuous efficacy endpoints during the DBTP will be conducted using the repeated measures linear mixed effects model including observed data without imputation.

For the descriptive summary of mean monthly value calculated using the monthly value from each of months 4, 5, and 6 **(week 13 through 24)** of the DBTP, if a subject has at least one monthly value at months 4, 5, and 6 **(week 13 through 24)**, then the subject contributes to the summary statistics.

If the proportion of missing data in primary endpoint is high (eg, > 20% for primary analysis at week 24), further analysis will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (eg, due to measurement or sample processing error)

### 8.3.3 Missing Post-baseline Evaluation in Open-label Treatment Period

**For the descriptive summary of mean monthly value calculated using the monthly value from each of months 11, 12, and 13 (week 41 through 52) of the DBTP, if a subject has at least one monthly value at months 11, 12, and 13 (week 13 through 24), then the subject contributes to the summary statistics.**

## 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 in the clinical study report (CSR). 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 timing of and 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).

### 8.7 Validation of Statistical Analyses

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

Tables, figures, and listings will be produced **and** validated **in accordance with SOP-430399. S**tandard macros **programs will be used when available**.

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

## 9. Statistical Methods of Analysis

### 9.1 General Considerations

Formal statistical analyses using statistical models and hypothesis testing will be performed for the nonopioid-treated cohort only. Descriptive statistics will be produced for the opioid-treated cohort. **The classification of cohorts (opioid-treated and nonopioid-treated) used for the primary analysis will be based on the cohort value determined at randomization. As sensitivity analysis, the primary endpoint, secondary endpoints, and change from baseline in mean monthly opioid/opioid-containing medication days will be summarized descriptively for the 'observed' opioid-treated subjects who reported >4 days of opioid medication use in the eDiary data during the last 28 days of baseline period.**

Summary statistics will be computed by treatment group and visit. For continuous endpoints, the following descriptive statistics will be computed: 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 dichotomous efficacy endpoints will be analyzed using the stratified Cochran-Mantel-Haenszel (CMH) test after the missing data is imputed as nonresponse. Continuous secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data at the monthly level. **In case more than 10% subjects had stratification error within non-opioid treated cohort (ie. stratified incorrectly between the with vs. without concomitant oral migraine preventive medication strata), sensitivity analysis will be conducted for the model-based analysis for primary and secondary endpoints, using the 'observed' concomitant oral migraine preventive medication reported by site as strata in CMH tests.**

The 2 erenumab dose groups will be compared with placebo for the primary and secondary efficacy endpoints in the nonopioid-treated cohort using a simple fixed sequence procedure with study-wise type I error rate $\alpha = 0.05$. The order of the endpoints to be tested is prespecified below. If any test is not significant at the $\alpha = 0.05$ level, then no further testing will be performed.

Primary and secondary endpoints in erenumab 140 mg versus placebo**:**

1. Absence of MOH at month 6 of DBTP (140 mg)
2. Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
3. Sustained MOH remission during DBTP (140 mg)

Primary and secondary endpoints in erenumab 70 mg versus placebo:

4. Absence of MOH at month 6 of the DBTP (70 mg)
5. Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)
6. Sustained MOH remission during DBTP (70 mg)

Patient reported outcome-related secondary endpoints for the non-EU region **(United States, Australia)**:

7. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 of the DBTP (140 mg)
8. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 of the DBTP (140 mg)
9. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 of the DBTP (70 mg)

10. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 of the DBTP (70 mg)

OR

Patient reported outcome-related secondary endpoints for the EU region **(including United Kingdom)**:

11. Change from baseline in mean HIT-6 score over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
12. Change from baseline in mean HIT-6 score over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

Analysis for efficacy endpoints during the OLTP will be summarized separately for nonopioid-treated and opioid-treated cohorts.

### 9.2 Subject Accountability

For the primary analysis at week-24 the disposition of all enrolled subjects will be tabulated by the randomized treatment group. The summary will include the number of subjects who are randomized, the number and percent of subjects who receive the double-blind IP, who complete double-blind IP, discontinue double-blind IP and reasons for discontinuing, who complete the 24-week DBTP, and who withdraw prematurely from the study before completion of the 24-week DBTP and their reasons for withdrawal. **Summary of subjects who discontinue investigational product/study due to COVID-19 control measures will be included.**

For the **primary and** final analysis, disposition of the OLTP and the entire study will be tabulated, which includes the number and percent of subjects who enter the OLTP, who receive the open-label erenumab who complete open-label erenumab, discontinue erenumab and reasons for discontinuing, who complete the study, and who withdraw prematurely from the study and their reasons for withdrawal. **Summary of subjects who discontinue investigational product/study due to COVID-19 control measures will be included.**

### 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. IPDs will be summarized by randomized treatment group. **Protocol**

