Title Page

Protocol Title:		Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine
Short Protocol Title:		Erenumab Treatment Satisfaction Study
Protocol Number:		20190389
Investigational Product:		Erenumab-aooe (AMG 334)
Trade Name:		Aimovig®
Sponsor	**Name of Sponsor:**	Amgen Inc.
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine, dated **18 March 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)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine
Short Protocol Title: Erenumab Treatment Satisfaction Study

Study Phase: 4

Indication: Preventive treatment of migraine in adults

Rationale

Migraine is a prevalent and disabling neurological disorder, with a significant impact on the individual, family, workplace, and society. Objectives commonly assessed in registrational clinical trials **for migraine prevention** include changes in monthly migraine days and use of acute migraine-specific medications. These parameters, however, do not fully capture the whole breadth of the impact of migraine preventive treatments on the daily lives of patients and their families, including their satisfaction with treatment.

There is interest in the migraine provider community not only for clinical outcomes data, but also associated patient-centric data (eg, treatment satisfaction and global impression of change in migraine from different perspectives such as those of patients, providers and key family members). Health systems are also tracking patient satisfaction as a metric for quality of care delivery. These factors begin to define a new treatment paradigm for migraine management that includes both clinical and treatment-related satisfaction outcomes.

The Erenumab Treatment Satisfaction Study is a phase 4 United States (US), open-label, interventional, prospective 24-week study evaluating treatment satisfaction with erenumab as a preventive treatment in adult subjects with episodic migraine (EM) or chronic migraine (CM) currently on 1 standard of care migraine prevention therapy. The study will measure change in subject satisfaction with erenumab and subject, clinician, and key family member global impression of change in subject's migraine condition over the life of the study.

This study seeks to mirror real-world US clinical practice by providing subjects and investigators the flexibility to optimize erenumab dosing while maintaining or discontinuing the existing migraine prevention therapy (ie, standard of care).

Objective(s) and Endpoint(s)/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab on medication-specific treatment satisfaction	• Change from baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM) overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4

Primary Estimand

The estimand for the primary efficacy objective consists of:

- The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
- The endpoint, which is the change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM
- There are 2 intercurrent events, discontinuation of investigational product (IP) due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive least 1 dose of IP and have a baseline score and at least 1 post-baseline score on the TSQM overall satisfaction scale. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation, defined by the worst postbaseline value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
- The treatment, which is erenumab 70 or 140 mg every 4 weeks
- The summary measure, which is the mean change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM

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

Secondary

• To assess the effect of erenumab on medication-specific treatment satisfaction	• Achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4

The estimand for the secondary efficacy objective on treatment satisfaction consists of:

- The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
- The endpoint, which is achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM
- There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value for Item 14 of the TSQM. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not satisfied after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
- The treatment, which is erenumab 70 or 140 mg every 4 weeks
- The summary measure, which is the proportion of subjects who achieves overall satisfaction at week 24

<table>
<tr><td colspan="2">The estimand for the secondary efficacy objective on treatment-related satisfaction is the proportion of subjects who achieves overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value for Item 14 of the TSQM. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not satisfied after IP discontinuation, while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.</td></tr>
<tr><td>• To assess the effect of erenumab on global impression of change in migraine (by subject, treating clinician, and key family member)</td><td>• Improvement in subject global impression at week 24, as defined by subject reporting of much improved or a little improved on the migraine Global Impression Item (mGI-I)
• Improvement in treating clinician’s global impression at Week 24, as defined by treating clinician’s reporting of much improved or a little improved on the mGI-I for each individual subject
• Improvement in key family member’s impression at week 24, as defined by key family member’s reporting of much improved or a little improved on the mGI-I for each individual subject</td></tr>
<tr><td colspan="2">The estimand for the secondary efficacy objectives on impression of change in migraine consists of:
• The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
• The endpoints, which include:
  • Improvement in subject global impression at week 24, as defined by subject reporting of much improved or a little improved on the mGI-I
  • Improvement in treating clinician’s global impression at week 24, as defined by the clinician’s reporting of much improved or a little improved on the mGI-I for each individual subject
  • Improvement in key family member’s global impression at week 24, as defined by family member’s reporting of much improved or a little improved on the mGI-I for each individual subject
• There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have at least 1 post-baseline value of each respective mGI-I item. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
• The treatment, which is erenumab 70 or 140 mg every 4 weeks
• The summary measure, which is the proportion of subjects who achieves impression of improvement at week 24.
The estimand for the secondary efficacy objective on impression of change in migraine is the proportion of subjects who achieves global impression of migraine improvement at week 24 as defined by subject, treating clinician, or family member reporting of much improved or a little improved on the mGI-I, in subjects with EM or CM who are currently on 1 standard of care</td></tr>
</table>

<table>
<tr><td colspan="2">migraine prevention therapy and who receive at least 1 dose of IP and have at least 1 post-baseline value of the respective mGI-I, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation, while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.</td></tr>
<tr><td>• To assess the effect of erenumab on subject functional impairment</td><td>• Change from baseline in physical function domain score at week 24, as measured by the Migraine Functional Impact Questionnaire (MFIQ)
• Change from baseline in usual activities domain score at week 24 as measured by MFIQ
• Change from baseline in emotional function domain score at week 24 as measured by MFIQ
• Change from baseline in social function domain score at week 24 as measured by MFIQ</td></tr>
<tr><td colspan="2">The estimand for the secondary efficacy objective on subject functional impairment consists of:
• The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
• The endpoints, which include:
  • Change from baseline in MFIQ physical function domain score at week 24
  • Change from baseline in MFIQ usual activities domain score at week 24
  • Change from baseline in MFIQ emotional function domain score at week 24
  • Change from baseline in MFIQ social function domain score at week 24
• There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of the respective MFIQ domain scores. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
• The treatment, which is erenumab 70 or 140 mg every 4 weeks
• The summary measure, which is change from baseline in each MFIQ domain score at week 24
The estimand for the secondary efficacy objective on subject functional impairment is the change from baseline at week 24 in each MFIQ domain score, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value in each MFIQ domain score, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive), while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.</td></tr>
</table>

Overall Design

The study will comprise the following periods:

- A combined screening/baseline period consisting of the following:
  - A screening visit (which may coincide with the first day of the baseline period) for the assessment of eligibility criteria
  - A baseline period of approximately 4 weeks (no less than 28 days; up to 35 days) to collect data on migraine headaches and acute headache medication use using electronic diary (eDiary) and to assess compliance in eDiary usage
- A 24-week open-label treatment period

Subjects will sign the informed consent and be screened at the screening visit; eligible subjects may enter the baseline period at the same visit or may delay baseline procedures up to 3 weeks after the screening visit. At completion of the baseline period, those who meet eligibility criteria and choose to proceed will be enrolled and will enter the open-label treatment period.

The treating clinician and a key family member (if available) for each participating subject will be invited to complete an mGI-I at weeks 12, 16, 20, and 24/End of Study (EOS). The key family member must sign an informed consent before completing any study-specific procedures. The same clinician and key family member of each subject should complete the mGI-I across all visits. If the clinician or key family member is unable to complete a visit, the assessment for that visit should be noted as missed.

Qualitative interviews will be conducted with a selected subset of subjects, their treating clinicians, and key family members as part of an optional substudy. These interviews will be used to provide qualitative information on satisfaction/improvement and details into the drivers of satisfaction and improvement that might not be captured by self-assessment alone.

Number of Subjects

Approximately 322 subjects will be enrolled into the main study. The ratio of EM:CM will be approximately 1:1 to allow for qualitative assessments of satisfaction and impression of change in migraine for the two migraine types. A subset of approximately 20 enrolled subjects at select sites, their clinicians, and key family members will be invited to participate in an optional qualitative interview-based substudy with interviews to be conducted at the start and end of the study.

Summary of Eligibility Criteria

Subjects eligible for the study include those who are ≥ 18 years of age, have a history of migraine with or without aura for ≥ 12 months before screening, have ≥ 4 migraine days per month on average over the 3 months prior to screening, can be classified as EM or CM, report to their provider intolerance or insufficient response with their current preventive treatment, and demonstrate at least 75% compliance with the eDiary during the baseline period.

Key family members eligible for the study should be a family member/caregiver of an enrolled patient and a person in the subject's life with whom s/he interacts significantly on a day-to-day basis.

Clinicians eligible for the study must be licensed and practicing healthcare practitioners (HCPs) in the US and be currently treating the subject on Study 20190389.

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

Treatments

Subjects will receive erenumab 70 or 140 mg once every 4 weeks (Q4W) by subcutaneous (SC) injections during the 24-week open-label treatment period. Erenumab will be packaged in a SureClick® Autoinjector (AI)/Pen(s) containing 1 mL of 70 mg/mL or 140 mg/mL of erenumab for SC injection.

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

All subjects will be required to enter the study on 1 standard of care preventive medication for their migraine. Post-baseline, at their and the investigator's discretion, subjects will be allowed to remain on their standard of care preventive treatment, or they may fully discontinue standard of care therapy. Any changes to standard of care preventive treatment, including dose adjustments or tapering off medication, should be completed by the week 12 visit. Standard of care dose adjustments are not permitted after week 12.

Statistical Considerations

Sample Size Considerations:

The total sample size of approximately 322 subjects (effective sample size of 289 assuming 10% dropout at Week 24) is driven by the precision of the proportion estimates for the binary secondary endpoints, which target a half-width of around 5% for estimated 95% confidence intervals (CIs) (see Table 9-1).

