## Title Page

| | | |
|---|---|---|
| **Protocol Title:** | | Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double-blind, Placebo-controlled Phase 4 Study |
| **Short Protocol Title:** | | Erenumab – Comprehensive Assessment of Efficacy in (High-Frequency) Episodic Migraine (EMBRACE) |
| **Protocol Number:** | | 20190008 |
| **Investigational Product:** | | Erenumab |
| **Trade Name:** | | AIMOVIG® |
| **Sponsor** | **Name of Sponsor:** | Amgen, Inc. |
| | **Address:** | One Amgen Center Drive<br>Thousand Oaks, CA 91320 |
| | **Telephone Number:** | 805-447-1000 |
| **Protocol Approver** | **Name:** | [redacted] |
| | **Function:** | Vice President of Global Development |
| **Key Sponsor Contact** | **Name:** | [redacted] |
| | **Address:** | One Amgen Center Drive<br>Thousand Oaks, CA 91320 |
| | **Telephone Number:** | [redacted] |
| | **Email Address:** | [redacted] |

| | |
|---|---|
| **EudraCT Number:** | 2019-003646-33 |
| **NCT Number:** | Not applicable |
| **Protocol Version Date:** | **Document Version** — **Date**<br>Original — 25 September 2019<br>Amendment 1 (v2.0) — 25 April 2022<br>**Superseded Amendment 1** — **29 June 2022** |
| **Data Elements Standards Version:** | Version 6.2 |

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

NCT Number: NCT04252742
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

**Confidentiality Notice**

**Investigator's Agreement:**

I have read the attached protocol entitled Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double-blind, Placebo-controlled Phase 4 Study, dated **29 June 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:
me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of investigator Date (DD Month YYYY)

## Table of Contents

## List of Tables



## List of Figures

# 1. Protocol Summary

## 1.1 Synopsis

**Protocol Title:** Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double-blind, Placebo-controlled Phase 4 Study

**Short Protocol Title:** Erenumab – Comprehensive Assessment of Efficacy in (High-Frequency) Episodic Migraine (EMBRACE)

**Study Phase:** 4

**Indication:** Preventive treatment of migraine in adults

**Rationale**

In phase 2 and 3 clinical studies, erenumab has demonstrated a reduction in monthly migraine days (MMD) as the primary endpoint. Since treatment benefits can extend beyond MMD, Study 20190008 will evaluate the impact of erenumab treatment on other aspects of migraine, including: duration and peak severity of pain, functional impairment, response to acute treatment, and non-ictal burden.

**Objective(s)/Endpoint(s)**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the treatment benefit of erenumab on headache duration of at least moderate pain intensity | • Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3 |
| **Secondary** | |
| • To evaluate the treatment benefit of erenumab on functional impairment | • Change from baseline in mean monthly function domain score as measured by the Migraine Functional Impact Questionnaire (MFIQ) over months 1, 2, and 3:<br>– Impact on physical functioning<br>– Impact on usual activities<br>– Impact on emotional functioning<br>– Impact on social functioning |
| • To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity | • Change from baseline in mean monthly average duration of at least moderate pain intensity in migraine attacks occurring over months 1, 2, and 3 **(migraine attacks as defined in Section 11.1)** |
| • To evaluate the treatment benefit of erenumab on peak migraine pain intensity | • Change from baseline in mean monthly average peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) over months 1, 2, and 3 |

**Overall Design**

Study 20190008 is a phase 4, interventional, prospective, double-blind, randomized, placebo-controlled, multicenter, global study, evaluating the effects of erenumab on aspects of migraine beyond MMD reduction in adult subjects with high-frequency episodic migraine (HFEM) who have previously failed at least 1 preventive treatment.

Subjects who meet eligibility criteria will be enrolled in a run-in period (2 weeks in duration), during which they will record oral triptan-treated migraine attacks in an episode electronic diary (eDiary). Details of what will be recorded in the eDiary are provided in Section 8.2.2. At the end of the run-in period, subjects who have at least 1 qualifying oral triptan-treated migraine attack (defined in Section 11.1) where pain freedom (defined as reduction of headache pain severity from moderate or severe to none) is not achieved within 1 hour following oral triptan intake during a migraine attack, will be eligible to enter the 4-week baseline period. If a subject reports more than 1 qualifying oral triptan-treated migraine attack where pain freedom is achieved in ≤ 1 hour following oral triptan intake during that migraine attack, the subject will be eligible to enter the 4-week baseline period as long as pain freedom in ≤ 1 hour following oral triptan intake occurs in < 50% of migraine attacks during the run-in period. During the baseline period, subjects will keep a daily eDiary. At the end of the baseline period, subjects who meet specific eligibility criteria will be able to enter the double-blind treatment period (DBTP).

The 4-month DBTP has 2 phases:

- Main DBTP (M-DBTP, months 1 to 3) that will assess the effect of erenumab on metrics such as time spent in at least moderate pain, peak migraine severity, and functional impairment
- Exploratory DBTP (E-DBTP, month 4) that will assess the impact of erenumab on the acute response to oral triptan therapy as well as non-ictal burden

Throughout both phases of the DBTP, investigational product will be administered every 4 weeks (Q4W). Data entry will follow a daily eDiary collection during the M-DBTP and transition to an episode eDiary during the E-DBTP.

**Number of Subjects**

Approximately 576 subjects will be enrolled in the study, with approximately 288 subjects per treatment group.

**Summary of Subject Eligibility Criteria**

Key inclusion criteria include:

- Age ≥ 18 years upon entry into initial screening
- Documented history of migraine with or without aura according to the International Headache Society (IHS) International Classification of Headache Disorders, Third Edition (ICHD-III) for ≥ 12 months
- Have HFEM: Defined as history of ≥ 7 to < 15 migraine days and < 15 headache days per month on average during the 3 months prior to screening
- History of ≥ 4 migraine attacks of at least moderate severity per month on average during the 3 months prior to screening
- History of treatment failure with at least 1 preventive treatment for migraine. Failure of preventive treatment for migraine is defined as treatment discontinuation due to lack of efficacy, adverse event, or general poor tolerability.
- Regular use of an oral triptan (using only eletriptan, rizatriptan, sumatriptan, or zolmitriptan) for acute migraine treatment, and typically initiating acute treatment with an oral triptan on > 50% of attacks of at least moderate pain intensity. Regular use is defined as ≥ 4 days of oral triptan use per month during the 3 months prior to screening.

Key exclusion criteria include:

- History of hemiplegic migraine, cluster headache, or other trigeminal autonomic cephalalgia
- Has any medical contraindication to the use of an oral triptan
- Previously treated with erenumab
- Previously treated with a gepant (small molecule calcitonin gene related peptide receptor [CGRP-R] antagonist) in a preventive fashion
- Previously treated with a ligand-based anti-CGRP monoclonal antibody (ie, fremanezumab, galcanezumab and/or eptinezumab) in a manner consistent with migraine prevention that either:
  (a) in the opinion of the investigator, did not offer any evidence of a therapeutic response
  OR
  (b) was discontinued for less than 12 weeks from the date of initial screening
  OR
  (c) was previously discontinued due to a known adverse drug reaction
- Currently being treated with lasmiditan and/or a gepant in the acute setting
- No therapeutic response with > 4 of the defined medication categories after an adequate therapeutic trial
- Currently has a history of consistent excellent response to oral triptans, defined as achievement of pain-freedom in ≤ 1 hour for ≥ 50% of treated attacks of at least moderate pain intensity during the 3 months prior to screening
- Use of triptans administered via a non-oral (eg, subcutaneous [SC] or intranasal delivery systems) or sublingual route at the time of screening, during the run-in and baseline periods, and throughout the study duration

For a full list of eligibility criteria, please refer to Section 5.1 and Section 5.2.

**Treatments**

Investigational product (140 mg erenumab [2 consecutive injections of 70 mg] or placebo [2 consecutive injections]) in prefilled syringes (PFS) will be administered by study staff Q4W during the 4-month treatment period.

**Procedures**

After signing the informed consent, subjects will enter the screening period. The total screening period is up to 9 weeks, which consists of an initial screening up to 3 weeks, a 2-week run-in period, and a 4-week baseline period. The clinical outcome assessments will be collected from subjects using a handheld device with an eDiary. The handheld device will have both an episode eDiary and a daily eDiary, which will be accessible by the subject during specified periods of the study. During the run-in period, eligible subjects will be instructed to interact with the episode eDiary for oral triptan-treated migraine attacks. Subjects will use the episode eDiary to report information about their migraine, migraine-related symptoms, and use of oral triptans. At the baseline visit, the investigator will use the subject's episode eDiary to confirm inclusion criteria for the baseline period have been met. Once the subject has completed the run-in period and is considered eligible to enter the baseline period, the subject will be instructed to interact with the daily eDiary. Subjects will use the daily eDiary to report information about their migraine and nonmigraine headaches, other migraine-related symptoms, and medication taken. At the day 1 visit, the investigator will use information collected during

the baseline period by the daily eDiary to confirm additional inclusion criteria have been met. Eligible subjects will then be enrolled and randomized into the 4-month DBTP and will begin to receive investigational product SC Q4W. During the M-DBTP (months 1 to 3), subjects will continue to use the daily eDiary and will use the device to complete additional clinical outcome assessments. During the E-DBTP (month 4), subjects will use the episode eDiary to complete additional clinical outcome assessments (Figure 1-1).

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Table 1-1.

**Statistical Considerations**

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

A sequential testing procedure will be used to maintain the family-wise type 1 error $\alpha = 0.05$ between the primary and secondary endpoints following the prespecified order below. An endpoint will only be tested for statistical significance if the endpoint tested in the previous step is statistically significant at 2-sided significance level of 0.05.

1. Primary endpoint: change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3
2. Secondary endpoints: change from baseline in mean monthly function domain score over months 1, 2, and 3, as measured by the MFIQ using the Hochberg procedure
    - Impact on physical functioning
    - Impact on usual activities
    - Impact on emotional functioning
    - Impact on social functioning
3. Secondary endpoint: change from baseline in mean monthly average duration of at least moderate pain intensity in migraine attacks occurring over months 1, 2, and 3 **(migraine attacks as defined in Section 11.1)**
4. Secondary endpoint: change from baseline in mean monthly average peak migraine pain intensity over months 1, 2, and 3, as assessed by the 11-point NRS

For a full description of statistical analysis methods, please refer to Section 9.