**Deviations (PDs) related to COVID-19 control measures will be summarized separately.**

### 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 double-blinded baseline, following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Ethnicity
- Race
- Region (North America vs Others)
- Height (cm)
- Weight (kg)
- Body mass index (BMI, $kg/m^2$)
- Targeted neurological disease diagnosis at baseline
- **Prior history of treatment with onabotulinumtoxinA**
- **Prior history of depression**
- Disease duration of migraine with or without aura
- **Disease duration of chronic migraine with or without aura**
- Age at onset of migraine
- Age at onset of chronic migraine
- **P**rior migraine preventive treatment and reasons for discontinuation **by medication category**
- **Concomitant oral migraine** preventive treatment by **by medication category**
- **Number of prior migraine preventive treatment failures by medication category**
- Acute headache medication used during baseline period:
  a) Migraine-specific
  b) Non-migraine-specific
- Monthly migraine days during baseline period
- **Monthly migraine-free days during baseline period**
- Monthly headache days during baseline period

- Monthly **headache** days with **at least** moderate pain intensity 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 opioid/opioid-containing medication days (opioid-treated cohort only)**
- **Overuse of acute headache medication during the baseline period**
- Overuse of triptan during the baseline period
- Overuse of simple analgesics/NSAIDs during the baseline period
- Overuse of combination analgesics during the baseline period
- Overuse of combination therapies during the baseline period
- Monthly average **headache** pain intensity during baseline period
- **Monthly average MPFID physical impairment score during baseline period**
- **Monthly average MPFID overall impact on everyday activities score during baseline period**
- Beck Depression Inventory (BDI)-II total score severity grade
- Headache Impact Test (HIT-6) total score
- MFIQ impact on physical functioning
- MFIQ impact on usual activities
- **MFIQ overall impact on usual activities**
- MFIQ impact on social functioning
- MFIQ impact on emotional functioning
- Allodynia Symptoms as measured by the Allodynia Symptoms Checklist 12-items (ASC-12)
- Migraine Disability Assessment Questionnaire MIDAS) **total score**
- **Migraine Disability Assessment Questionnaire (MIDAS) presenteeism score**
- **Migraine Disability Assessment Questionnaire (MIDAS) total score**
- Generalized Anxiety Disorder 7-Item Scale (GAD-7) score

### 9.5 Efficacy Analyses

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

**Table 9-1. Primary Efficacy Endpoint Summary Table**

| Endpoint | Primary Summary and Analysis Method | Sensitivity Analysis |
|---|---|---|
| Absence of MOH at month 6 **(week 24)** as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5 and 6 **(week 13 through 24)** where AHMD include any eDiary day in which an acute headache medication intake is reported. | 1. The **responder rate** of subjects with absence of MOH by treatment group with **missing data imputed as** non-response imputation **(NRI)**<br>2. **A stratified CMH test with NRI adjusted by original stratified values**<br>3. **Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the original stratification factors** | **1. Same as primary analysis method but using observed concomitant oral preventive medication status as the stratification factor.**<br>**2. Same as primary analysis method but only include subjects with observed monthly AHMD and MHD in each of the month over month 4, 5 and 6** |

**Table 9-2. Secondary Efficacy Endpoints Summary Table**

| Endpoint | Primary Summary and Analysis Method | Sensitivity Analysis |
|---|---|---|
| 1. Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP<br><br>(*Note: Result at each timepoint during DBTP will also be generated in the same model.*) | 1. Summary statistics by visit using observed data **and 95% CI of mean change from baseline at each visit by treatment group**<br>2. Least squares means by visit using a linear mixed effects repeated measure model adjusted by baseline value, **original** stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data at monthly level<br>3. Treatment difference between each erenumab dose group and placebo) with the 95% CI, and p-value **from the model in #2** | **Least squares means by visit using a linear mixed effects repeated measure model adjusted by baseline value, observed concomitant oral migraine preventive medication status, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data at monthly level** |

| Endpoint | Primary Summary and Analysis Method | Sensitivity Analysis |
|---|---|---|
| 2. Sustained MOH remission during DBTP, as defined by absence of MOH at months 3 **(week 12)** and 6 **(week 24)** of the DBTP, and "absence of MOH" is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period | **Same as primary endpoint** | **Same as primary analysis method but using observed concomitant oral preventive medication status as stratification factor.** |
| 3. Change from baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (non-EU region)<br>4. Change from baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (non-EU region)<br>5. Change from baseline in mean HIT-6 total score over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (EU region)<br>(*Note: Result at each timepoint during DBTP will also be generated in the same model.*) | **Same as above** | **Same as above** |

### 9.5.1 Analyses of Primary Efficacy Endpoint

The primary comparison of absence of MOH at month 6 between each erenumab group and placebo will be analyzed using a stratified CMH test with nonresponse imputation. The proportion of subjects with absence of MOH will be reported for each treatment group. The odds ratio between each erenumab group and placebo, the corresponding 95% CI and p-value will be reported. **Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the strata.**

As a supportive analysis, the primary efficacy endpoint will also be analyzed including subjects with observed AHMD and MHD data at each month during months 4, 5, and 6 **(week 13 through 24)**.