Planned Analyses:

The final analysis will be conducted when all enrolled subjects have completed the week 24/EOS visit **and the data have been entered, cleaned, and locked**.

The primary endpoint will be analyzed using a repeated measures mixed effects model, including baseline TSQM overall satisfaction scale score, visit, the prevailing erenumab dose from week 12 onward, and baseline monthly migraine days (MMD) **based on observed data**. The least-squares mean (LSM) change from baseline in the TSQM overall satisfaction scale score at week 24 will be estimated, and the corresponding 95% CI will be provided.

Analysis of all secondary proportion endpoints will be descriptive only, where point estimates of the proportion and the corresponding 95% CI will be provided for each endpoint. All other secondary endpoints will be analyzed in a similar manner to the primary endpoint.

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

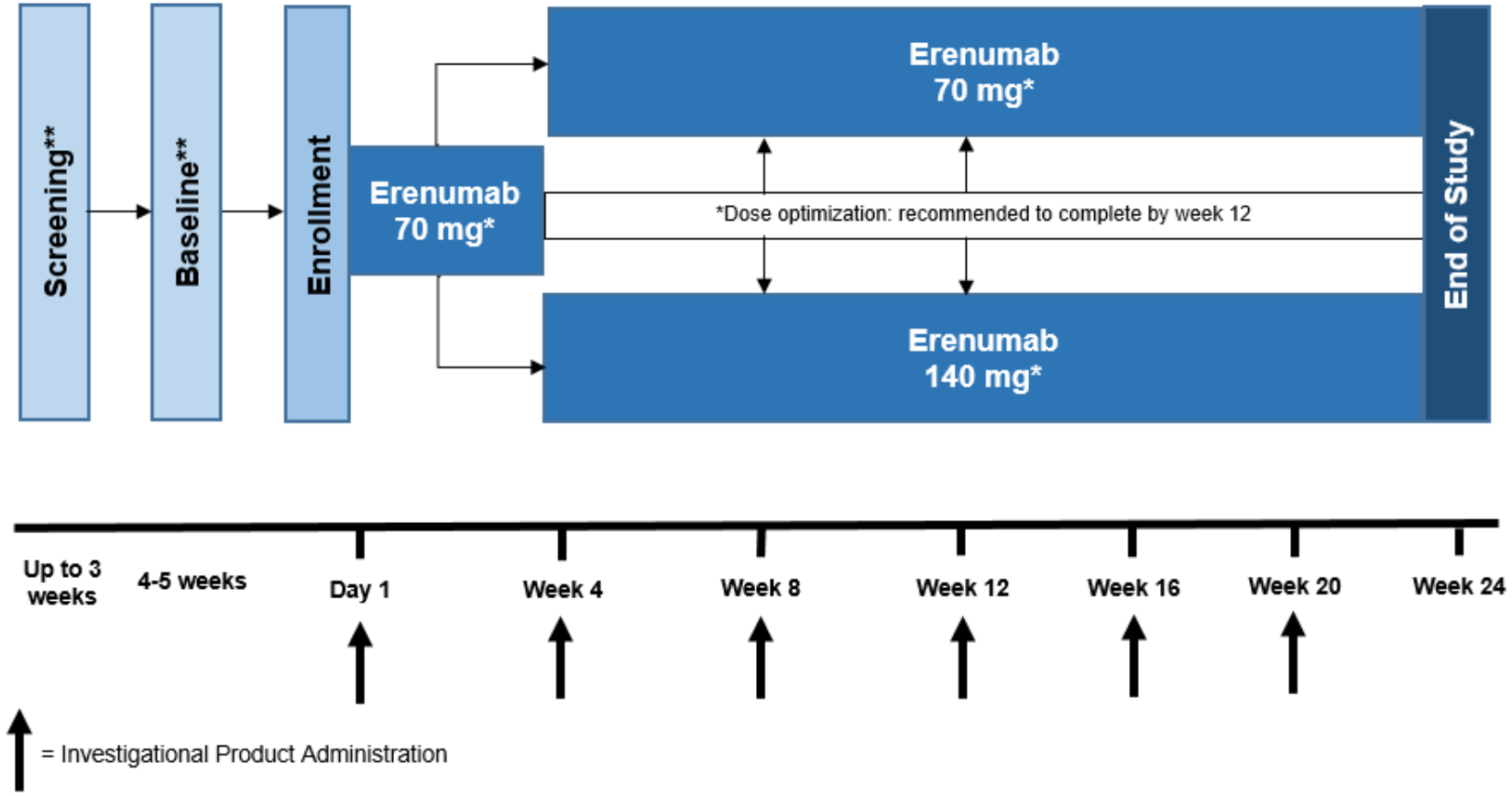
Statistical Hypotheses

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

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



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

1.3 Schedule of Activities (SoA)

Table 1-1. Subject Study Visits Through Open-label Treatment Phase

PROCEDURE	Screening (up to 3 weeks before baseline)[c]	Baseline (4-5 weeks before day 1)[c]	Open-label Treatment Period (24 weeks)							Notes
			Day 1[e]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ EOS	
GENERAL ASSESSMENTS										
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographics	X									
Medical history	X									
Neurological medical history	X									
Gastrointestinal medical history	X									
Headache and migraine frequency medical history	X									
Migraine preventive medications review	X	X	X	X	X	X	X	X	X	At screening, a review of the subject's history of migraine preventive use (past and current) will be conducted. At subsequent visits, information will be collected regarding concomitant standard of care preventive status (ie, whether still taking and at what dose).
Prior therapies review	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.
Concomitant therapies review	X	X	X	X	X	X	X	X	X	
Eligibility criteria after baseline period			X							Compliance with eDiary usage will be assessed on day 1 to determine eligibility before any other day 1 assessments.
Physical measurements			X							Height/weight for BMI

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Footnotes are defined on the last page of this table.

Table 1-1. Subject Study Visits Through Open-Label Treatment Phase

PROCEDURE	Screening (up to 3 weeks before baseline)[c]	Baseline (4-5 weeks before day 1)[c]	Open-label Treatment Period (24 weeks)							Notes
			Day 1[e]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ EOS	
SAFETY ASSESSMENTS										
Adverse events			X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	
Adverse device effects			X	X	X	X	X	X		
Product complaints			X	X	X	X	X	X		
LABORATORY ASSESSMENTS										
Urine pregnancy test (females of childbearing potential only)	X		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.
CLINICAL OUTCOME ASSESSMENTS										
eDiary		Daily				Daily				
ETS			X							
GAD-7			X			X			X	
MFIQ			X			X	X	X	X	
mGI-I						X	X	X	X	To be completed by subject and clinician
MIBS-4			X			X	X	X	X	
MSSS			X			X	X	X	X	
PHQ-9	X[d]		X			X			X	
TSQM version 1.4			X			X	X	X	X	TSQM will assess satisfaction with standard of care migraine preventive medication at day 1 and only investigational product at subsequent time points.
STUDY TREATMENT										
Amgen investigational product administration[e]			X	X	X	X	X	X		

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Footnotes are defined on the last page of this table.

Table 1-1. Subject Study Visits Through Open-Label Treatment Phase

PROCEDURE	Screening (up to 3 weeks before baseline)[c]	Baseline (4-5 weeks before day 1)[c]	Open-label Treatment Period (24 weeks)							Notes
			Day 1[e]	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ EOS	
STUDY VISITS										
Onsite visit[a]	X	X	X			X			X	
Remote visit – site staff phone call with subject[b]				X	X		X	X		

BMI = body mass index; eDiary = electronic diary; EOS = End of Study; ETS = Expectation of Treatment Scale; GAD-7 = General Anxiety Disorder Scale; MFIQ = Migraine Functional Impact Questionnaire; mGI-I = Migraine Global Impression Item; MIBS-4 = Migraine Interictal Burden Scale; MSSS = Migraine Symptom Severity Scale; PHQ-9 = Patient Health Questionnaire; TSQM = Treatment Satisfaction Questionnaire for Medication

[a] Screening, Baseline, day 1, week 12, and week 24/EOS visits are required to take place onsite. Subjects will be provided the doses necessary to continue erenumab monthly treatment at a non-investigative site (eg, subject's home). Additional onsite visits are optional at the investigator's discretion.

[b] For remote visits (ie, visits not conducted onsite), visit data will be collected by site staff via telephone or via electronic device as applicable (eg, clinical outcomes assessments).

[c] Baseline may start on the same day as the screening visit.

[d] Screening PHQ-9 is to assess eligibility and will be collected on a paper form. On-study PHQ-9 assessments will be collected on the subject's eDiary device.

[e] All day 1 procedures must be completed before investigational product is administered.

Table 1-2. Schedule of Activities for Key Family Members

PROCEDURE	**Screening** (up to 3 weeks before baseline)[a]	**Baseline** (4-5 weeks before day 1)[a]	**Open-Label Treatment Period (24 weeks)**							**Notes**
			Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24/ EOS**	
GENERAL ASSESSMENTS										
Informed consent for key family members	X									Signing of informed consent can occur any time at or before the week 12 visit. Informed consent must be signed before the week 12 mGI-I is administered.
CLINICAL OUTCOMES ASSESSMENTS										
mGI-I						X	X	X	X	

EOS = End of Study; mGI-I = Migraine Global Impression Item
[a] Baseline may begin on the same day as the screening visit.