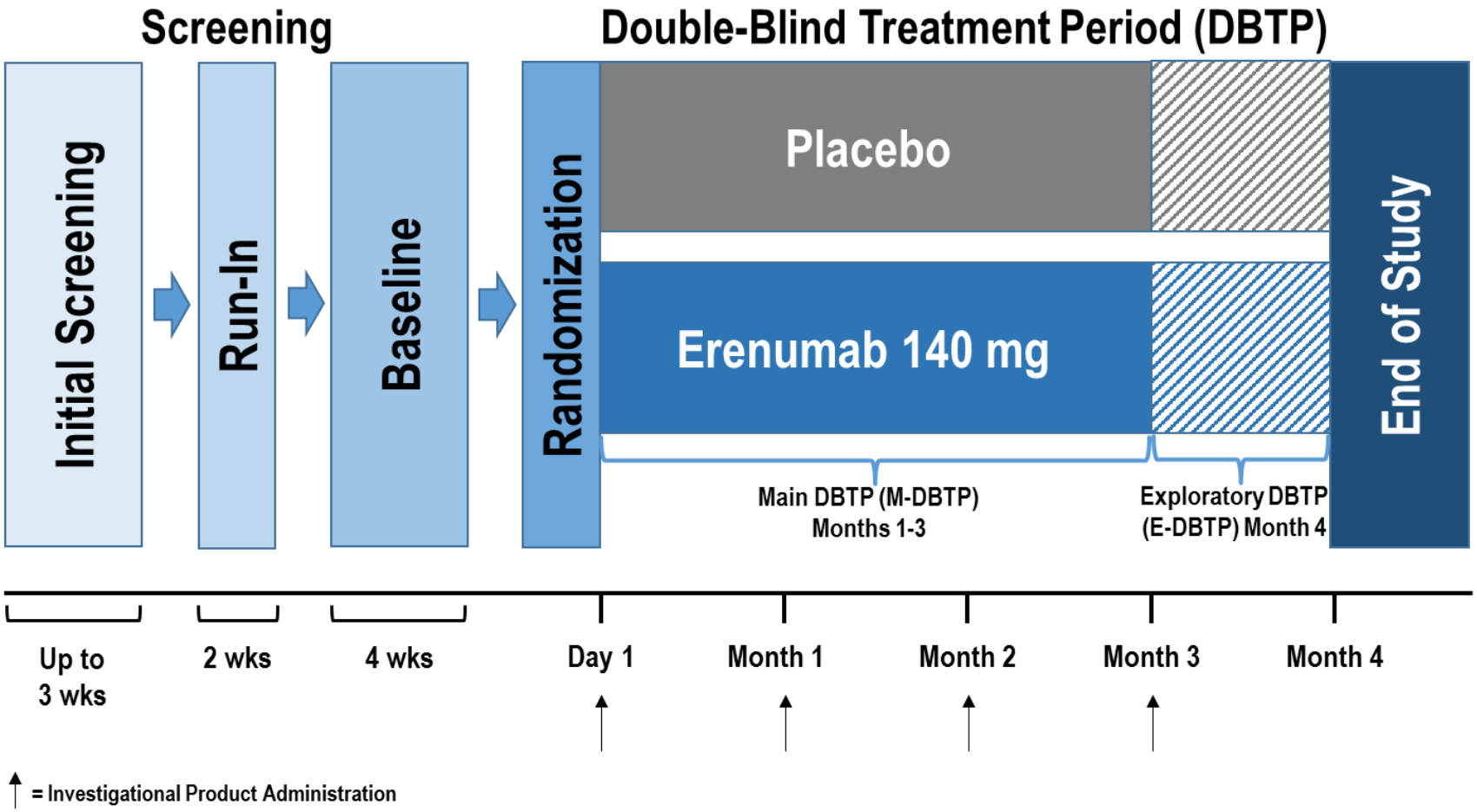
**Statistical Hypotheses**

The primary hypothesis is that preventive treatment with monthly administration of erenumab is superior to placebo in reducing duration of moderate or severe headache pain in subjects with HFEM who have previously failed at least 1 migraine preventive treatment.

**Sponsor Name:** Amgen, Inc.

## 1.2 Study Schema

**Figure 1-1. Study Schema**



## 1.3 Schedule of Activities (SoA)

**Table 1-1. Schedule of Activities**

| PROCEDURE | Screening Period | | | Double-blind Treatment Period (weeks)[c] (± 3 days) | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening (up to 3 weeks, 21 days) | Run-in[a] (2 weeks, 14 days [+4 days]) | Baseline Period[b] D -28 to D -1 (+7 days) | Day 1 (± 3 days) | W 4 (± 3 days) | W 8 (± 3 days) | W 12[d] (± 3 days) | W 16/ EOS[d] (± 3 days) | |
| **GENERAL AND SAFETY ASSESSMENTS** | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Inclusion and exclusion criteria | X | | X[e] | X[e] | | | | | |
| Demographics | X | | | | | | | | |
| Physical measurements | X | | | | | | | | Height and weight |
| Medical history | X | | | | | | | | |
| Neurological medical history | X | | | | | | | | |
| Headache and migraine frequency medical history | X | | | | | | | | |
| Cardiovascular medical history | X | | | | | | | | |
| Cardiac risk factors medical history | X | | | | | | | | |
| Gastrointestinal medical history | X | | | | | | | | |
| Prior migraine preventive medication history | X | | | | | | | | |
| Substance use history | X | | | | | | | | Substances: drugs, alcohol, tobacco |

Page 1 of 4

Footnotes defined on the last page of the table.

## Table 1-1. Schedule of Activities

| PROCEDURE | Screening Period | | | Double-blind Treatment Period (weeks)[c] (± 3 days) | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening (up to 3 weeks, 21 days) | Run-in[a] (2 weeks, 14 days [+4 days]) | Baseline Period[b] D -28 to D -1 (+7 days) | Day 1 (± 3 days) | W 4 (± 3 days) | W 8 (± 3 days) | W 12[d] (± 3 days) | W 16/ EOS[d] (± 3 days) | |
| **GENERAL AND SAFETY ASSESSMENTS (CONTINUED)** | | | | | | | | | |
| Prior/concomitant therapies review | X | X | X | X | X | X | X | X | Includes all prior medications (other than prior migraine preventive medications) that were being taken/used within 120 days prior to screening through the signing of the informed consent and all concomitant medications. |
| PHQ-9 | X | | | | | | | | |
| Adverse events | | | | X | X | X | X | X | |
| Serious adverse events | X | X | X | X | X | X | X | X | After end of study, serious adverse events suspected to be related to investigation product will be reported to Amgen. |
| Adverse device effects | | | | X | X | X | X | X | |
| Product complaints | | | | X | X | X | X | X | |



Footnotes defined on the last page of the table.

## Table 1-1. Schedule of Activities

| PROCEDURE | Screening Period | | | Double-blind Treatment Period (weeks)[c] (± 3 days) | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening (up to 3 weeks, 21 days) | Run-in[a] (2 weeks, 14 days [+4 days]) | Baseline Period[b] D -28 to D -1 (+7 days) | Day 1 (± 3 days) | W 4 (± 3 days) | W 8 (± 3 days) | W 12[d] (± 3 days) | W 16/ EOS[d] (± 3 days) | |
| **LABORATORY ASSESSMENTS** | | | | | | | | | |
| Urine pregnancy test (females of childbearing potential only) | X | | | X | | | | X | Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations |
| Urine drug testing | X | | | | | | | | Urine drug testing can be done as needed throughout the study per investigator discretion. |
| **BIOMARKER AND PHARMACOGENETIC ASSESSMENTS (OPTIONAL)** | | | | | | | | | |
| Biomarker development, blood | | | | X | | | | | |
| Pharmacogenetic studies[f] | | | | X | | | | | |



Footnotes defined on the last page of the table.

## Table 1-1. Schedule of Activities

| PROCEDURE | Screening Period | | | Double-blind Treatment Period (weeks)[c] (± 3 days) | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|
| | Initial Screening (up to 3 weeks, 21 days) | Run-in[a] (2 weeks, 14 days [+4 days]) | Baseline Period[b] D -28 to D -1 (+7 days) | Day 1 (± 3 days) | W 4 (± 3 days) | W 8 (± 3 days) | W 12[d] (± 3 days) | W 16/ EOS[d] (± 3 days) | |
| **CLINICAL OUTCOME ASSESSMENTS** | | | | | | | | | |
| Episode eDiary | | X[g] | | | | | | X[g] | |
| Daily eDiary | | | Daily | Daily | | | | | |
| MFIQ | | | | X | X | X | X | | |
| MSSS | | | | X | X | X | X | | |
| Change in most troublesome symptom | | | | X | | | X | | |
| PGI-S | | | | X | | | X | | |
| MIBS-4 | | | | X | X | X | X | X | |
| HIT-6 | | | | X | X | X | X | | |
| PCS | | | | X | | | X | | |
| **STUDY-RELATED DEVICE ASSIGNMENT** | | | | | | | | | |
| Assign eDiary device | | X | | | | | | | |
| **STUDY TREATMENT** | | | | | | | | | |
| Amgen investigational product | | | | X | X | X | X | | Site staff will administer the dose as the last procedure of the visit. |

Page 4 of 4

D = day; eDiary = electronic diary; EOS = End of Study; HIT-6 = Headache Impact Test; MFIQ = Migraine Functional Impact Questionnaire; MIBS-4 = Migraine Interictal Burden Scale; MSSS = Migraine Symptom Severity Score; PCS = Pain Catastrophizing Scale; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire; W = Week

[a] The run-in period ends when at the end of the period the subject does not meet inclusion criterion 108 or enters the baseline period (see Section 8.1.2).

[b] The baseline period starts when the subject has met all initial eligibility criteria, has completed the run-in period, and has met inclusion criterion 108. The baseline period ends when the subject does not meet inclusion criterion 109 through to 112 and is screen-failed or when subject meets all eligibility criteria and is enrolled and randomized. The total duration of the baseline period must be at least 28 days and no more than 35 days (see Section 8.1.3).

[c] The day 1 visit (randomization day) must occur 29 to 35 days after baseline entry. Study visits after day 1 may be completed within ± 3 days of the scheduled visit. All study visit target dates are to be calculated from the day 1 study date. All study procedures for a given study visit are to be completed on the same day (see Section 8.1.4).

[d] The end of study visit occurs at week 16 or 4 weeks after last dose of investigational product for subjects who discontinue the study. If a subject discontinues treatment or the study prior to week 12, the week 12 assessments should be conducted for their early termination visit (see Section 8.1.5).

[e] At the start of the baseline period, data collected during the run-in period will be assessed to determine if the subject meets the eligibility criteria to enter the baseline period. On day 1, data collected during the baseline period will be assessed to determine if the subject meets the eligibility criteria to enter the double-blind treatment period.

[f] For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample. Therefore, additional sampling is not required.