### 9.5.2 Analyses of Secondary Efficacy Endpoints

The continuous secondary endpoints will be analyzed using a linear mixed effects repeated measure model will include treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. If applicable, 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.

The dichotomized secondary endpoint will be analyzed using the same method as for the primary endpoint in Section 9.5.1.

### 9.5.3 Analyses of Exploratory Efficacy Endpoints in Double-blind Treatment Period

For exploratory efficacy endpoints during the DBTP, summary statistics and analysis method will be conducted in the same way as that for the primary and secondary efficacy endpoints as described in Section 9.5.1 and in Section 9.5.2. **No sensitivity analysis is planned for exploratory endpoints except the sensitivity analysis for opioid-treated cohort as specified in section 9.1. For continuous endpoints collected only at one or two timepoints post-baseline during the DBTP, analysis of covariance (ANCOVA) adjusting baseline value and stratification factor will be used instead. BDI-II and PGIC will be summarized by category score using observed data. The shift from baseline in severity category score of BDI-II will be analyzed at week 12 and week 24 using observed data.**

### 9.5.4 Analyses of Exploratory Efficacy Endpoints in Open-label Treatment Period

For the OLTP of the study, descriptive summaries of efficacy endpoints will be tabulated by visit based on observed data without imputation.

## 9.6 Safety Analyses

### 9.6.1 Analyses of Primary Safety Endpoint(s)

For safety endpoints **during the DBTP**, all randomized subjects who received at least one dose of investigational product (ie, Safety Analysis Set) will be analyzed based on

the randomized treatment unless a subject has received the incorrect dose during the entire period of interest (treatment period or study). Safety analyses will be repeated for the non-opioid treated cohort, opioid-treated cohort, and overall. For safety analyses of **vital signs** in OLTP, descriptive summaries **of change from baseline values** will be tabulated based on observed data using pre-OLTP baseline.

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 2**5**.**1** or later will be used to code all events categorized as adverse events to a system organ class and a preferred term. 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 for the DBTP and be repeated using exposure-adjusted subject incidence for **the DBTP and** the OLTP.

The subject incidence of AEs will be summarized by SOC in alphabetical order and PT in descending order of frequency for all treatment-emergent adverse events (TEAEs), serious AEs, **serious TEAE occuring on or after the COVID infection,** AEs leading to **discontinuation** of investigational product, fatal AEs, **device-related 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)
- **COVID-19 SMQ (Narrow)**

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

Subject incidence of all TEAEs, SAEs, AEs leading to withdrawal of investigational product, and fatal AEs will be tabulated by PT in descending order of frequency. In addition, summaries of all TEAEs occurring in at least 3% of the subjects by PT in any treatment arm will be provided **by PT** in descending order of frequency.

Summaries of all TEAEs and SAEs will be tabulated by SOC, PT, and grade.

### 9.6.3 Vital Signs

The analyses of vital signs (systolic/diastolic blood pressure (SBP/DBP), **and heart rate**) will include summary statistics of change from baseline over time by treatment group.

Subject incidence at each time-point within the following defined categories for each treatment period:

- Increase from baseline ≥ 10 mmHg in DBP with DBP > 90 mmHg
- Increase from baseline ≥ 10 mmHg in DBP with DBP ≤ 90 mmHg
- Increase from baseline ≥ 20 mmHg in SBP with SBP > 140 mmHg
- Increase from baseline ≥ 20 mmHg in SBP with SBP ≤ 140 mmHg
- Change from baseline in heart rate of ≥ 15 bpm (increase) or heart rate ≥ 120 bpm
- Change from baseline in heart rate of ≤ -15 bpm (decrease) or heart rate ≤ 50 bpm

### 9.6.4 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group and treatment period. The number and percentage of subjects with dose change, reason for dose change and duration of exposure to investigational product in days will be summarized by treatment group.

### 9.6.5 Exposure to Concomitant Medication

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

## 9.7 Other Analyses

### 9.7.1 Analyses of Health Economic Endpoints

**Health Resource Utilization Questionnaire (HRU)**

The questionnaire is designed to collect data on HRU. Specifically, the aim is to capture frequency of **headache**-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.

## 10. Changes From Protocol-specified Analyses

**During the development of SAP amendment, it was realized that there are protocol-specified analyses that cannot be implemented/performed and the**

**protocol is not required to be amended. Ditans is included in the list of acute headache medications in Section 5.1. The definition of efficacy analysis set stated in the protocol is not applicable to all efficacy endpoints and has been corrected in Section 6.2 to what was intended. These changes will also be documented in the clinical study report.**

## 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 for biomarker development
- Data from the optional interview-based substudy

## 13. Appendices

Not applicable