Table 1-3. Optional Substudy: Schedule of Activities for Participating Subjects, Clinicians, and Key Family Members

PROCEDURE	Screening (up to 3 weeks before baseline)[a]	Baseline (4-5 weeks before day 1)[a]	Open-Label Treatment Period (24 weeks)							Notes
			Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ EOS	
HEALTH ECONOMIC ASSESSMENTS										
Qualitative substudy informed consent	X									Written consent will be collected from subject and key family member. Signing of informed consent and participant screening can occur any time at or before the day 1 visit.
Qualitative substudy interviews (conducted by third-party interviewer)[b]			X						X	Participating subjects' clinicians will also be interviewed. Interviewers will attempt to conduct the interview as soon as possible and within 7 days after day 1 and week 24/EOS visits.

EOS = End of Study
[a] Baseline may begin on the same day as the screening visit.
[b] Each participant (subject, clinician, and key family member) will be interviewed separately by the third-party interviewer.

2. Introduction

2.1 Study Rationale

Migraine is a prevalent and disabling neurological disorder, with a significant impact on the individual, family, workplace, and society. Objectives commonly assessed in registrational clinical trials **for migraine prevention** include changes in monthly migraine days (MMD) and use of acute migraine-specific medications. These parameters, however, do not fully capture the whole breadth of the impact of migraine preventive treatments on the daily lives of patients and their families, including their satisfaction with treatment.

There is interest in the migraine provider community not only for clinical outcomes data, but also associated patient-centric data (eg, treatment satisfaction and global impression of change in migraine from different perspectives such as those of patients, providers, and key family members). Health systems are also tracking patient satisfaction as a metric for quality of care delivery. These factors begin to define a new treatment paradigm for migraine management that includes both clinical and treatment-related satisfaction outcomes.

The Erenumab Treatment Satisfaction Study is a phase 4 United States (US), open-label, interventional, prospective 24-week study evaluating treatment satisfaction with erenumab as a preventive treatment in adult subjects with episodic migraine (EM) or chronic migraine (CM) currently on 1 standard of care migraine prevention therapy. The study will measure change in subject satisfaction with erenumab and subject, clinician, and key family member global impression of change in subject's migraine condition over the life of the study.

This study seeks to mirror real-world US clinical practice by providing subjects and investigators the flexibility to optimize erenumab dosing and maintain or discontinue the existing migraine prevention therapy (ie, standard of care).

The study will be the first to evaluate patient satisfaction in a real-world migraine setting using the Treatment Satisfaction Questionnaire for Medication (TSQM), a questionnaire validated in the migraine population. It will also be the first to validate the migraine Global Impression Item (mGI-I) in migraine patients, their treating clinician, and key family member. With this validation work, it will be the first study to allow the capture of information on impression of improvement in the patient's overall condition from multiple perspectives: patient, clinician, and key family member.

2.2 Background

2.2.1 Disease

Migraine is a disabling disorder characterized by primary recurrent headaches (referred to as attacks) with or without aura (ie, visual, sensory, and/or speech symptoms that occur just before or at the onset of migraine headache), lasting 4 to 72 hours (if not treated) with at least 2 of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. Migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia). Migraine affects more than 10% of the world's population (Robbins and Lipton, 2010), and the prevalence of migraine is approximately 11.7% in the United States, 14.6% in Canada, and 14.7% in Europe (Stovner and Andree, 2010; Lipton et al, 2007).

The patient burden and disability, as well as the societal impact, increase with higher attack frequency. For this reason, migraine is categorized in 2 major classifications, according to frequency of migraine days per month: EM is typically defined as 0 to 14 headache days per month (Katsarava et al, 2012). **According to the International Classification of Headache Disorders (ICHD)-4 interim recommendations in 2020, EM is better defined as "Headache occurring on < 15 days a month over the last 3 months, which on some days is migraine" (Goadsby & Evers, 2020). Chronic migraine is defined** as 15 or more headache days per months, at least 8 of which have to be typical migraine days**,** with migraine prevention typically considered in individuals with ≥ 4 MMD (Headache Classification Committee of the International Headache Society, 2018). All patients suffering from migraine can be treated with acute medications, and those suffering from frequent/long-lasting attacks and/or significant disability induced by the attacks should be considered for preventive treatment (The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice, 2018; Antonaci et al, 2010; Evers et al, 2006). Reports suggest that out of the approximately 25% of patients with migraine in need of migraine prevention, only half of them receive migraine preventive treatments (Lipton et al, 2007).

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 complex and inhibits the action of CGRP.

Calcitonin gene-related peptide belongs to the calcitonin family of peptides and is expressed in both the central and peripheral nervous systems. It is prominently involved in the pathophysiology of migraine through nociceptive modulation in the trigeminovascular system (Goadsby et al, 2002; Tajti et al, 1999).

As of the date of approval of this protocol, erenumab 70 mg and 140 mg subcutaneously (SC) every 4 weeks (Q4W) or once monthly (QM) has been approved in more than 60 countries, including the US, Australia, Switzerland, and the European Union.

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

2.3 Benefit/Risk Assessment

Benefits

Globally, the totality of data from phase 2 and phase 3 studies in subjects with CM and EM provides substantial evidence for the efficacy and safety of erenumab in adults with migraine. The key benefits of erenumab include reduction in MMD, reduction in acute migraine-specific medication use, as well as improvements in a range of other patient-reported outcomes (PROs), favorable tolerability, low treatment discontinuation rates, convenience (Q4W injections with the option of self-administration), and rapid onset of effect.

Risks

The safety profile of erenumab has been favorable in clinical trials and in the post-marketing setting. A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritus) have been identified at low frequencies (< 5%) in clinical trials. In the long-term use of erenumab, the safety profile remained consistent through 5 years of open-label treatment. In post-marketing settings, **hypertension,** hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions), and constipation with serious complications have been reported. In addition, oral sores (eg, stomatitis, mouth ulceration, oral mucosal blistering), alopecia and rash (eg, rash papular, exfoliative rash, rash erythematous, urticaria, blister) have been observed in post-marketing surveillance.

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

3. Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab on medication-specific treatment satisfaction	• Change from baseline in the Treatment Satisfaction Questionnaire for Medication (TSQM) overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM version 1.4
Primary Estimand	
The estimand for the primary efficacy objective consists of: • The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy • The endpoint, which is the change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM • There are 2 intercurrent events, discontinuation of investigational product (IP) due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive least 1 dose of IP and have a baseline score and at least 1 post-baseline score on the TSQM overall satisfaction scale. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation, defined by the worst postbaseline value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored. • The treatment, which is erenumab 70 or 140 mg every 4 weeks • The summary measure, which is the mean change from baseline in TSQM overall satisfaction scale score at week 24, as measured by items 12 to 14 of the TSQM The primary estimand for the primary efficacy objective is the mean change from baseline in TSQM overall satisfaction scale score at week 24 in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have a baseline and at least 1 post-baseline TSQM overall satisfaction scale score, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive), while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.	
Secondary	
• To assess the effect of erenumab on medication-specific treatment satisfaction	• Achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM version 1.4
The estimand for the secondary efficacy objective on treatment satisfaction consists of: • The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy • The endpoint, which is achievement of overall satisfaction at week 24 as defined by subject reporting of satisfied, very satisfied, or extremely satisfied on Item 14 of the TSQM	

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There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value for Item 14 of the TSQM. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not satisfied after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
The treatment, which is erenumab 70 or 140 mg every 4 weeks
The summary measure, which is the proportion of subjects who achieves overall satisfaction at week 24

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

</td><td>

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

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<tr><td colspan="2">
The estimand for the secondary efficacy objectives on impression of change in migraine consists of:

The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
The endpoints, which include:

Improvement in subject global impression at week 24, as defined by subject reporting of much improved or a little improved on the mGI-I
Improvement in treating clinician’s global impression at week 24, as defined by the clinician’s reporting of much improved or a little improved on the mGI-I for each individual subject
Improvement in key family member’s global impression at week 24, as defined by family member’s reporting of much improved or a little improved on the mGI-I for each individual subject

There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have at least 1 post-baseline value of each respective mGI-I item. A composite strategy will be used

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<tr><td colspan="2">for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation. A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
• The treatment, which is erenumab 70 or 140 mg every 4 weeks
• The summary measure, which is the proportion of subjects who achieves impression of improvement at week 24.
The estimand for the secondary efficacy objective on impression of change in migraine is the proportion of subjects who achieves global impression of migraine improvement at week 24 as defined by subject, treating clinician, or family member reporting of much improved or a little improved on the mGI-I, in subjects with EM or CM who are currently on 1 standard of care migraine prevention therapy and who receive at least 1 dose of IP and have at least 1 post-baseline value of the respective mGI-I, and a composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event where they will be defined as not improved after IP discontinuation, while a hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.</td></tr>
<tr><td>• To assess the effect of erenumab on subject functional impairment</td><td>• Change from baseline in physical function domain score at week 24, as measured by the Migraine Functional Impact Questionnaire (MFIQ)
• Change from baseline in usual activities domain score at week 24 as measured by MFIQ
• Change from baseline in emotional function domain score at week 24 as measured by MFIQ
• Change from baseline in social function domain score at week 24 as measured by MFIQ</td></tr>
<tr><td colspan="2">The estimand for the secondary efficacy objective on subject functional impairment consists of:
• The target population, which includes subjects with EM or CM currently on 1 standard of care migraine prevention therapy
• The endpoints, which include:
  • Change from baseline in MFIQ physical function domain score at week 24
  • Change from baseline in MFIQ usual activities domain score at week 24
  • Change from baseline in MFIQ emotional function domain score at week 24
  • Change from baseline in MFIQ social function domain score at week 24
• There are 2 intercurrent events, discontinuation of IP due to lack of efficacy or adverse event, and discontinuation of IP due to other reasons. The treatment effect of interest will be assessed for all subjects who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of the respective MFIQ domain scores. A composite strategy will be used for subjects who discontinued IP due to lack of efficacy or adverse event with data after IP discontinuation defined by the worst postbaseline value observed up to IP discontinuation (inclusive). A hypothetical strategy will be used for those subjects who discontinued IP due to other reasons with data collected after IP discontinuation censored.
• The treatment, which is erenumab 70 or 140 mg every 4 weeks
• The summary measure, which is change from baseline in each MFIQ domain score at week 24</td></tr>
</table>