[g] The episode eDiary will be collected based on episodes during the run-in period and during weeks 13 to 16.

# 2. Introduction

## 2.1 Study Rationale

Impact on monthly migraine days (MMD) has served as 1 of the most common standards in assessing efficacy of treatments for migraine prevention. Reduction in MMD has often been associated with improvements of migraine-related impairments and disability in physical function, emotional wellness, work productivity, and general daily routine (Silberstein, 2015; Buse et al, 2009). However, therapeutic benefit can extend beyond the commonly evaluated MMD reduction and its subsequent effects. Patients who may not have experienced a decrease in the number of days spent with migraine following preventive treatment have anecdotally reported improvement, which has been described as attacks of lesser severity and duration, migraine-associated symptoms of lesser severity, and faster and/or better response to acute medications.

In phase 2 and 3 clinical studies, erenumab demonstrated a reduction in MMD as the primary endpoint as well as improvement in function (Dodick et al, 2018; Goadsby et al, 2017; Tepper et al, 2017). Study 20190008 will evaluate the impact of erenumab treatment on other aspects of migraine, including duration and peak severity of pain, functional impairment, response to acute treatment, and non-ictal burden.

## 2.2 Background

### 2.2.1 Disease

Migraine is a debilitating disease with worldwide prevalence of approximately 11.7% in the United States (US), 14.6% in Canada, 14.7% in Europe, and 8.4% in Japan (Stovner and Andree, 2010; Lipton et al, 2007; Sakai and Igarashi, 1997). Migraine is characterized by primary recurrent headaches with or without aura lasting 4 to 72 hours with at least 2 of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia). Migraine is divided into 2 broad classifications based on the frequency of attacks: episodic migraine (EM) and chronic migraine (CM). Episodic migraine is characterized by < 15 headache days per month, while CM is characterized by ≥ 15 headache days per month of which 8 or more days must meet criteria for migraine with or without aura, for more than 3 months. Episodic migraine and CM share many common features in their clinical presentation, which include headache pain features and associated symptoms. Although EM and CM are arbitrarily distinguished based on migraine headache frequency, numerous lines of evidence

support that they are a continuum of the same disorder. A common pathophysiology is supported by similar clinical symptoms and functional imaging results demonstrating the activation of similar brain regions (Aurora and Wilkinson, 2007; Afridi et al, 2005; Aurora et al, 2005; Welch et al, 2001).

Migraine attacks are typically treated acutely with nonspecific symptomatic agents such as combination analgesics containing caffeine, non-steroidal anti-inflammatory drugs, and migraine-specific abortive medications such as triptans. Acute treatments are used to reduce the impact of attacks (ie, pain severity and duration) once a migraine begins. Patients experiencing frequent and/or disabling migraine attacks often require prevention (prophylaxis) (Silberstein et al, 2012; Evers et al, 2009) in addition to acute medications for breakthrough attacks. Preventive treatments are used to reduce the frequency and overall severity of attacks in such individuals.

Approximately 25% to 30% of the migraine population has 4 or more migraine days per month (Houle et al, 2013; Lipton et al, 2007), which is generally considered a threshold for recommending preventive therapy. However, based on published epidemiologic data, only 12.4% of people with migraine received any preventive therapy due in part to limited efficacy and significant tolerability and safety issues associated with available preventive therapies (Lipton et al, 2007). Thus, migraine prophylaxis remains an area of unmet medical need.

### 2.2.2 Amgen Investigational Product Background: Erenumab

Erenumab is a human immunoglobulin G2 monoclonal antibody that is directed against the canonical calcitonin gene-related peptide (CGRP) receptor, blocking the action of CGRP. Erenumab has an approximate molecular weight of 150 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

As of the date of approval of this protocol, erenumab has been approved in over 70 countries. The recommended dosage is 70 mg once monthly (QM) and, in most countries, 140 mg QM is indicated for some patients who may benefit from a higher dose. The erenumab dose being used in this study is 140 mg. For additional information, refer to Section 4.3.

A detailed description of the chemistry, pharmacology, efficacy, and safety of erenumab is provided in the Investigator's Brochure.

### 2.3 Benefit/Risk Assessment

Erenumab 140 mg has demonstrated a favorable benefit risk profile for prevention of migraine in adults in pivotal and supportive phase 2 and 3 studies. The key benefits of erenumab include reduction in frequency of MMDs, reduction in acute medication use, reduction in the impact of migraine on physical functioning (as measured by the Migraine Physical Function Impact Diary), as well as improvements in a range of other patient-reported outcomes, favorable tolerability (over oral standard of care prophylactics), low treatment discontinuation rates, convenience (QM self-administered injections), and rapid onset of effect.

Specifically in Study 20120296, the pivotal study of 70 mg and 140 mg erenumab compared with placebo in subjects with EM, there was a statistically significant greater mean reduction in the change in mean MMD from baseline to the last 3 months (months 4, 5, and 6) of the 24-week double-blind treatment phase for 70 mg and 140 mg erenumab compared with placebo (difference in least square mean [LSM] [95% CI] of -1.40 [-1.88, -0.92] for 70 mg and -1.85 [-2.33, -1.37] for 140 mg) (Goadsby et al, 2017). The benefits of the 140 mg QM dose in a difficult-to-treat EM patient population with a history of 2 to 4 prior preventive treatment failures were further confirmed by a phase 3b randomized controlled trial where 30% of patients treated with erenumab experienced ≥ 50% reductions from their baseline MMD compared with 14% in the placebo group (odds ratio 2.7 [95% CI 1.4-5.2]; p = 0.002) (Reuter et al, 2018).

Overall, the safety profile of erenumab has been favorable in clinical studies. No important identified risks or important potential risks have been observed. Furthermore, a limited number of adverse drug reactions (injection site reactions, constipation, and muscle spasms) have been identified at low frequencies ($<$ 5%) in clinical studies. In postmarketing settings, immune system disorders (hypersensitivity reactions including rash, angioedema, and anaphylactoid reactions); gastrointestinal disorders (constipation with serious complications and oral sores); and skin and subcutaneous tissue disorders (alopecia and rash) have been observed.

The safety and efficacy of erenumab have not been established in migraine patients with major cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening), in the long-term use of erenumab, or in elderly patients $>$ 65 years of age.

In conclusion, erenumab addresses an unmet need as an effective, safe, and tolerable preventive treatment of migraine. The key benefits of erenumab outweigh the risks in this population.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure and Prescribing Information, where approved, for further data on erenumab.

## 3. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the treatment benefit of erenumab on headache duration of at least moderate pain intensity | • Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3 |
| **Secondary** | |
| • To evaluate the treatment benefit of erenumab on functional impairment | • Change from baseline in mean monthly function domain score as measured by the Migraine Functional Impact Questionnaire (MFIQ) over months 1, 2, and 3:<br>– Impact on physical functioning<br>– Impact on usual activities<br>– Impact on emotional functioning<br>– Impact on social functioning |
| • To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity | • Change from baseline in mean monthly average duration of at least moderate pain intensity in migraine attacks occurring over months 1, 2, and 3 **(migraine attacks as defined in Section 11.1)** |
| • To evaluate the treatment benefit of erenumab on peak migraine pain intensity | • Change from baseline in mean monthly average peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) over months 1, 2, and 3 |

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| Main Double-blind Treatment Period (month 1 to 3) | |
| • To evaluate the treatment benefit of erenumab on duration of oral triptan-treated migraine attacks | • Change from baseline in mean monthly hours of at least moderate pain intensity for **qualifying** oral triptan-treated migraine attacks over months 1, 2, and 3 **(qualifying oral triptan-treated migraine attacks as defined in Section 11.1)** |
| • To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity for **oral** triptan-treated migraine attacks | • Change from baseline in mean monthly average duration of at least moderate pain intensity in **qualifying** oral triptan-treated migraine attacks occurring over months 1, 2, and 3 **(qualifying oral triptan-treated migraine attacks as defined in Section 11.1)** |
| • To evaluate the treatment benefit of erenumab on migraine symptoms | • Change from baseline in Migraine Symptom Severity Score (MSSS) total score at assessment time points |
| | • Change from baseline in the most troublesome symptom at month 3 |
| | • Change in Patient Global Impression of Severity (PGI-S) total score at month 3 |
| | • Change from baseline in mean monthly total migraine freedom days (defined in Section 11.1) over months 1, 2, and 3 |
| • To evaluate the treatment benefit of erenumab on interictal burden of migraine | • Change from baseline in Migraine Interictal Burden Scale (MIBS-4) total score at assessment time points |
| | • Achievement of no or mild interictal burden as measured by the MIBS-4 at assessment time points |
| • To evaluate the treatment benefit of erenumab on functional impairment | • Change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6) total score at assessment time points |
| | • Change from baseline in physical function domain score as measured by MFIQ at assessment time points |
| | • Change from baseline in usual activities domain score as measured by MFIQ at assessment time points |
| | • Change from baseline in social function domain as measured by MFIQ at assessment time points |

| | |
|---|---|
| | • Change from baseline in emotional function domain score as measured by MFIQ at assessment time points |
| | • Change from baseline in overall impact on usual activities global item score as measured by MFIQ at assessment time points |

| **Objectives** | **Endpoints** |
|---|---|
| **Exploratory (Continued)** | |
| Main Double-blind Treatment Period (month 1 to 3) (Continued) | |
| • To evaluate the treatment benefit of erenumab on headache-related cognitions and beliefs | • Change from baseline in pain catastrophizing as measured by the Pain Catastrophizing Scale (PCS) at month 3 |
| • To evaluate the treatment benefit of erenumab on monthly migraine days (MMD) | • Change from baseline in mean MMD over months 1, 2, and 3 |
| Following 2 endpoints will be calculated from months with at least 1 migraine attack | |
| • To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity in months with at least 1 migraine attack **(migraine attacks as defined in Section 11.1)** | • Change from baseline in mean monthly average duration of at least moderate pain intensity per migraine attack over months 1, 2, and 3 |
| • To evaluate the treatment benefit of erenumab on peak migraine pain intensity in months with at least 1 migraine attack **(migraine attacks as defined in Section 11.1)** | • Change from baseline in mean monthly average peak migraine pain intensity as assessed by the 11-point NRS over months 1, 2, and 3 |
| Exploratory Double-blind Treatment Phase (month 4) | |
| • To evaluate the treatment benefit of erenumab on interictal burden of migraine | • Change from baseline in Migraine Interictal Burden Scale (MIBS-4) total score at month 4 |
| For the first qualifying oral triptan-treated attack (defined in Section 11.1) with complete data at 2-hour assessment: | |
| • To evaluate the treatment benefit of erenumab on achieving and sustaining pain freedom following treatment with an oral triptan | • Achievement of pain freedom at 2 hours post-triptan dose for the first attack at month 4 |
| | • Achievement of 24-hour sustained pain freedom post-triptan dose for the first attack at month 4 |
| | • Achievement of pain freedom at 30 and 60 minutes post-triptan dose for the first attack at month 4 |
| • To evaluate the treatment benefit of erenumab on achieving pain relief following treatment with an oral triptan | • Achievement of pain relief (defined in Section 11.1) at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4 |

| | |
|---|---|
| • To evaluate the treatment benefit of erenumab on achieving freedom from the most bothersome symptom following treatment with an oral triptan | • Achievement of freedom from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4 |
| • To evaluate the treatment benefit of erenumab on achieving relief from the most bothersome symptom following treatment with an oral triptan | • Achievement of relief from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4 |
| • To evaluate the treatment benefit of erenumab on migraine recurrence following treatment with an oral triptan | • Migraine recurrence (defined in Section 11.1) during 24 hours post-triptan dose for the first attack at month 4 |
| **Exploratory Double-blind Treatment Phase (month 4) - Continued** | |
| • To evaluate the treatment benefit of erenumab on use of migraine rescue medication following treatment with an oral triptan | • Use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4 |
| **For the first qualifying oral triptan-only-treated attack with complete data at 2-hour assessment:** | |
| • To evaluate the treatment benefit of erenumab on achieving and sustaining pain freedom following treatment with oral triptan only | • Achievement of pain freedom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack in which complete data is obtained (at least 2 hours timepoint) at month 4 |
| • To evaluate the treatment benefit of erenumab on achieving pain relief following treatment with oral triptan only | • Achievement of pain relief at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4 |
| • To evaluate the treatment benefit of erenumab on achieving freedom from the most bothersome symptom following treatment with oral triptan only | • Achievement of freedom from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4 |
| • To evaluate the treatment benefit of erenumab on achieving relief from the most bothersome symptom following treatment with oral triptan only | • Achievement of relief from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4 |

# 4. Study Design

## 4.1 Overall Design

Study 20190008 is a phase 4, interventional, prospective, double-blind, randomized, placebo-controlled, multicenter global study, evaluating the effects of erenumab on aspects of migraine beyond MMD reduction in adult subjects with high-frequency episodic migraine (HFEM) who have previously failed at least 1 preventive treatment.

Subjects who meet eligibility criteria will be enrolled in a run-in period (2 weeks in duration), during which they will record oral triptan-treated migraine attacks in an episode electronic diary (eDiary). Details of what will be recorded in the eDiary are

provided in Section 8.2.2. At the end of the run-in period, subjects will be eligible to enter the 4-week baseline period only if they have 1 or more qualifying oral triptan-treated migraine attacks (defined as migraine attacks of at least moderate peak pain intensity that are treated with an oral triptan within 2 hours of pain reaching at least moderate severity) and if pain freedom is not achieved within 1 hour following oral triptan intake for > 50% of their qualifying migraine attacks. During the baseline period, subjects will keep a daily eDiary. At the end of the baseline period, subjects who meet specific eligibility criteria will be able to enter the double-blind treatment period (DBTP).

The 4-month DBTP has 2 phases:

- Main DBTP (M-DBTP, months 1-3) that will assess the effect of erenumab on metrics such as time spent in at least moderate pain, peak migraine severity, and functional impairment
- Exploratory DBTP (E-DBTP, month 4) that will assess the impact of erenumab on the acute response to treatment with oral triptan therapy as well as non-ictal burden

Throughout both phases of the DBTP, investigational product will be administered every 4 weeks (Q4W). Data entry will follow a daily eDiary collection during the M-DBTP and transition to an episode eDiary during the E-DBTP.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

### 4.2 Number of Subjects

Approximately 576 subjects will be enrolled in the study, with approximately 288 subjects per treatment group.

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

#### 4.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

#### 4.2.2 Number of Sites

Approximately 76 investigative sites in North America and Europe will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

### 4.3 Justification for Investigational Product Dose

The erenumab dose being used in this study is in accordance with the term of its marketing authorization in the US and most regions of the EU.

The 140 mg dose has been selected as the treatment dose because it achieved incremental efficacy in a comparable patient population during phase 2 and 3 clinical studies. In phase 3 Study 20120296 (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention [STRIVE]) in subjects with EM, the erenumab 140 mg treatment arm experienced a numerically greater reduction from baseline in MMD compared with 70 mg (Goadsby et al, 2019). Furthermore, in a post-hoc analysis of STRIVE, subjects with 2 or more prior treatment failures in the 140 mg erenumab arm had an average MMD reduction nearly 2-fold greater than those in the 70 mg erenumab arm. The safety profile of both erenumab doses was comparable to placebo with only slightly greater incidence rates of constipation adverse events and influenza adverse events for the 140 mg dose compared with the 70 mg dose (Goadsby et al, 2019).

## 4.4 End of Study

### 4.4.1 End of Study Definition

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

**End of Study:** The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up, additional antibody testing), as applicable. For this study, the end of study date is the date when the last subject has completed the assessments for week 16.

### 4.4.2 Study Duration for Subjects

The total study duration for subjects who successfully complete the study will be up to 25 weeks.

## 4.5 Patient Input on Study Design

Patient input was not collected during study design.

# 5. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during initial screening to allow entry into the run-in period, after the run-in period to allow entry into the baseline period, and after the baseline period to allow entry into the DBTP.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

### 5.1 Inclusion Criteria

Subjects are eligible to be included in the study and enter the run-in period only if all of the following criteria apply:

101 Have provided informed consent prior to initiation of any study specific activities/procedures.

102 Age ≥ 18 years upon entry into initial screening.

103 Documented history of migraine with or without aura according to the International Headache Society (IHS) International Classification of Headache Disorders, Third Edition (ICHD-III) for ≥ 12 months.

104 Have HFEM: Defined as history of ≥ 7 to < 15 migraine days and < 15 headache days per month on average during the 3 months prior to screening.

105 History of ≥ 4 migraine attacks of at least moderate severity per month on average during the 3 months prior to screening.

106 History of treatment failure with at least 1 preventive treatment for migraine. Failure of preventive treatment for migraine is defined as treatment discontinuation due to lack of efficacy, adverse event, or general poor tolerability.

107 Regular use of an oral triptan (using only eletriptan, rizatriptan, sumatriptan, or zolmitriptan) for acute migraine treatment, and typically initiating acute treatment with an oral triptan on > 50% of attacks of at least moderate pain intensity. Regular use is defined as ≥ 4 days of oral triptan use per month during the 3 months prior to screening.

Subjects are eligible to enter the baseline period of the study only if they have completed the run-in period and the following criterion applies (based on the episode eDiary):

108 Have at least 1 qualifying triptan-treated migraine attack during the run-in period (using 1 of the specified 4 oral triptans from inclusion criteria 107) where pain freedom has not been achieved within the first hour from triptan intake during that migraine attack. If a subject reports more than 1 qualifying oral triptan-treated migraine attack where for > 50% of migraine attacks during the run-in period pain freedom is not achieved in ≤ 1 hour following oral triptan intake during that migraine attack, the subject will be eligible to enter the 4-week baseline period.

Subjects are eligible to enter the DBTP of the study only if they have completed the baseline period and all of the following criteria apply (based on daily eDiary):

109 Must be the same migraine type as the initial screening period (ie, if a subject meets HFEM criteria in the 3 months prior to screening, then the subject must meet HFEM criteria during baseline).

110 Must have ≥ 4 migraine attacks of at least moderate severity during the baseline period.

111 Demonstrated at least 80% compliance with the daily eDiary during the baseline period.

112 Subject must treat qualifying migraine attacks with the same oral triptan as used during run-in period using 1 of the specified 4 oral triptans from inclusion criteria 107.

## 5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

**Disease Related**

201 Older than 50 years of age at migraine onset.

202 History of hemiplegic migraine, cluster headache, or other trigeminal autonomic cephalalgia.

**Other Medical Conditions**

203 Currently diagnosed with fibromyalgia and/or chronic pelvic pain.

204 History of major psychiatric disorder (eg, schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of moderately severe depression based on a Patient Health Questionnaire (PHQ-9) total score of ≥ 15 at initial screening.

205 Has any medical contraindication to the use of an oral triptan.

**Prior/Concomitant Therapy**

206 Previously treated with erenumab or gepants (small molecule CGRP-R antagonist) in a manner consistent with migraine prevention,

OR

Previously treated with a ligand-based anti-CGRP monoclonal antibody (ie, fremanezumab, galcanezumab and/or eptinezumab) in a manner consistent with migraine prevention that either:

a) in the opinion of the investigator, did not offer any evidence of a therapeutic response

OR

b) was discontinued for less than 12 weeks from the date of initial screening

OR

c) was previously discontinued due to a known adverse drug reaction

207 Currently being treated with lasmiditan and/or a gepant in the acute setting.

208 No therapeutic response with > 4 of the following medication categories after an adequate therapeutic trial:

- Category 1: Topiramate
- Category 2: Other antiepileptics (eg, divalproex sodium, sodium valproate, gabapentin)
- Category 3: Beta blockers
- Category 4: Tricyclic antidepressants
- Category 5: Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors)
- Category 6: Calcium channel blockers (eg, verapamil, amlodipine, cinnarizine, lomerizine) or calcium antagonists (eg, flunarizine)
- Category 7: Angiotensin receptor blockers (eg, candesartan) or angiotensin-converting enzyme (ACE) inhibitors (eg, lisinopril)
- Category 8: Onabotulinum toxin
- Category 9: Other drugs used for migraine prevention

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) and is based on the investigator's assessment.

The following scenarios do not constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

209 Use of an excluded medication, device, or procedure (refer to Section 6.1.6 for the list of excluded medications, devices, or procedures and corresponding time period for exclusion).

210 Currently has a history of consistent excellent response to oral triptans, defined as achievement of pain freedom in ≤ 1 hour for ≥ 50% of treated attacks of at least moderate pain intensity during the 3 months prior to screening.

211 Use of triptans administered via a non-oral (eg, subcutaneous [SC] or intranasal delivery systems) or sublingual route at the time of screening, during the run-in and baseline periods, and throughout the study duration.

**Prior/Concurrent Clinical Study Experience**

212 Currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

**Other Exclusions**

213 Female subject who are pregnant or breastfeeding or who plan to become pregnant or breastfeeding while on study and for an additional 16 weeks after the last dose of investigational product.

214 Female subjects of childbearing potential unwilling to use protocol specified method of contraception, see Appendix 5 (Section 11.5) during treatment and for an additional 16 weeks after the last dose of investigational product.