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

Exploratory	
• To explore the effect of erenumab on the change from baseline in monthly medication-specific treatment satisfaction	• Change from baseline in TSQM overall satisfaction scale score at weeks 12, 16, and 20 and mean over weeks 16, 20, and 24 • Change from baseline in TSQM sub-scale domain scores at weeks 12, 16, 20 and 24 and mean over weeks 16, 20, and 24: – effectiveness – side effects – convenience
• To explore the effect of erenumab on monthly global impression of improvement in migraine	• Improvement in subject global impression at weeks 12, 16, and 20, as defined by subject reporting of much improved or a little improved on the mGI-I • Improvement in treating clinician's global impression at weeks 12, 16, and 20, as defined by treating clinician's reporting of much improved or a little improved on the mGI-I • Improvement in key family member's global impression at weeks 12, 16, and 20, as defined by key family member's reporting of much improved or a little improved on the mGI-I
• To explore the effect of erenumab on the change from baseline in monthly functional impairment	• Change from baseline in MFIQ functional impairment domain scores, at weeks 12, 16, and 20, and mean over weeks 16, 20, and 24: – Impact on physical function – Impact on usual activities – Impact on emotional function – Impact on social function
• To explore the effect of erenumab on the change from baseline in the burden of migraine	• Change from baseline in the Migraine Symptom Severity Scale (MSSS) total score at weeks 12, 16, 20, and 24 and mean over weeks 16, 20, and 24 • Change from baseline in the Migraine Interictal Burden Scale (MIBS-4) total

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

4. Study Design

4.1 Overall Design

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

- A combined screening/baseline period consisting of the following:
  - A screening visit (which may coincide with the first day of the baseline period) for the assessment of eligibility criteria
  - A baseline period of approximately 4 weeks (no less than 28 days; up to 35 days) to collect data on migraine headaches and acute headache medication use using electronic diary (eDiary) and to assess compliance in eDiary usage
- A 24-week open-label treatment period

Subjects will sign the informed consent and be screened at the screening visit; eligible subjects may enter the baseline period at the same visit or may delay baseline procedures up to 3 weeks after the screening visit. At completion of the baseline period,

those who meet all eligibility criteria and choose to proceed will be enrolled and will enter the open-label treatment period.

For visits that take place onsite, study assessments will be performed by staff onsite with the exception of investigational product administration, which can be completed by site staff or by subject self-administration. Subjects will be provided the doses necessary to continue erenumab monthly treatment at a non-investigative site (eg, subject's home) between onsite visits, as detailed in the Schedule of Activities (Table 1-1). Site staff will contact subjects by telephone between scheduled onsite visits to perform a remote visit as described below and determine potential need for an onsite visit. Changes in erenumab dosing may require an onsite visit. Subjects may also contact the site at any time in between scheduled onsite visits and the investigator will determine if an additional unscheduled onsite visit is necessary.

For visits not performed onsite, safety assessments, concomitant therapies review, and standard of care migraine preventive medication status will be performed by site staff on a telephone call with the subject and recorded in the subject's medical record and electronic case report form (eCRF). After speaking with site staff, subject or designee will administer investigational product to subject at a non-investigative site (eg, subject's home). The subject will record dose and lot number in their eDiary. The dose data will be transcribed into the subject's medical record and eCRF at the next onsite visit.

All clinical outcomes assessments (COAs) detailed in the Schedule of Activities (Table 1-1) will be performed on the subject's eDiary device regardless of visit location.

The treating clinician and a key family member (if available) for each participating subject will be invited to complete an mGI-I at weeks 12, 16, 20, and 24/EOS. The key family member should be a person in the subject's life with whom s/he interacts significantly on a day-to-day basis. This person should have a deep understanding of the impact migraine has on the subject. They should also be able to provide their perspective of change in the subject's migraines over time. The person the subject chooses to nominate can be anyone such as a spouse, daughter or son, parent, sibling, or other relative or the person with whom the subject is in a de facto relationship. The key family member must sign an informed consent before completing any study-specific procedures. The same clinician and key family member of each subject should complete the mGI-I across all visits. If the clinician or key family member is unable to complete a visit, the assessment for that visit should be noted as missed.

4.2 Patient Input into the Study Design

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

Approximately 322 subjects will be enrolled in the study. The ratio of EM:CM will be approximately 1:1 to allow for qualitative assessments of satisfaction and impression of change in migraine for the 2 migraine types. A subset of approximately 20 enrolled subjects at selected sites, their clinicians and key family members will be invited to participate in an optional qualitative interview-based substudy with interviews to be conducted at the start and end of the study.

Subjects in this clinical investigation shall be referred to as "subjects." Clinicians and key family members will be referred to as "participants." For the sample size justification, see Section 9.2.

4.3 Justification for Investigational Product Dose

Erenumab 70 and 140 mg SC Q4W are approved in Europe and the US for the prevention of migraine in adults. Regulatory approval was granted on the basis of established superiority against placebo for each dose in 4 independent randomized clinical studies (1 CM and 3 EM) (Sun et al, 2016; Goadsby et al, 2017; Tepper et al, 2017; Dodick et al, 2018).

4.4 End of Study

An individual subject is considered to have completed the study if he/she has completed the last visit shown in the Schedule of Activities. The total study duration for an individual subject, including the screening/baseline period and 24-week open-label treatment period, is approximately 28 to 32 weeks.

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), as applicable.

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). This log may be completed and updated via an Interactive Response Technology (IRT) system.

Eligibility criteria will be evaluated during screening and baseline period.

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 only if all of the following criteria apply:

101 Age ≥ 18 years upon entry into screening

102 Subject has provided informed consent prior to initiation of any study specific activities/procedures.

103 History of migraine (with or without aura) for ≥ 12 months before screening according to the International Headache Society (IHS) Classification ICHD-III (Headache Classification Committee of the International Headache Society, 2018) based on medical records and/or patient self-report

104 Migraine frequency: ≥ 4 migraine days per month on average across the 3 months prior to screening

105 History of CM or EM migraine across the 3 months prior to screening:

- CM is defined as: ≥ 15 headache days **a month** of which ≥ 8 headache days meet criteria as migraine days per subject self-report and investigator assessment
- EM is defined as: < 15 headache days **a month over the last 3 months,** which **on some** days **is migraine, but does not fulfil ICHD-3** criteria **for CM** per subject self-report and investigator assessment

106 **Subject** reports to their provider intolerance or insufficient response with their current preventive treatment. Insufficient response is defined as insufficient reduction in headache frequency, duration, **or** severity at the generally accepted therapeutic dose for at least 6 weeks and is based on the investigator's assessment.

107 Concomitant treatment with 1 migraine preventive medication is required under the following conditions:

- Drug regimen (ie, formulation, frequency of use and dose) is stable for ≥ 2 months prior to baseline period start **or injection paradigm is stable for 2 injection cycles (acceptable range of injection frequency is every 10 to 16 weeks)** AND
- Drug regimen **or injection paradigm** is at generally accepted doses and frequency for its use in migraine AND
- Drug regimen **or injection paradigm** is not anticipated to change during the baseline period AND
- Drug regimen **or injection paradigm** is either:
  - not anticipated to change post-baseline OR
  - anticipated to be fully discontinued irrespective of tapering off schedules by no later than end of week 12

- Medication is 1 of the following:
  - Divalproex sodium, sodium valproate, topiramate
  - Beta blockers (eg, atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
  - Tricyclic antidepressants (eg, amitriptyline, nortriptyline, protriptyline)
  - Duloxetine, milnacipran
  - Verapamil
  - Lisinopril, candesartan
  - Clonidine, guanfacine
  - Cyproheptadine
  - **OnabotulinumtoxinA (subjects using concomitant onabotulinumtoxinA for migraine prevention are allowed [but not required] to also take one oral preventive migraine medication)**

During the baseline period:

108 Must have ≥ 4 MMD based on the eDiary data during the last 28 days of the baseline (if longer than 28 days)

110 Must have demonstrated ≥ 75% compliance with the eDiary, based on the last 28 days of the baseline period (if longer than 28 days)

5.2 Exclusion Criteria

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

Disease Related

201 > 50 years of age at migraine onset

202 History of cluster headache or hemiplegic migraine headache

203 Unable to differentiate migraine from other headaches

Other Medical Conditions

204 Malignancy (except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ) within the last 5 years

205 Evidence of substance-related disorders (eg, abuse, misuse, or addiction), addictive disorders (eg, pathological gambling), or "recreational use" of illicit drugs within 12 months prior to initial screening, based on medical records, patient self-report, or positive urine drug test performed locally at investigator's discretion during screening (with the exception of prescribed medications such as opioids or barbiturates that may result in a positive urine drug test)

206 Active chronic pain syndromes (eg, fibromyalgia and chronic pelvic pain)

207 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 or severe depression based on a Patient Health Questionnaire-9 (PHQ-9) total score ≥ 15 at screening

- Subjects with history of anxiety disorder and/or major depressive disorder are permitted in the study if they are considered by the investigator to be stable

(with PHQ-9 < 15) and are taking no more than 1 medication for each disorder.