215 Female subjects of childbearing potential with a positive pregnancy test assessed at screening by a highly sensitive urine or serum pregnancy test.

216 Subject has known sensitivity to any of the products or components to be administered during dosing.

217 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, clinical outcome assessments) to the best of the subject and investigator's knowledge.

218 History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

### 5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (screening period starts when the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via interactive response technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

### 5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the condition that led to screen failure is expected to be transient. Refer to Section 8.1.1.

### 5.5 Run-in and Baseline Periods

Subjects enrolled in the study will complete the run-in period and baseline period prior to treatment assignment/randomization described in Section 6.4.1. To qualify for the baseline period, subjects must have at least 1 qualifying oral triptan-treated migraine attack (defined in Section 11.1) during the run-in period and meet inclusion criterion 108. Upon completion of the baseline period, subjects must meet inclusion criteria 109 to 112 to qualify for treatment assignment/randomization.

Subjects who do not meet the eligibility criteria for the run-in or baseline periods will discontinue the study.

## 6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 6-1 below.

## 6.1 Treatment(s) Administered

### 6.1.1 Investigational Products

**Table 6-1. Study Treatments**

| Study Treatment Name | Amgen Investigational Product:[a] Aimovig (erenumab) | Placebo |
|---|---|---|
| **Dosage Formulation** | Erenumab will be supplied as a 70 mg/mL solution formulated with sodium acetate, sucrose, and polysorbate 80. | Placebo will be presented in identical containers and stored/packaged the same as erenumab. |
| **Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency** | 140 mg once every 4 weeks (2 consecutive injections of 70 mg) | Placebo once every 4 weeks (2 consecutive injections) |
| **Route of Administration** | SC injection | SC injection |
| **Accountability** | The quantity, start date, injection site, and box number(s) of IP are to be recorded on each subject's CRF. | |
| **Dosing Instructions** | Treatment doses to be administered at study visits after all scheduled assessments by authorized investigational site study staff. The 140-mg dose is administered as 2 consecutive SC injections of 70 mg each. The anatomical sites for administration of IP are the upper arm, upper thigh, or abdomen. | |
| **Device** | PFS | |

CRF = case report form; IP = investigational product; PFS = prefilled syringe; SC = subcutaneous.
[a] Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

### 6.1.2 Medical Devices

The investigational medical device provided by Amgen for use in this study is the prefilled syringe (PFS) (Table 6-1). The investigational product PFS is a single-use, disposable, handheld manual injection device for fixed dose SC injection of 70 mg/mL in a 1-mL deliverable volume. It will be administered as 2 consecutive SC injections for 140 mg/mL dosing. Additional details are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

### 6.1.3 Other Protocol-required Therapies

There are no other protocol-required therapies in this study.

### 6.1.4 Other Treatment Procedures

There are no other treatment procedures in this study.

### 6.1.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational product, device, or combination product provisioned and/or repackaged/modified by Amgen (eg, PFS).

Any product complaint(s) associated with an investigational product, device, or combination product supplied by Amgen are to be reported according to the instructions provided in the IPIM.

### 6.1.6 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Excluded treatments, medical devices, and procedures are provided in Table 6-2.

**Table 6-2. Excluded Treatments, Medical Devices, and Procedures**

| Prohibited Medications | Time Period for Exclusion |
|---|---|
| Use of concomitant oral migraine preventive medications, including the following:[a]<br>• Antiepileptics (eg, divalproex sodium, sodium valproate, topiramate, carbamazepine, levetiracetam)<br>• Angiotensin receptor blockers (eg, candesartan) or ACE inhibitors (eg, lisinopril)<br>• Beta blockers<br>• Calcium channel blockers (eg, verapamil, amlodipine, cinnarizine) or calcium antagonists (eg, flunarizine)<br>• Tricyclic antidepressants<br>• Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors)<br>• Other drugs or supplements used for migraine prevention (eg, clonidine, guanfacine, methysergide, cyproheptadine, pizotifen, butterbur, feverfew, magnesium [≥ 500 mg/day], riboflavin [≥ 400 mg/day], coenzyme $Q_{10}$). | 2 months before the start of the screening period and throughout the study |
| Frequent use of an allowed acute medication for migraine in a pattern that would categorize prevention of migraine attacks (ie, in the absence of aura or headache)[a] | 2 months before the start of the screening period and throughout the study |
| Use of the following acute medications for the acute treatment of migraine:[a]<br>Opioid and/or opioid containing analgesics<br>• Long-acting formulations, more than 4 days<br>• Short acting more than 15 days | 2 months before the start of the screening period and throughout the study |
| All anti-CGRP monoclonal antibodies other than erenumab study supply are expected to have been discontinued 12 weeks before start of screening and are prohibited to be taken from 12 weeks before screening throughout the study. | 12 weeks before the start of screening and throughout the study |
| Lasmiditan **and gepants** | From the start of the screening period and throughout the study |
| Investigational medications | 30 days or 5 half-lives (whichever is longer) before the start of the screening period and throughout the study |
| Onabotulinum toxin (in the head and/or neck region) | 4 months before the start of the screening period and throughout the study |

Page 1 of 2

Footnotes defined on next page of table

**Table 6-2. Excluded Treatments, Medical Devices, and Procedures**

| Prohibited Procedures or Devices | Time Period for Exclusion |
|---|---|
| CBD-containing products with systemic absorption | 6 months before the start of the screening period and throughout the study |
| For any indication<br>Infusion Therapy (eg, steroids, valproate sodium, dihydroergotamine)<br>Note: infusion therapy may be allowed during DBTP if medically justified | 3 months before the start of the screening period and throughout the study |
| For any indication<br>Devices (eg, neuromodulation devices) or procedures (eg, nerve blocks, trigger-point injections, and acupuncture), depending on anatomic region and impact. | 3 months before the start of the screening period and throughout the study |
| Cognitive Behavioral Therapy, Biofeedback, and Psychotherapy<br>Note: Subjects on a stable, maintenance phase of these therapies for migraine will be allowed to participate.<br>Note: Stable, maintenance phase of CBT is defined as ≥ 6 weekly or biweekly sessions administered by adequately trained psychologists and only "booster" sessions at a monthly, bimonthly, or quarterly frequency at least 3 months before the start of the screening period | 3 months before the start of the screening period and throughout the study |

Page 2 of 2

ACE = angiotensin-converting-enzyme; CBD = cannabidiol; CBT = cognitive behavioral therapy; CGRP = canonical calcitonin gene related peptide; DBTP = double-blind treatment period.

[a] Participants currently taking a medication which can exert migraine prevention effect, but is used for a non-migraine indication, can be allowed into the study if the medication has been stable for at least 1 month prior to screening and will remain so throughout the study. This allowance is limited to 1 "migraine preventative" medication for a non-migraine indication.

## 6.2 Dose Modification

### 6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

There will be no dose changes or dose stopping rules as part of this study.

### 6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Dose adjustments, delays, or withholding are not permitted.

### 6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

No samples assessing hepatotoxicity will be collected in this study.

### 6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product and/or device during the study are provided in the IPIM.

### 6.4 Measures to Minimize Bias: Randomization and Blinding

#### 6.4.1 Method of Treatment Assignment

Subjects will be randomized in a 1:1 allocation ratio to either erenumab or placebo in a double-blind manner after meeting all the post-baseline randomization requirements described in Section 5.5.

The randomization number will be assigned by the IRT. The randomization number is different than the subject identification number and will not be used by the site as a subject identifier.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

#### 6.4.2 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

##### 6.4.2.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

##### 6.4.2.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators, or subjects prior to the study being formally unblinded except as specified (eg, Section 6.4.2.1).

### 6.5 Treatment Compliance

Administration of investigational product will be conducted by authorized investigational site study staff on scheduled visits.

Noncompliance is to be documented in the medical file/source documentation and will be reflected in the electronic CRF. Noncompliant subjects are to be re-educated on the importance of adhering to the investigational product administration schedule and reminded that repeated cycles of noncompliance could be a reason for discontinuation of study treatment.

### 6.6 Treatment of Overdose

Overdose with this product has not been reported. No specific antidote exists. In the case of an overdose, the subject should be treated symptomatically, and supportive measures implemented as necessary.

### 6.7 Prior and Concomitant Treatment

#### 6.7.1 Prior Treatment

For prior migraine preventive medications, which are required to have ended 2 months prior to screening (6 month prior to screening in case of cannabidiol [CBD]-containing products) per Table 6-2, therapy name, indication, dose, unit, frequency, start and stop dates will be collected in the prior migraine preventive medication CRF.

For all other prior therapies that were being taken/used within 120 days prior to screening through the signing of the informed consent, therapy name and start and stop dates will be collected in the concomitant medication CRF.

#### 6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.6.

Concomitant therapies are to be collected from signing of the informed consent form through the end of study visit.

## 7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

### 7.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 1-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and device-related events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments may include any of the following:

- Decision by **s**ponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Pregnancy or breastfeeding

### 7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent

will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

### 7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not applicable to this study.

### 7.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

## 7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

# 8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

## 8.1 General Study Periods

### 8.1.1 Screening Period

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in IRT and screen the subject to assess eligibility for participation. The screening period is up to 9 weeks, which consists of an initial screening up to 3 weeks (21 days), a 2-week run-in period (14 days, but no more than 18 days), and a 4-week (28 days, but no more than 35 days) baseline period.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time if the condition that led to screen failure is expected to be transient.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 9-week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

### 8.1.2 Run-in Period

The run-in period is 2 weeks (but can be extended to a maximum of 18 days, if needed) and starts when the subject has met all the eligibility criteria in the initial screening period

(refer to Section 5.1 and Section 5.2). The run-in period ends when the subject does not meet the additional eligibility criterion at the end of the period (inclusion criterion 108) or when subject meets inclusion criterion 108 and enters the baseline period.

#### 8.1.3 Baseline Period

The baseline period starts when the subject has met all initial eligibility criteria (refer to Section 5.1 and Section 5.2), has completed the run-in period, and has met inclusion criterion 108. The baseline period ends when the subject does not meet all the additional eligibility criteria (inclusion criteria 109 through 112) and is screen failed or when subject meets all eligibility criteria and is enrolled and randomized. The total duration of the baseline period must be at least 28 days and no more than 35 days.

#### 8.1.4 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Study visits after day 1 may be completed within ± 3 days of the scheduled visit. All study procedures for a given study visit are to be completed on the same day. Investigational product is to be administered Q4W as the last procedure during each visit that it is required.

Subjects who discontinue investigational product are encouraged to remain in the study and complete all remaining procedures and study visits.