- For subjects taking antianxiety and/or antidepressant medication, dose must be stable for at least **3** months prior to the start of the baseline phase.

208 The subject is at risk of self-harm or harm to others as evidenced by past suicidal behavior.

Prior/Concomitant Therapy

209 No therapeutic response with > 3 of the following 9 medication categories for preventive treatment of migraine after an adequate therapeutic trial. These medication categories are:

- 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: 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) 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

210 Used a prohibited medication, device, or procedure listed in Section 6.1.7 and Table 6-2.

211 Anticipated to require any excluded medication, device, or procedure during the study.

220 **Any prior exposure to erenumab.**

221 **Use of gepants for migraine prevention.**

222 **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 < 12 weeks from the date of initial screening, OR

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

Prior/Concurrent Clinical Study Experience

212 Currently receiving treatment in another investigational device or drug study, or less than 90 days or 5 half-lives (for investigational drugs), whichever is longer, since ending treatment on another investigational device or drug study(ies).

Other Exclusions

213 Female subjects of childbearing potential unwilling to use 1 acceptable method of contraception (see Section 11.5) during treatment and for an additional 16 weeks after the last dose of investigational product

214 Female subjects who are breastfeeding or who plan to breastfeed while on study through 16 weeks after the last dose of investigational product

215 Female subjects planning to become pregnant while on study through 16 weeks after the last dose of investigational product

216 Female subjects of childbearing potential with a positive pregnancy test assessed at screening and/or day 1 by a urine pregnancy test

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

218 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, COAs) to the best of the subject and investigator's knowledge.

219 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 or key family members 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 and key family member 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. This should occur on study day 1, after completion of the screening/ baseline period. The investigator is to document this decision and date in the subject's medical record and in/on the Subject Enrollment eCRF.

Each subject who enters into the screening period for the study (defined as when the subject signs 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 by the IRT system. 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.

Sites that do not enroll subjects within 3 months of site initiation may be closed.

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, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if, in the opinion of the investigator, the reason for the initial screen failure has been resolved or is no longer applicable. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), 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.

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

Study Treatment Name	**Amgen Investigational Product:**[a] Erenumab
Dosage Formulation	Erenumab will be packaged in a SureClick® AI/Pen containing 1 mL of 70 or 140 mg/mL of erenumab formulated with sodium acetate, sucrose, and polysorbate 80.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Erenumab 70 or 140 mg will be administered subcutaneously every 4 weeks.
Route of Administration	Subcutaneous injection
Accountability	The quantity, start date, and lot number(s) of investigational product are to be recorded on each subject's eCRF.
Dosing Instructions	On day 1, erenumab may be administered by site staff or self-administered by the subject, under site staff's supervision, at the investigator's discretion. At remaining onsite visits, erenumab will be administered to subjects by site staff or by subject self-administration. Between onsite visits, subjects will continue dosing by self-administration or administration by a designated person every 4 weeks in a non-investigator site setting (eg, at subject's home).
Device	AI/Pen

AI = autoinjector; eCRF = electronic case report form
[a] Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

Non-investigational products will not be used in this study.

6.1.3 Medical Devices

The investigational medical device provided by Amgen for use in this study is the erenumab SureClick® Autoinjector Pen (AI/Pen) (Table 6-1).

The erenumab SureClick® AI/Pen is a single use disposable, handheld mechanical "spring-based" device for fixed dose SC injection of erenumab 1 mL deliverable volume.

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

Non-Amgen 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.

6.1.4 Other Protocol-required Therapies

Other protocol-required therapies will not be used in this study.

6.1.5 Other Intervention Procedures

Other intervention procedures will not be used in this study.

6.1.6 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**/noninvestigational** product(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen **SureClick® AI pen**.

Any product complaint(s) associated with an investigational product(s)**,** **noninvestigational** product(s), devices(s), or combination product(s) supplied by Amgen are to be reported.

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

Subjects are required to be on 1 migraine preventive medication to be eligible for the study. In addition to the 1 migraine preventive medication required for eligibility, subjects may be taking up to 1 additional medication from the list provided below, provided that this medication (1) is being taken for an indication other than migraine prevention, (2) has been stable for at least 3 months prior to the start of the baseline period, and (3) is expected to remain stable during the study. **If a subject is receiving onabotulinumtoxinA for migraine prevention, one oral migraine preventive medication in addition to onabotulinumtoxinA is permitted.**

Initiation of any new oral migraine preventive medication is prohibited from 2 months before the start of the baseline period and throughout the study. Such medications include:

- Antiepileptics (eg, divalproex sodium, sodium valproate, topiramate, carbamazepine, levetiracetam)
- Angiotensin receptor blockers (eg, candesartan) or ACE inhibitors (eg, lisinopril)
- Beta blockers
- Calcium channel blockers (eg, verapamil, amlodipine, cinnarizine) or calcium antagonists (eg, flunarizine)
- Tricyclic antidepressants
- Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors)
- Other drugs or supplements used for migraine prevention (eg, clonidine, guanfacine, methysergide, cyproheptadine, pizotifen)

Initiation of botulinum toxin for any indication involving the head, face, or neck region is prohibited if less than 2 injection cycles of dose stability and injection paradigm. Only onabotulinumtoxinA formulation will be allowed in the head, face, or neck region. All other botulinum toxin formulations are only allowed in anatomic regions outside of the head, face, and neck.

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

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

Prohibited Medications, Devices, and Procedures	Time Period for Exclusion
Ergotamine-derivatives, steroids, and triptans used for migraine prevention	2 months before the start of the baseline period and throughout the study
Use of the following medications for the acute treatment of migraine for ≥ 4 days/month: • Barbiturates and/or butalbital-containing analgesics • Opioid and/or opioid-containing analgesics	2 months before the start of the baseline period and throughout the study
Gepants for migraine prevention (eg, atogepant) **Use of the following medications for acute treatment of migraine for ≥ 6 days/month:** • **Gepants (eg, rimegepant and ubrogepant)** • Lasmiditan	**Throughout screening and** baseline**,** and **while on** study

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Prohibited Medications, Devices, and Procedures	Time Period for Exclusion
Anti-CGRP monoclonal antibodies (ie, eptinezumab, galcanezumab, gremanezumab)	**12 weeks before the start of the screening period, and throughout the study**
Previously treated and currently being treated with erenumab	**At any time in the past, throughout screening/baseline, and while on study**
Investigational medications	90 days or 5 half-lives (whichever is longer) before the start of the screening period and throughout the study
For any indication: Devices (eg, neuromodulation devices) or procedures (eg, nerve blocks, trigger-point injections, and acupuncture) **depending on anatomic region and impact.**	2 months before the start of the baseline period and throughout the study
Cognitive behavioral therapy (CBT), biofeedback, and psychotherapy for migraine prevention. Note: Subjects on a stable, maintenance phase of these therapies for migraine will be allowed to participate. 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 baseline period and throughout the study Note: Subjects who have discontinued CBT within 3 months prior to the start of the baseline phase are eligible for the study provided that there is evidence of CBT failure/lack of efficacy prior to initial screening (per medical records or investigator's assessment).

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ACE = angiotensin-converting enzyme; CBT = cognitive behavioral therapy**; CGRP = calcitonin gene related peptide.**

6.2 Dose Modification

6.2.1 Dose-[group/cohort] Study Escalation/De-escalation and Stopping Rules

Dose-cohort study escalation/de-escalation and stopping rules do not apply to this study.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation of Amgen Investigational Product: Erenumab

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

be made if deemed medically necessary by the investigator. All erenumab dose changes, regardless of timing, will require an onsite visit.

The reason for each dose change of erenumab is to be recorded on each subject's eCRF(s).

At any time during the study, the investigator may discontinue investigational product administration for any subject who experiences a severe or life-threatening adverse event reported by the investigator to be related to investigational product. Refer to Section 8.4.2 for details regarding adverse event reporting.

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 drug accountability for the investigational product and device will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria and enroll in the study will be assigned to treatment with erenumab 70 mg initially, as defined in Section 6.2.2.

The enrollment date is to be documented in the subject's medical record and on the Subject Enrollment eCRF.

6.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.5 Treatment Compliance

Site staff will train subjects on self-administration of erenumab at the day 1 visit. At subsequent onsite visits, subjects will receive erenumab administration directly from the investigator or designee or will self-administer the dose in the clinic under medical supervision. The date and lot number of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

When subjects self-administer erenumab at home, they should enter the dose and lot number in the eDiary for each dose. The data will be transcribed into the subject's medical record and eCRF at the next onsite visit.

Noncompliance is to be documented in the medical file and will be reflected in the eCRF. 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 Migraine Preventive Medications

All prior and current migraine preventive therapies will be collected.

All subjects will be required to enter the study on 1 standard of care preventive medication for their migraine. Subjects will be allowed to remain on their standard of care therapy during the study or fully discontinue the standard of care therapy by the week 12 visit. Standard of care therapy status (ie, continued or discontinued) is to be recorded.

6.7.2 Prior Treatment

All prior therapies other than prior migraine preventive medications that were being taken/used from 120 days before screening through the signing of the informed consent will be collected in the concomitant medication eCRF.

6.7.3 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 6.1.7.

Concomitant therapies are to be collected from the signing of informed consent through the end of study in the concomitant medication eCRF.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

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 Section 7.

7.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product and/or procedures 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 or procedures 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 and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or procedures 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.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Lack of efficacy
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Pregnancy

7.2 Subject Discontinuation/Withdrawal 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. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

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

Washout, run-in, or invasive procedures do not apply 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 should 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).

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, Enrollment and/or Randomization

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 the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 21 days.

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.

The baseline period can begin on the same day as the screening visit or up to 3 weeks after the screening visit. The baseline period begins when the subject has met all the screening eligibility criteria and begins baseline study procedures and ends the day before the day 1 visit. The total duration of the baseline period must be at least 28 days and no more than 35 days.

If a subject has not met all eligibility criteria at the end of the baseline period, the subject will be registered as a screen failure. Subjects who have screen-failed may be re-screened only once if, in the opinion of the investigator, the reason for the initial screen failure has been resolved or is no longer applicable. 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 screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 45 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1). On-study visits may be completed within ± 7 days. The date of the first dose of erenumab is defined as day 1.

All subsequent doses and study visits will be scheduled based on the day 1 date. Erenumab is to be administered by site staff or by subject self-administration as the last procedure of the onsite visits. All other doses of erenumab are to be administered by subject or designee at a non-investigative site setting (eg, at home), unless a site visit is deemed warranted by the investigator (eg, for changes in erenumab dose).

8.1.3 End of Study

The end of study visit occurs at week 24 (± 7 days) or when a subject discontinues from the study before the week 24 visit. All assessments will be performed at the end of study visit as per the Schedule of Activities (Table 1-1).

8.2 General Assessments

8.2.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed. Key family members must also sign an informed consent prior to completing any mGI-I assessments.

8.2.2 Demographics

Subject 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 and satisfaction.

8.2.3 Medical History

The Investigator or designee will collect a complete subject medical history that started within 120 days prior to screening through baseline. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history eCRF. 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 on the appropriate eCRF for neurologic medical history, gastrointestinal medical history, and headache and migraine frequency medical history.

8.2.4 Physical Measurements

The subject’s height (in centimeters) should be measured without shoes. Weight (in kilograms) should be measured without shoes.

8.3 Efficacy Assessments

8.3.1 Treatment Satisfaction Questionnaire for Medication

The TSQM version 1.4 is a 14-item instrument designed to measure important dimensions of patients' experiences with their medication. It has 4 domains: effectiveness, side effects, convenience, and global satisfaction. Scores range from 0 to 100 with higher scores indicating greater satisfaction. The recall period is the last 2 to 3 weeks, or since the medication was last used.

8.3.2 Migraine Global Impression Item

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

8.3.3 Migraine Functional Impact Questionnaire

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

8.3.4 Expectation of Treatment Scale

The Expectation of Treatment Scale (ETS) is a 5-item questionnaire. Responses are scored on a 5-point Likert scale, and subjects' item scores are summed to provide a total score ranging between 5 and 20. Higher scores indicate higher perceived expectations.

8.3.5 Migraine Symptom Severity Scale

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: 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.

8.3.6 Migraine Interictal Burden Scale

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).

8.3.7 Generalized Anxiety Disorder Scale

The GAD-7 is a self-administered 7-item instrument that uses some of the Diagnostic and Statistical Manual (of Mental Disorders) fifth edition (DSM-V) criteria for general anxiety disorder (GAD) to identify probable cases of GAD along with measuring anxiety symptom severity. Responders are asked to rate the frequency of anxiety symptoms in the last 2 weeks on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). Items are summed to provide a total score. Score interpretation is as follows: 1 to 4 minimal symptoms, 5 to 9 mild symptoms, 10 to 14 moderate symptoms, and 15 to 21 severe symptoms. Changes of 5 points or more are clinically meaningful.

8.3.8 Patient Health Questionnaire

The PHQ-9 is a self-administered questionnaire, widely used for diagnosis and severity assessment of depression in primary care settings. The PHQ-9 is a 9-question, self-administered instrument for screening, diagnosing, monitoring, and measuring the severity of depression. It incorporates Diagnostic and Statistical Manual (of Mental Disorders) fourth edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. The tool rates the frequency of the symptoms which factors into the scoring severity index. The PHQ-9 scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). The score is calculated as the sum of the item responses and corresponds to 1 of the 5 severity categories: Minimal or None = 0 to 4, Mild = 5 to 9, Moderate = 10 to 14, Moderately Severe = 15 to 19, and Severe = 20 to 27. Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.

8.3.9 Electronic Diary

The eDiary will collect migraine-related parameters at home, including the following:

- presence or absence of headache and whether the headache is a migraine
- presence or absence of aura
- use of acute headache medications and whether the acute headache medication is a triptan
- worst headache severity

At the start of the baseline period, which may coincide with the screening visit, the site staff will instruct the subject on eDiary use (eg, accessing the application, navigating screens, transmitting data, contacting the help desk for technical assistance). The subject will be instructed to interact with the eDiary as per the Schedule of Activities (Table 1-1). At the day 1 visit, the investigator will use the subject's eDiary to review all data entered during the baseline period and confirm the relevant inclusion and exclusion criteria.

8.4 Safety Assessments

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

8.4.1 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.

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). Note: the only protocol-required laboratory assessment is the urine pregnancy test for women of childbearing potential.

8.4.2 Adverse Events and Serious Adverse Events

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

8.4.2.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.2.1.1 Adverse Events

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

8.4.2.1.2 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 Events eCRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator's awareness 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.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, **if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be** left to the investigator's judgment to **also** report these abnormalities as serious adverse events. **Laboratory abnormality with clinical significance will be reported as an adverse event. If an adverse event associated with a laboratory abnormality meets the criteria of a serious event, it will be reported as a serious adverse event based upon the investigator's judgment. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.**

8.4.2.1.3 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**. **Per local requirements in some countries, investigators are** required **to report serious adverse events that they become aware of** after end of study. **If** serious adverse events **are** reported, the investigator **is to report** them **to Amgen within 24 hours following the investigator's awareness of the event**. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them 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.

8.4.2.2 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.

8.4.2.3 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 awareness 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 Events CRF.

8.4.2.4 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.

8.4.2.5 Safety Monitoring Plan

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

8.4.2.6 Pregnancy and Lactation

A urine pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

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 (Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed at intervals of every 12 weeks (+/- 7 days) during treatment with protocol-required therapies and at the end of study.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion, if there is suspicion that a female subject is pregnant, or as required per local laws and regulations.

Details of all pregnancies and/or lactation in female 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, ectopic pregnancy) are considered serious adverse events.

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

8.4.2.7 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 6.1.6.

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

8.5 Optional Substudy: Qualitative Interviews

8.5.1 Substudy Background and Rationale

Qualitative interviews enable access to qualitative aspects of experiences of clinical trial participants to supplement the quantitative data collected as part of the study. For example, treatment satisfaction can be assessed to understand which aspects of the treatment are valued by subjects such as symptom benefit, delivery method, and safety and tolerability. Interviewing clinical trial participants at the start and end of the

treatment period can also help identify benefits most relevant and meaningful to patients. This can also complement and help interpret the quantitative data collected using COA instruments in the clinical trial.

Regulatory agencies are showing increasing interest in understanding patients' experiences of the risk-benefit related to new interventions being tested in clinical trials (FDA, 2017). Qualitative interviews at the start and end of clinical trials help to understand the patient experience of the treatment in the trial setting: their experience of the convenience of treatment, changes they perceive as result of treatments, and informal assessments of trade-offs on benefit and risks they perceive about the treatment.

8.5.2 Research Question and Objectives of the Qualitative Interview Substudy

The aim of this substudy is to collect qualitative data to assess the experience of treatment from a subset of adults who have participated in Study 20190389, their clinicians, and key family members to provide a more in-depth understanding of patients' experience with migraine and the impact of migraine, including perception of symptoms and burden of disease. The objectives are to elicit the subject's, clinician's, and family member's perceptions of migraine, associated symptoms, and symptom impact/burden and interference on the subject's life, subject perceptions of meaningful changes in experience of migraine, and to explore subject experience with treatment administration.

8.5.3 Substudy Design

Qualitative interviews will be conducted with approximately 20 subjects, their clinicians, and key family members (collectively referred to as "participants") who opt in to this optional substudy. The substudy sample size is based on a convenience sample to allow for sufficient numbers of EM and CM subjects enrolled. Best efforts will be made to ensure that the sample includes subjects with diverse demographic characteristics from the pool of trial subjects.

Interviews will be conducted at study entry, within 7 days of the first investigational product dose (Day 1), and at study exit, within 7 days of the week 24 visit or within approximately 14 days of the early termination visit. If possible, within 7 days from early termination notification will be targeted. **No protocol deviation will occur if these interviews are conducted outside of these timeframes.**

Note: Subjects must have received a first dose of investigational product before the entry interview is conducted.

8.5.4 Summary of Substudy Participation Criteria

Study subjects must meet the following criteria to be considered for enrollment into the substudy:

1) Be enrolled in Study 20190389;

2) Have provided supplementary informed consent to participate in the substudy;

3) Be willing and able to participate in 2 telephone interviews lasting approximately 1 hour each;

4) Be able to read, understand, and speak English sufficiently to participate in the interviews;

5) Be willing to be audio-recorded during the interview sessions.