#### 8.1.5 End of Study

The end-of-study visit occurs at week 16 or 4 weeks after last dose of investigational product for subjects who discontinue the study. If a subject discontinues treatment or the study prior to week 12, the week 12 assessments should be conducted for their early termination visit. Assessments will be performed at the end-of-study visit as per Schedule of Activities (Table 1-1).

### 8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

#### 8.2.1 General Assessments

##### 8.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

#### 8.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

#### 8.2.1.3 Medical History

The investigator or designee will collect a complete medical history that started within 120 days prior to screening. Medical history will include information on the subject's concurrent medical conditions. In addition to the medical history, migraine history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

Targeted medical history is to be recorded in the neurologic medical history CRF, headache and migraine frequency medical history CRF, cardiovascular medical history CRF, cardiac risk factors medical history CRF, and gastrointestinal medical history CRF.

#### 8.2.1.4 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes.

#### 8.2.1.5 Substance Use History

Obtain information about any prior history of diagnosed substance-related disorders.

### 8.2.2 Efficacy Assessments

The clinical outcome assessments will be collected by subjects using a handheld device with an eDiary. The handheld device will have both the episode eDiary and the daily eDiary, which will be accessible by the subject during specified periods of the study.

Study site staff will assign and provide a handheld device with the eDiary to the subject at the run-in visit (after confirming the subject's eligibility to enter the run-in period). During the run-in period, only the episode eDiary will be available to the subject. The study site staff will train the subject on how to use the handheld device (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the episodic eDiary questions. The subject will be instructed to interact with the episode eDiary for oral triptan-treated migraine attacks and to bring the handheld device to the baseline visit. At the baseline visit, the investigator will confirm if inclusion criterion 108 has been met based on the run-in eligibility report. The episode eDiary will be made available to the subject again during study weeks 13 to 16 (month 4) of the DBTP. The episode eDiary will collect the following clinical

outcome assessments for oral triptan-related migraine attacks at the subject's own physical location (eg, home):

- Date and time of start of each headache
- Date and time of end of each headache
- Worst pain severity per headache day
- Pain features and additional symptoms of migraine attack
- The most bothersome symptom (ie, nausea, vomiting, photophobia, or phonophobia) and the severity following treatment with oral triptan
- Use of oral triptan (triptan name and dosing)

Once the subject has completed the run-in period and is considered eligible to enter the baseline period, the subject will be instructed to interact with the daily eDiary every day and to bring the device to site during every study visit. The daily eDiary will collect the following clinical outcome assessments every day at the subject's own physical location (eg, home):

- Date and time of start of each headache (ie, migraine or nonmigraine headache)
- Date and time of end of each headache
- Worst pain severity per headache day
- Pain features (eg, 1-sided, throbbing, worsens with exercise/physical activity)
- Symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute medications (medication name/type [from pre-entered list], date of dosing)

At the day 1 visit prior to randomization, the investigator will use the information collected during the baseline period by the subject's daily eDiary to review all data entered and confirm the relevant inclusion criteria (inclusion 109 through 112) are met.

The handheld device will also be used for the completion of the following patient-reported outcome measures:

- Migraine Functional Impact Questionnaire (MFIQ)
- Migraine Symptom Severity Score (MSSS)
- Change in most troublesome symptom
- Patient Global Impression of Severity (PGI-S)
- Migraine Interictal Burden Scale (MIBS-4)
- Headache Impact Test (HIT-6)
- Pain Catastrophizing Scale (PCS)

#### 8.2.2.1.1 Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning (ie, Physical, Usual Activities, Social, and Emotional). It has 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. The scores are calculated as the sum of the item responses and the sum is rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period is the past 7 days.

#### 8.2.2.1.2 Migraine Symptom Severity Scale (MSSS)

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

#### 8.2.2.1.3 Change in Most Troublesome Symptom

The change in most troublesome symptom will be measured by a 7-point Likert-type scale. It will be a single question asking the patients to rate how their most troublesome “non-headache pain” symptom (during and between migraine attacks) has changed since the start of the study on a scale of 1 (Very Much Improved) to 7 (Very Much Worse).

#### 8.2.2.1.4 Patient Global Impression of Severity (PGI-S)

The PGI-S is a single question that rates the severity of the patient’s condition at the time of assessment, relative to the patient’s experience prior to treatment. It is a 7-point scale that ranks severity of illness using 1 of the following response categories:
1 = Normal, not at all ill, 2 = Borderline ill, 3 = Mildly ill; 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, and 7 = Most extremely ill.

#### 8.2.2.1.5 Migraine Interictal Burden Scale (MIBS-4)

The MIBS-4 measures interictal migraine-related burden with 4 questions that assess impairment in work or school, impairment in family and social life, difficulty making plans

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

#### 8.2.2.1.6 Headache Impact Test (HIT-6)

The HIT-6 is a short-form self-administered questionnaire based on the Internet-HIT question pool. The HIT-6 was developed as a global measure of adverse headache impact to assess headache severity in the previous month and change in a subject's clinical status over a short period of time. Six questions cover severe pain, limitation of daily activity (household, work, school and social), wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling "fed up" or irritated because of headache, and headache limiting ability to concentrate or work on daily activities. Each of the 6 questions is responded to using 1 of 5 response categories: "never," "rarely," "sometimes," "very often," or "always".

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. HIT-6 scores are 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. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.

#### 8.2.2.1.7 Pain Catastrophizing Scale (PCS)

The PCS is a 13-item self-report measure designed to convey a subject’s characteristic level of pain-related, catastrophic thinking during painful experiences (Sullivan et al, 1995). The measure consists of 3 subscales, which are Rumination (4 items), Magnification (3 items), and Helplessness (6 items). Participants are asked to recall a painful experience and to rate the extent to which the thoughts and emotions listed in each item had occurred. For each item, subjects are requested to provide a response in a 5-point Likert scale (0 “not at all,” 1 “to a slight degree,” 2 “to a moderate degree,” 3 “to a great degree,” 4 “all the time”). Higher scores in PCS indicate higher levels of catastrophizing and both the original PCS and its headache version have been well validated across both experimental studies as well as clinical samples. Both

versions of the PCS have demonstrated strong internal consistency and test-retest reliability (Sullivan et al, 1995; Osman et al, 1997; Holroyd et al, 2007).

### 8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1).

### 8.2.4 Adverse Events and Serious Adverse Events

#### 8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

##### 8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of study are reported using the Event CRF.

##### 8.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through end of study are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's knowledge of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. The investigator is to determine whether these grade 4 abnormalities are serious adverse events based on the definition of serious adverse events as per Appendix 4 (Section 11.4).

##### 8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

After End of Study, there is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product. If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

#### 8.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

#### 8.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

#### 8.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

#### 8.2.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

#### 8.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 16 weeks after the last dose of investigational product.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

#### 8.2.4.7 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Product complaints are described in Section 6.1.5.

Further details regarding adverse device effects can be found in Section 11.4.

### 8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

**Pregnancy Testing**

A urine pregnancy test should be completed for females of childbearing potential as per the Schedule of Activities (Table 1-1).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-3). Refer to Section 11.5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

### 8.2.6 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of migraines and/or to identify subjects who may have positive or negative response to erenumab. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from the cell pellet collected in the plasma tube used for the biomarker development sample.

The final disposition of samples is described in Section 11.6.

### 8.2.7 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

#### 8.2.7.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

If consent is provided by subjects, biomarker discovery samples collected at the time points specified in the Schedule of Activities will be retained for future biomarker development as described in Appendix 6 (Section 11.6).

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to erenumab to investigate and further understand migraines.

## 9. Statistical Considerations

### 9.1 Statistical Hypotheses

The primary hypothesis is that preventive treatment with monthly administration of erenumab is superior to placebo in reducing duration of moderate or severe headache pain in subjects with HFEM who have previously failed at least 1 migraine preventive treatment.

## 9.2 Sample Size Determination

A total sample size of 576 subjects (288 subjects per group including 10% dropouts) provides at least a 90% power for the primary efficacy hypothesis. The statistical power for secondary efficacy hypotheses ranges from 81% to > 99% (Table 9-1).

**Table 9-1. Sample Size Assumptions and Statistical Powers for Primary and Secondary Efficacy Endpoints for a Total Sample Size of 576 Subjects Including a 10% Attrition Rate due to Dropout**

| Hypothesis | Assumed Treatment Effect (Common SD) | Power |
|---|---|---|
| Primary:<br>Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3 | -16.7 (50) | 96% |
| Secondary: Change from baseline in mean monthly | | |
| MFIQ physical function domain score over months 1, 2, and 3 | -9.2 (18.0) | > 99% |
| MFIQ usual activities domain score over months 1, 2, and 3 | -7.5 (19) | > 99% |
| MFIQ emotional function domain score over months 1, 2, and 3 | -11.5 (22) | > 99% |
| MFIQ social function domain score over months 1, 2, and 3 | -6.9 (20) | 97% |
| Average duration of at least moderate migraine pain intensity in migraine attacks occurring over months 1, 2, and 3[a] | -2.0 (8) | 81% |
| Average peak migraine pain intensity over months 1, 2, and 3 | -0.11 (0.44) | 81% |

MFIQ = Migraine Functional Impact Questionnaire.
Note: All power calculations are based on a 2-sided significance level of 0.05. The assumed treatment effects and common standard deviations are derived or chosen from a subset of placebo-treated and erenumab-140 mg-treated subjects in erenumab Study 20120296 with high-frequency episodic migraine (ie, 7 to 14 monthly migraine days) and having at least 4 moderate-to-severe migraine attacks at baseline.
[a] If a subject did not have any migraine attacks in a given month, the duration of at least moderate migraine pain intensity was counted as 0.

## 9.3 Analysis Sets, Subgroups, and Covariates

### 9.3.1 Analysis Sets

#### 9.3.1.1 Full Analysis Set

The full analysis set consists of all subjects who were randomized in the study. Analysis of disposition, demographic and baseline characteristics, and important protocol deviations will utilize this analysis set.

#### 9.3.1.2 Efficacy Analysis Set

The respective efficacy analysis set consists of a subset of subjects from full analysis set who receive at least 1 dose of investigational product and have a baseline value and at least 1 post baseline value for the endpoint of interest. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Primary analysis of the efficacy endpoints will utilize the respective efficacy analysis set.

#### 9.3.1.3 Safety Analysis Set

The respective safety analysis set 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 has received the incorrect dose during the entire DBTP. Analysis for safety endpoints and summary of investigational product administration will utilize the respective safety analysis set.

### 9.3.2 Covariates

Model-adjusted analyses of efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed, if applicable.