The key family member should be a family member/caregiver of an enrolled patient and should be the person in the subject's life that s/he interacts with the most on a day-to-day basis. Key family members must meet the following criteria to be considered for enrollment into the substudy:

1) Should have a deep understanding of the impact migraine has on the subject. They should also be able to provide their perspective of change in the subject's migraines over time. The person the subject chooses to nominate can be anyone such as a spouse, daughter or son, parent, sibling, or other relative or the person the subject is in a de facto relationship with.

2) Have provided informed consent to participate in the substudy;

3) Be willing and able to participate in 2 telephone interviews lasting approximately 1 hour each;

4) Be able to read, understand, and speak English sufficiently to participate in the interviews;

5) Be willing to be audio-recorded during the interview sessions.

Clinicians must meet the following criteria to be considered for enrollment into the substudy:

1) Be a US-licensed and practicing healthcare practitioner (HCP) at the clinical site (eg, neurologist, headache specialist, primary care physician, nurse practitioner, physician assistant) currently treating the subject on Study 20190389;

2) Be willing and able to participate in 2 telephone interviews lasting approximately 1 hour each;

3) Be able to read, understand, and speak English sufficiently to participate in the interviews;

4) Be willing to be audio-recorded during the interview sessions.

Meeting any of the following criteria will exclude a subject, key family member, or clinician from enrollment into the substudy:

1) Expected to be unable to complete entry interview within 7 days from first investigational product dose;

2) Expected to be unable to complete exit interview within 7 days prior to week 24 visit or within approximately 14 days post early termination visit;

3) Has any clinically relevant medical or psychiatric condition that, in the opinion of the investigator and/or study coordinator, would interfere with the completion of the substudy activities. This includes but is not limited to language, speech, hearing or cognitive disorders that could impact a participant's ability to participate in an interview-based discussion.

8.5.5 Substudy Duration and Substudy Procedures

Subjects, clinicians, and key family members will participate in 2 telephone interviews, lasting approximately 1 hour each. Entry interviews will be conducted within 7 days from first investigational product dose (day 1); exit interviews will be conducted within 7 days prior to week 24 visit or within approximately 14 days post early termination visit. If possible, within 7 days from early termination notification will be targeted. **No protocol deviation will occur if these interviews are conducted outside of these timeframes.**

Subjects enrolled in Study 20190389 will be approached by clinic staff for recruitment and possible enrollment into this substudy.

At participating sites, subjects will be provided an option to opt-in to the qualitative interview substudy and be provided with additional information about the substudy either at time of screening for the main study or after enrollment and successful dosing with investigational product, depending on site preference. Clinical site staff will explain the substudy objectives and procedures to the subject and their selected key family member and obtain a supplementary written informed consent from each participant. Each subject and key family member will sign 2 copies of the consent form. Sites will send a

wet-ink version of the informed consent to Evidera, the third-party supplier who is performing the substudy, and will retain a copy of the signed informed consent for their study records. Clinic site staff will provide Evidera contact information for each participant enrolled in the substudy and Evidera will subsequently contact each participant to schedule interviews.

Once consent has been obtained, the subject ID and site details can be communicated by the site to the interview scheduler from Evidera along with potential dates for the day 1 and week 24 visits. The interview scheduler will obtain contact information and schedule tentative dates and times for the interviews with the subject, clinician, and key family member. Evidera will confirm with the site that the subject has completed study procedures for the day 1 and week 24 visits before confirming the interview dates and times of the interviews to ensure compliance to the substudy protocol.

Evidera staff, who are trained and experienced in qualitative data collection, will conduct telephone interviews using a semi-structured interview guide. Participants will be interviewed about the subject's pre-treatment status, any perceived changes during the study, and the meaningfulness of the changes experienced. During the interviews, interviewers will ask participants for specific examples to qualitatively illustrate the subjects' experience.

Participants will be specifically asked about the subject's functional abilities during and between migraine attacks after the start of the study; ie, perceptions of migraine, associated symptoms, and symptom impact/burden and interference on the subject's life; perceptions of meaningful changes in experience of migraine; and experience with treatment administration.

After open-ended questions, if participants do not mention concepts associated with the domains of the COA instrument in the clinical trial, the interviewer will specifically probe about those concepts. The interviewers will also explore what aspects of improvement or worsening of the subject's migraine (eg, frequency, severity, and duration) drove the changes, as well as the meaningfulness of change/no change reported by the subject.

8.5.6 Variables

8.5.6.1 Substudy Outcome Variable(s)

Qualitative data on changes resulting from treatment received in the open-label treatment period will be collected via telephone interview. Concepts that emerge from the qualitative interviews in relation to migraine impact, treatment efficacy, and migraine

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

8.5.6.2 Exposure Variable(s)

Subjects will be started on the 70 mg dose of erenumab with provider discretion for dose optimization. Dose optimization will allow patients to remain on 70 mg, increase the dose from 70 to 140 mg and if needed decrease the dose back down from 140 to 70 mg. After week 12, all subjects are highly recommended to remain on the week 12 erenumab dose for the rest of the study. Dose changes are permitted at the investigator's discretion, but are not recommended unless medically necessary.

8.5.7 Substudy Data Analysis

Audio recordings from the interviews will be transcribed for qualitative analyses. Evidera will develop a separate data analysis plan that will detail how the qualitative data will be analyzed. The analyses of interview data will help to illustrate subjects' perceptions of meaningful change or difference, migraine functional impacts, and treatment efficacy or benefit. Subjects will be grouped by migraine type, and other exploratory subgroups may be determined based on the characteristics of the final sample. The qualitative report will discuss perceived treatment benefit and changes, if any, in relation to entry-interview discussion of the functional impacts of migraine.

A qualitative content analysis approach will be used to analyze data collected from qualitative interviews using coding dictionaries and ATLAS.ti qualitative data analysis software. The cleaned transcripts will be entered into ATLAS.ti qualitative analysis software version 7.0 or higher (Friese and Ringmayr, 2013). Qualitative data coded in ATLAS.ti can be systematically organized into analysis outputs. ATLAS.ti software is designed to facilitate the storage, coding, and retrieval of qualitative data.

Coding will be an iterative process that marks the beginning of the qualitative analysis process. Concept codes will be used to capture symptoms or impacts of the disease most important and relevant to participants. Qualitative data will be coded according to the coding dictionary as outlined in the analysis plan. The initial coding dictionary will be based on the structure of the main themes and content of the discussion guide to allow the text data to be coded with key concepts codes. The coding dictionary will be iteratively updated with emerging themes and concepts from discussions.

Evidera proposes to conduct longitudinal qualitative research analyses (Calman et al, 2013; Saldana, 2003), which is distinguished from a traditional qualitative approach by

the fact that the key focus of analysis is on how and why the subject experiences/ perceptions change over time. This innovative approach will be used to characterize changes in subjects' perceptions and experiences over time, particularly in concepts the subjects perceive as most important.

A list of each key concept identified at analysis of entry interviews will be provided to interviewers ahead of the follow-up interviews, so that these may be probed at the follow-up interviews. For each concept, a category will be assigned to show changes in concepts that occurred between the 2 time points (newly emerged, not changed/stable, improved, worsened, not experienced anymore, and missing) in the concept tracker. Each of the concepts probed during the follow-up interviews will be categorized and compared to the entry interview. An analysis will then be conducted on the data from groups of participants to document the changes observed over time.

All analysis and reporting will be conducted by Evidera staff with experience in qualitative research.

Subject characteristics collected in the clinical trial will be summarized for describing the sample. Descriptive statistics (eg, n, mean, SD, and/or frequency) will be used to characterize the sample in terms of questionnaire data, sociodemographic, and clinical characteristics.

The results of this sub-study will be reported separately from the main study.

8.5.8 Collection of Safety Information and Product Complaints

There will be no substudy-specific safety database for collection, recording, and reporting of adverse events reported during the conduct of the substudy. All safety data collection, recording, and reporting will be performed through the parent study and will follow the detailed procedures outlined in Study Protocol 20190389. Adverse events, serious adverse events, or product complaints reported during the conduct of an interview will be reported to Amgen and to investigational sites within 1 business day of awareness.

8.5.8.1 Definition of Safety Events

Refer to Section 11.4 for definition of safety events.

8.5.8.2 Safety Reporting Requirements

The clinical site investigator is responsible for ensuring that safety events (adverse events, product complaints, and other safety findings) are reported in accordance with Amgen's Study 20190389 protocol. Evidera will report any adverse events to the clinical

site and Amgen within 1 business day of awareness; the site investigator will be responsible for reconciling the reporting to Amgen.

Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) which will be the responsibility of the subject's clinic site in accordance with the Study 20190389 protocol.

9. Statistical Considerations

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

The total sample size of approximately 322 subjects (effective sample size of 289 assuming 10% dropout at week 24) is driven by the precision of the proportion estimates for the binary secondary endpoints, which targets a half-width of 95% confidence intervals (CIs) around 5%. The half-width of the 95% CI will be the widest when the estimated percentage is 50% given a fixed sample size and will become narrower if the percentage moves further away from 50% (see Table 9-1).