### 9.3.3 Subgroups

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

- Number of prior treatment failures (1, 2, and 3 or more treatment failures)
- Medication overuse status at baseline (yes vs no)

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

### 9.3.4 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 time point. For this study, efficacy endpoints will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe how missing data will be handled.

For the endpoints derived from daily diary during month 1 to 3, if at least 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements (eg, migraine days, headache days) will be prorated based on the number of days with available information.

Missing items in each clinical outcome assessment questionnaire will be handled based on the scoring algorithm for each assessment.

Missing data after above methods will either be handled by the linear mixed effects model under missing-at-random assumption or imputed as non-responders for binary endpoint.

Missing data in safety data will not be imputed.

## 9.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.1.

### 9.4.1 Planned Analyses

#### 9.4.1.1 Primary Analysis

The primary analysis (or final analysis since there is only 1 milestone analysis for this study) will occur after all subjects have completed their week 16 visit (or discontinued from the study). The DBTP treatment assignment will be unblinded and all efficacy and safety analyses will be conducted and reported by the DBTP treatment group.

### 9.4.2 Methods of Analyses

#### 9.4.2.1 General Considerations

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

A sequential testing procedure will be used to maintain the family-wise type 1 error $\alpha = 0.05$ between the primary and secondary endpoints following the prespecified order below. An endpoint will only be tested for statistical significance if the endpoint tested in the previous step is statistically significant at 2-sided significance level of 0.05.

1. Primary endpoint: change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3

2. Secondary endpoints: change from baseline in mean monthly function domain score over months 1, 2, and 3, as measured by the MFIQ using the Hochberg procedure
   - Impact on physical functioning
   - Impact on usual activities
   - Impact on emotional functioning
   - Impact on social functioning
3. Secondary endpoint: change from baseline in mean monthly average duration of at least moderate pain intensity **in** migraine attack**s occuring** over months 1, 2, and 3 **(migraine attacks as defined in Section 11.1)**
4. Secondary endpoint: change from baseline in mean monthly average peak migraine pain intensity over months 1, 2, and 3, as assessed by the 11-point NRS

#### 9.4.2.2 Efficacy Analyses

| Endpoint | Statistical Analysis Methods |
|---|---|
| **Primary** | The primary endpoint will be analyzed using a linear mixed effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. |
| **Secondary** | The secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. |
| **Exploratory** | Detailed primary analysis method for exploratory endpoints will be described in the SAP. |

#### 9.4.2.3 Safety Analyses

##### 9.4.2.3.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

##### 9.4.2.3.2 Exposure to Investigational Product

The total length of investigational product exposure, the number of doses, and the proportion of subjects receiving each dose will be summarized using descriptive statistics.

#### 9.4.2.3.3 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by medication category for each treatment group.

## 10. References

Afridi SK, Giffin NJ, Kaube H, et alet al. A positron emission tomographic study in spontaneous migraine. *Arch Neurol*. 2005;62:1270-1275.

Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. *Cephalalgia*. 2007;27:1442-1453.

Aurora SK, Barrodale P, Chronicle EP, Mulleners WM. Cortical inhibition is reduced in chronic and episodic migraine and demonstrates a spectrum of illness. *Headache*. 2005;45:546-552.

Buse DC, Rupnow MFT, Lipton RB. Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life. *Mayo Clin Proc*. 2009; 84:422-435.

Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalagia*. 2018;38:1026-1037.

Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. *Eur J Neurol*. 2009;16:968-981.

Goadsby PJ, Paemeleire, Broessner G, et al. Efficacy and safety of erenumab (AMG334) in episodic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalagia*. 2019;39(7):817-826.

Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. *N Engl J Med*. 2017;377:2123-2132.

Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, 3rd edition. (ICHD-III) *Cephalalgia*. 2018;38(1):1–211.

Holroyd KA, Drew JB, Cottrell CK, Romanek KM, Heh V. Impaired functioning and quality of life in severe migraine: the role of catastrophizing and associated symptoms. *Cephalalgia*. 2007;27:1156–1165.

Houle TT, Turner DP, Houle TA, et al. Rounding behavior in the reporting of headache frequency complicates headache chronification research. *Headache*. 2013;53:908-919.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. AMPP Advisory Group: migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.

Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *J Behav Med*. 1997;20:589-605.

Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392:2280-2287.

Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia*. 1997;17:15-22.

Silberstein SD. Preventive migraine treatment. *Continuum (Minneap Minn)*. 2015; 21: 973-989.

Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345

Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *J Headache Pain*. 2010;11:289-299.

Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. *Psychol Assess*. 1995;7:524–532.

Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16:425-434.

Welch KM, Nagesh V, Aurora S, Gelman N. Periaqueductal gray matter dysfunction in migraine and chronic daily headache may be due to free radical damage. *J Headache Pain*. 2001;2(Suppl 1):33-41.

# 11. Appendices

## 11.1 Appendix 1. List of Abbreviations and Definitions of Terms

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ACE | angiotensin-converting enzyme |
| CBD | cannabidiol |
| CFR | Code of Federal Regulations |
| CGRP | calcitonin gene-related peptide |
| CM | chronic migraine |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBTP | double-blind treatment period |
| E-DBTP | exploratory double-blind treatment period |
| EDC | electronic data capture |
| eDiary | electronic diary |
| EM | episodic migraine |
| End of Study for Individual Subject | defined as the last day that protocol-specified procedures are conducted for an individual subject |
| End of Study (primary completion) | 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 |
| End of Study (end of trial), EOS | defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable |
| End of Treatment | defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject |
| Enrollment | defined as the day a subject has met all run-in and baseline period eligibility criteria and is enrolled and randomized into the study (subjects are randomized same day) |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| Headache | a migraine or non-migraine headache |
| Headache day | Any calendar day in which the subject experiences a qualifying headache (initial onset, continuation, or recurrence of the headache). A qualifying headache is defined as:<br>• a qualifying migraine headache (including an aura-only event that is treated with acute migraine-specific medication) or<br>• a qualifying non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualifying migraine headache or<br>• a headache of any duration for which acute headache treatment is administered |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| HFEM | high-frequency episodic migraine |
| HIT-6 | Headache Impact Test-6 |
| HRT | hormone replacement therapy |
| ICH | International Council for Harmonisation |
| ICHD-III | International Classification of Headache Disorders, Third Edition |
| IEC | Independent Ethics Committee |
| IHS | International Headache Society |
| IPIM | Investigational Product Instruction Manual |
| IRB | Institutional Review Board |
| IRT | interactive response technology that is linked to a central computer in real time as an interface to collect and process information |
| IUD | intrauterine device |
| IUS | intrauterine hormonal-releasing system |
| LSM | least squares mean |
| M-DBTP | main double-blind treatment phase |
| MFIQ | Migraine Functional Impact Questionnaire |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIBS-4 | 4-item Migraine Interictal Burden Scale |
| Migraine attack | An episode of any qualifying migraine headache. The following rules will be used to distinguish an attack of long duration from 2 attacks, or to distinguish between attacks and relapses:<br>a. A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as 1 attack and not 2.<br>b. An attack treated successfully with medication but with relapse within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as 1 attack. |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| Migraine day | A migraine day is defined as any calendar day in which the subject experiences a qualifying migraine headache (onset, continuation or recurrence of the migraine headache).<br>A qualifying migraine headache is defined as a migraine with or without aura lasting for ≥ 30 minutes, and meeting at least 1 of the following criteria (a and/or b):<br>a. ≥ 2 of the following pain features:<br>• Unilateral<br>• Throbbing<br>• Moderate to severe<br>• Exacerbated with exercise/physical activity<br>b. ≥ 1 of the following associated symptoms:<br>• Nausea and/or vomiting<br>• Phonophobia and photophobia<br>If the subject took a migraine-specific medication (ie, triptan, or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. |
| Migraine recurrence | return of any headache of at least moderate pain intensity in patients who were pain-free at 2 hours post-dose |
| MMD | monthly migraine days |
| MSSS | Migraine Symptom Severity Score |
| NCT | National Clinical Trials |
| NRS | Numeric Rating Scale |
| pain relief | reduction from moderate/severe pain to mild/no pain |
| PCS | Pain Catastrophizing Scale |
| PFS | prefilled syringes |
| PGI-S | Patient Global Impression of Severity |
| PHQ-9 | Patient Health Questionnaire |
| Q4W | every 4 weeks |
| QM | once monthly |
| Qualifying **oral** triptan-treated attacks **(run-in period/month 4)** | migraine attacks of at least moderate peak pain intensity that are treated with an oral triptan within 2 hours of pain reaching at least moderate severity |
| **Qualifying oral triptan-treated attacks (baseline/ month 1, 2, and 3)** | **migraine attacks that are treated with an oral triptan** |
| Randomization | defined as the day a subject has met all run-in and baseline period eligibility criteria and is enrolled and randomized into the study (subjects are enrolled same day) |
| SAP | statistical analysis plan |
| SC | subcutaneous(ly) |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| Source **d**ata | information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value. |
| Study **d**ay 1 | defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject |
| Total migraine freedom days | Days where there is an absence of headache and aura, photophobia, phonophobia, and nausea/vomiting |
| US | United States |

## 11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 11-1. Analyte Listing**

| Analyte | Notes |
|---|---|
| Urine pregnancy test | |
| Urine drug test | |
| Biomarker development | Optional; sent to central laboratory |
| Pharmacogenetic assessment | Optional; sent to central laboratory |

## 11.3 Appendix 3. Study Governance Considerations

### Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

### Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such

as patient advocacy groups. Also, digital recruitment strategies may also be used. All patient facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC.

**Informed Consent Process**

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the [IRB/IEC] or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Subject

withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 30 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use optional portions of this study. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

**Data Protection/Subject Confidentiality**

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

**Publication Policy**

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are

to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

**Investigator Signatory Obligations**

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An **i**nvestigator who provided significant contributions to either the design or interpretation of the study
- An **i**nvestigator contributing a high number of eligible subjects

**Data Quality Assurance**

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

**Source Documents**

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The **i**nvestigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the [IRB/IEC] and Amgen
- Investigational product-related correspondence including [Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

**Study and Site Closure**

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the **i**nvestigator reserve the right to terminate the investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

### Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

## 11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

**Definition of Adverse Event**

| **Adverse Event Definition** |
|---|
| • An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment.<br>• Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.<br>• Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP). |

| **Events Meeting the Adverse Event Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. |

| **Events NOT Meeting the Adverse Event Definition** |
|---|
| • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

**Definition of Serious Adverse Event**

| **A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:** |
|---|
| **Results in death (fatal)** |
| **Immediately life-threatening**<br>The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **Requires in-patient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event. |
| **Results in persistent or significant disability/incapacity**<br>The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **Is a congenital anomaly/birth defect** |

| **A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:** |
|---|
| **Other medically important serious event**<br>Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.<br><br>Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

**Definition of Adverse Device Effect**

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 6.1.2 for the list of Amgen medical devices).

| **Adverse Device Effect Definition** |
|---|
| An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device. |

**Recording Adverse Events and Serious Adverse Events**

| **Adverse Event and Serious Adverse Event Recording** |
|---|
| • When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.<br>• The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF).<br>• The investigator must assign the following adverse event attributes:<br>  ○ Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);<br>  ○ Dates of onset and resolution (if resolved);<br>  ○ Severity (or toxicity defined below);<br>  ○ Assessment of relatedness to investigational product and<br>  ○ Action taken.<br>• If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF.<br>• It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page.<br>• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.<br>• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event. |

**Evaluating Adverse Events and Serious Adverse Events**

| **Assessment of Severity** |
|---|
| The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:<br><br>The Common Terminology Criteria for Adverse Events, version 4.03 which is available at the following location:<br>http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. |

**Assessment of Causality**

- The investigator is obligated to assess the relationship between investigational product, device and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

**Follow-up of Adverse Event and Serious Adverse Event**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

**Reporting of Serious Adverse Event**

| **Serious Adverse Event Reporting via Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system.<br>• If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's knowledge of the event.<br>• The site will enter the serious adverse event data into the electronic system as soon as it becomes available.<br>• After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 11-2).<br>• Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event. |

**Adverse Device Effects: Recording, Evaluating and Reporting**

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

## Figure 11-1. Sample Electronic Serious Adverse Event Contingency Form

General Instructions

**The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.**

**Types of Events to be reported on this form**

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   **Site Number*** – Enter your assigned site number for this study

   **Investigator*, Country*, Reporter*, Phone No., and Fax No.** – Enter information requested

2. **Subject Information**

   **Subject ID Number*** – Enter the entire number assigned to the subject

   **Age at event onset, Sex, and Race** – Enter the subject's demographic information

   **End of Study date** – If the subject has already completed the study or terminated the study early, enter the End of Study date

***If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.***

3. **Serious Adverse Event**

   **Provide the date the Investigator became aware of this Information**

   **Serious Adverse Event Diagnosis or Syndrome*** –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   **Date Started*** – Enter date the adverse event first started (not the date on which the event met serious criteria )rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   **Date Ended** – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   **If event occurred before the first dose of Investigational Product (IP)/drug under study**, add a check mark in the corresponding box.

   **Is event serious?* – Indicate Yes or No. This is a mandatory field.**

   **Serious Criteria Code* – This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   **Relationship to IP** – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   **Relationship to Amgen device*** – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   **Outcome of Event*** – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   **If event is related to a study procedure**, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

***At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.***

5. **IP Administration including Lot # and Serial # when known / available.**

   **Blinded or open-label** – If applicable, indicate whether the investigational product is blinded or open-label

*FORM-056006* *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

**Completion Instructions - Electronic Adverse Event Contingency Report Form**
**(for use for Studies using Electronic Data Capture [EDC])**

**Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.**

**Initial Start Date** – Enter date the product was first administered, regardless of dose.
**Date of Dose Prior to or at the time of the Event** – Enter date the product was last administered prior to, or at the time of, the onset of the event.
**Dose, Route, and Frequency at or prior to the event** – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
**Action Taken with Product** – Enter the status of the product administration.

6. **Concomitant Medications**
**Indicate if there are any medications.**
**Medication Name, Start Date, Stop Date, Dose, Route, and Frequency** – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
**Co-suspect** – Indicate if the medication is co-suspect in the event
**Continuing** – Indicate if the subject is still taking the medication
**Event Treatment** – Indicate if the medication was used to treat the event

7. **Relevant Medical History**
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**
**Indicate if there are any relevant laboratory values.**
**For each test type,** enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**
**Indicate if there are any tests, including any diagnostics or procedures.**
**For each test type,** enter the date, name, results and units (if applicable).

***At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.***

10. **Case Description**
**Describe Event** – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

**Complete the signature section at the bottom of page 3 and fax the form to Amgen.** *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

## Figure 11-2. Sample Serious Adverse Event Report Form

| A<br>**Study # 20190008**<br>**AMG 334** | **Electronic Serious Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

**Reason for reporting this event via fax**

**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

*<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>*

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

**If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:** _____
**and start date:** Day ____ Month ____ Year _____

**3. SERIOUS ADVERSE EVENT**

**Provide the date the Investigator became aware of this information:** Day____ Month____ Year____

| Serious Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP | Is event serious? | If serious enter Serious Criteria code (see codes below) | Relationship<br>Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP?<br>Erenumab No✓ Yes✓ / PFS No✓ Yes✓ / <Device> No✓ Yes✓ / <Device> No✓ Yes✓ | Outcome of Event<br>Resolved<br>Not resolved<br>Fatal<br>Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|
| | | | | ☐Yes ☐No | | | | |
| | | | | ☐Yes ☐No | | | | |
| | | | | ☐Yes ☐No | | | | |

**Serious Criteria:** 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

**5. Was IP/drug under study administered/taken prior to this event?** ☐No ☐Yes If yes, please complete all of Section 5

| IP/Amgen Device: | | Date of Initial Dose<br>Day Month Year | Prior to, or at time of Event<br>Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| Erenumab | ☐ blinded ☐ open label | | | | | | | Lot #_____ ☐ Unknown Serial #_____ ☐ Unavailable / Unknown |
| PFS | ☐ blinded ☐ open label | | | | | | | Lot #_____ ☐ Unknown Serial #_____ ☐ Unavailable / Unknown |

*FORM-056006* *Version 7.0 Effective Date: 1 February 2016*

Page 1 of 3

| A<br>**Study # 20190008**<br>**AMG 334** | **Electronic Serious Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**6. CONCOMITANT MEDICATIONS (eg, chemotherapy)** Any Medications? ☐ No ☐ Yes If yes, please complete:

| Medication Name(s) | Start Date (Day Month Year) | Stop Date (Day Month Year) | Co-suspect No✓ | Co-suspect Yes✓ | Continuing No✓ | Continuing Yes✓ | Dose | Route | Freq. | Treatment Med No✓ | Treatment Med Yes✓ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**7. RELEVANT MEDICAL HISTORY** ***(include dates, allergies and any relevant prior therapy)***

**8. RELEVANT LABORATORY VALUES** ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Test | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unit | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**9. OTHER RELEVANT TESTS** ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

| A<br>**Study # 20190008**<br>**AMG 334** | **Electronic Serious Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**10. CASE DESCRIPTION** ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| | | |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| Signature of Investigator or Designee -<br>_____<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | Title | Date |

## 11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female subjects of childbearing potential are outlined in Section 5.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 16 weeks after the last dose of protocol-required therapies.

**Definition of Females of Childbearing Potential**

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Methods for Female Subjects**

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

**Unacceptable Methods of Birth Control for Female Subjects**

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

**Collection of Pregnancy Information**

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of investigational product.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-3). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 16 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-3) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Collection of Lactation Information**

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 213.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after discontinuing protocol-required therapies.

## Figure 11-3. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

**AMGEN Pregnancy Notification Form**

**Report to Amgen at:** USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

**1. Case Administrative Information**

**Protocol/Study Number:** 20190008

**Study Design:** ■ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** (____)_____ **Email** _____

**Institution** _____

**Address** _____

**3. Subject Information**

**Subject ID #** _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____(in years)

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| Erenumab | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

## AMGEN Lactation Notification Form

**Report to Amgen at:** USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

### 1. Case Administrative Information

**Protocol/Study Number:** 20190008

**Study Design:** ■ **Interventional** ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** (____)_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject age (at onset):**____(in years)

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| Erenumab | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

## 11.6 Appendix 6. Sample Storage and Destruction

Any blood (biomarker or pharmacogenetic) sample collected according to the Schedule of Activities (Table 1-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand migraines, the dose response and/or prediction of response to erenumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

**Superseded Amendment 1**

# Protocol Title: Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double blind, Placebo controlled Phase 4 Study

Amgen Protocol Number: Erenumab, 20190008

EudraCT Number: 2019-003646-33

Amendment Date: 29 June 2022

**Rationale:**

This protocol is being amended to clarify terminology used in secondary endpoint within statistics section in the protocol.

**Amendment 1**

**Protocol Title: Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double blind, Placebo-controlled Phase 4 Study**

Amgen Protocol Number Erenumab 20190008

EudraCT Number: 2019-003646-33

Amendment Date: 25 April 2022

**Rationale:**

This protocol is being amended to:

- Update the secondary and exploratory objectives and endpoints language in the objectives and endpoints sections
- Update overall design language to incorporate the qualifying oral triptan-treated migraine attack definition; to update the eligibility criteria for the end of the run-in period
- Update the key inclusion and exclusion criteria language of the summary of subject eligibility criteria in the synopsis
- Update schedule of activities (SoA) language in the following rows: Prior/concomitant therapies review, Serious adverse events, Urine pregnancy test, Urine drug testing, Pharmacogenetic studies, Episode (electronic diary) eDiary, Change in most troublesome symptom, and footnotes
- Update the Amgen investigational product background language for erenumab to clarify that the number of countries erenumab has been approved are over 70-countries; to clarify that the recommended dose in most countries is 70 mg once monthly (QM), and 140 mg QM, as indicated, for some patients
- Update benefit/risk assessment section to clarify that immune system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders have been observed in in postmarketing settings in addition to hypersensitivity reactions
- Update the number of North America and Europe investigative sites from 60 to 76 in the number of sites section

- Remove the primary completion date definition in end of study definition section
- Update language in the Inclusion and exclusion criterion sections
- Update table 6-2 in Section 6.1.6 to notify that opioids and/or opioids containing analgesics of different acting formulations (ie, long acting or short acting), anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies, and cannabidiol (CBD)-containing products with systemic absorption are prohibited medications each with their respective time period for exclusion; to add a footnote to clarify that certain medications with migraine preventative effects, but are used for non-migraine indications, are allowed under restrictive use
- Update prior treatment language in Section 6.7.1 to clarify that prior migraine preventative medications containing CBD need to be discontinued 6 months before start of screening
- Add language in screening period section to clarify that a 2 week and 4 week run-in and baseline periods can't be extended for more than 18 days and 35 days, respectively; similar language was used in the run-in period section
- Update the pain catastrophizing scale (PCS) language
- Update subgroup language to clarify that primary and secondary endpoints will be analyzed in the subgroups number of prior treatment failures, and in the medication overuse status at baseline
- Update the statistical analysis methods language for the primary, secondary, and exploratory endpoints in the efficacy analysis section
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.