Table 9-1. Half-width of 95% CI for Various Estimated Percentages With Effective Sample Size of 289 Subjects

Percentage estimate	Half-width of 95% CI with effective sample size = 289
50%	5.8%
60%	5.6%
70%	5.3%
80%	4.6%

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Full Analysis Set	The full analysis set (FAS) consists of all subjects enrolled in the study. Analysis of disposition, demographic and baseline characteristics, and important protocol deviations will utilize the FAS.
Efficacy Analysis Set	The respective efficacy analysis set consists of a subset of subjects from FAS 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. Analysis of the primary and secondary efficacy endpoints (except for the global impression Patient Reported Outcomes [PRO] endpoints) will utilize the respective efficacy analysis set.
Global Impression PRO Analysis Set	The global impression PRO analysis set consists of a subset of subjects from FAS who receive at least 1 dose of investigational product and have at least 1 post baseline value for **the** global impression PRO endpoints **of interest**. Analysis of each of the 3 global impression PRO endpoints will utilize this analysis set.
Safety Analysis Set	The safety analysis set (SAS) will consist of a subset of subjects from FAS who received at least 1 dose of investigational product. Analysis of safety endpoints and summary of investigational product administration will utilize the safety analysis set.

9.3.1 Covariates

All model-adjusted analyses of primary and secondary efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed, **if applicable,** and baseline MMD.

9.3.2 Subgroups

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

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

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

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Not applicable.

9.4.1.2 Primary Analysis

Not applicable.

9.4.1.3 Final Analysis

The final analysis will be conducted when all enrolled subjects have completed the week 24/EOS visit **and the data have been entered, cleaned, and locked**.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

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

Due to lack of a control arm, all analyses should be considered as descriptive in nature. Data on any endpoints collected after treatment discontinuation due to lack of efficacy or adverse event will be defined based on the worst observed value (for continuous endpoints) or non-response (for binary endpoints) using a composite strategy. Data collected after treatment discontinuation due to other reasons will be censored based on a hypothetical strategy and not be used in efficacy analyses as described in Section 9.4.2.2.

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Primary	In the event of IP discontinuation due to lack of efficacy or adverse event, the TSQM overall satisfaction scale score after treatment discontinuation will be defined as the worst postbaseline value observed up to IP discontinuation (inclusive). Any TSQM data collected after treatment discontinuation due to other reasons will be censored and not included in the analysis. The primary endpoint will be analyzed using a repeated measures mixed effects model, including baseline TSQM overall satisfaction scale score, visit, the prevailing erenumab dose from week 12 onwards, and baseline MMD **based on observed data**. The mean change from baseline in TSQM overall satisfaction scale score at week 24 will be estimated from the least-squares mean (LSM) of the mixed effects model, and the corresponding 95% CI will be provided. The nominal p-value will be reported by comparing the mean change from baseline in TSQM overall satisfaction scale score at week 24 to zero with a two-sided 5% significance level.
Secondary	In the event of IP discontinuation due to lack of efficacy or adverse event, the binary secondary endpoint after IP discontinuation will be classified as not achieving overall satisfaction or global impression on improvement; and the continuous MFIQ domain scores after treatment discontinuation will be defined as the worst postbaseline value observed before treatment discontinuation. Data collected after IP discontinuation due to other reasons will be censored and not included in the analysis. A generalized linear mixed effects model with the appropriate link function will be used to analyze each secondary endpoint **based on observed data**. The model will include the corresponding baseline value for the endpoint being analyzed (except for the global impression endpoints), visit, the prevailing erenumab dose from week 12 onwards, and baseline MMD. For binary secondary endpoints, logit link function will be used, and the proportions and the corresponding 95% CI at week 24 will be estimated from the LSM (with inverse link function) of the mixed effects model. For the continuous MFIQ domain score endpoints, identity link function will be used, and mean change from baseline in each domain score at week 24 with the corresponding 95% CI will be estimated from the LSM of the mixed effects model, and p-values comparing with zero at a 2-sided 5% significance level will be reported.
Exploratory	Will be described in the statistical analysis plan (SAP) finalized before database lock

9.4.2.3 Safety Analyses

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

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 discontinuation from investigational product and treatment-emergent adverse events of interest 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 number and percentage of subjects with dose change, reason for dose change and duration of exposure to investigational product in days will be summarized over time.

9.4.2.3.3 Exposure to Concomitant Medication

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

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ACE	angiotensin-converting enzyme
AI	autoinjector
CBT	cognitive behavioral therapy
CFR	U.S. Code of Federal Regulations
CGRP	calcitonin gene related peptide
COA	clinical outcomes assessment
CM	chronic migraine
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	Electronic Case Report Form
eDiary	electronic diary
EDC	electronic data capture
EM	episodic migraine
EOS	end of study
ETS	Expectation of Treatment Scale
FAS	full analysis set
FSH	follicle stimulating hormone
GAD	general anxiety disorder
GAD-7	General Anxiety Disorder scale
GCP	Good Clinical Practice
HCP	healthcare practitioner
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD	International Headache Classification Disorders
IEC	Independent Ethics Committee
IHS	International Headache Society
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MFIQ	Migraine Functional Impact Questionnaire

mGI-I	Migraine Global Impression Item
MIBS-4	Migraine Interictal Burden Scale
MMD	monthly migraine days
MSSS	Migraine Symptom Severity Scale
NCT	National Clinical Trials
QTL	quality tolerance limit parameter
PHQ-9	Patient Health Questionnaire
PRO	patient reported outcome
Q4W	every 4 weeks
QM	once monthly
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous
TSQM-14	Treatment Satisfaction Questionnaire for Medication
US	United States

11.2 Appendix 2. Clinical Laboratory Tests

A urine pregnancy test will be performed locally for women of childbearing potential as specified in the Schedule of Activities (Table 1-1).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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. 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 participant population.

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

Participants must be informed that their participation is voluntary. Participants 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 subject's 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 and the subject's agreement or refusal of his/her notification of the primary care physician 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 or the subject's legally authorized representative.

Data Protection/Subject Confidentiality

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

The 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 electronic Case Report Form (eCRF) 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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The Sponsor uses access-controlled systems to house, review, and analyze subject data. These systems are backed up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The Sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

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 Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator 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 (eCRF) 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 eCRF.

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

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 eCRF 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 eCRFs, 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, eCRFs 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.

Quality tolerance limit parameters (QTLs) will be pre-defined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability of the study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

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

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 eCRFs 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 eCRF 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 Interactive Response Technology (IRT) system (if used, such as subject ID and randomization number) and eCRF entries if the eCRF 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 or certain demographic information).

Data entered in the eCRF 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 Investigator 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 eCRFs, 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), and 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 Investigator 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 a separate 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. • 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. • Note: Treatment-emergent adverse events will be defined in the 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). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • 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. • "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. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- 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 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 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 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
Other medically important serious event 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.

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 6.1.3 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, but are not limited to, 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. **A combination product is a product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.**

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.
• The investigator will then record all relevant adverse event/serious adverse event information in the Event electronic case report form (eCRF).
• The investigator must assign the following mandatory adverse event attributes:
  • Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  • Dates of onset and resolution (if resolved);

- Did the event start prior to first dose of investigational product, other protocol-required therapies;
- Assessment of seriousness;
- Severity (or toxicity defined below);
- Assessment of relatedness to investigational product, devices, and/or study-mandated activity and/or procedures;
- Action taken; and
- Outcome of event.

- 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 eCRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event eCRF page.
- 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.
- 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:

The **Common Terminology Criteria for Adverse Events**, version 4.03, which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product, device(s), and/or study-mandated activity and/or procedure(s) 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 eCRF.
- 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.
- If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's awareness of the event.

- The site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- 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.
- 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 system has been taken off-line, then the site can report this information on a paper Serious Adverse Event Contingency Report Form (see Figure 11-1).
- **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 eCRF 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 Report Form (paper-based form)

AMGEN
Study # 20190389
AMG 334

Electronic Serious Adverse Event Contingency Report Form
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 If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *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 Day Month Year	Date Ended 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: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG 334 No✓	AMG 334 Yes✓	Sureclick Autoinjector No✓	Sureclick Autoinjector Yes✓	<Other>	<Other>	<Other>	<Other>	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure 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 Day Month Year	Date Discharged 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 Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 334	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Sureclick Autoinjector	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial #

FORM-056006 Version 7.0 Effective Date: 1 February 2016

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AMGEN Study # 20190389 AMG 334	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

								☐ Unavailable / Unknown

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											
	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

AMGEN Study # 20190389 AMG 334	Electronic Serious Adverse Event Contingency Report Form 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 - _____ *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 an additional 16 weeks after the last dose of IP.

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 hormone 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
- Intrauterine hormonal-releasing system
- 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, postovulation 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 protocol-required therapies.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness 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 consent 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 IP through 16 weeks after the last dose 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 11-2) 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 consent 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 consent 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 study drug.
- 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 awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 218.
- With the female subjects signed consent 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 IP.

Figure 11-2. 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: 20190389

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
				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 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: 20190389

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
				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

Amendment 2

Protocol Title: Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine

Amgen Protocol Number 20190389

Amendment Date: 18 March 2022

Rationale:

This protocol is being amended to remove restrictions to inclusion criteria and to update the list of excluded medications in order to encourage study enrolment.

Amendments to the protocol include:

- Removal of the prior anti-calcitonin gene related peptide exposure exclusion
- Removal of the restriction of the use of concomitant botulinum toxin
- Clarification of the definition of episodic migraine in the protocol
- Clarification of the excluded medications in the protocol
- Update to the safety reporting language in the protocol based on the protocol template.
- Update of administrative details, correction of formatting and typographical errors throughout the document

Amendment #1

Protocol Title: Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine

Amgen Protocol Number 20190389

Amendment Date: 18 December 2020

Rationale:

The protocol is being amended to:

- Remove Schedule of Activities for clinicians as it no longer applies
- Clarify scale of measurement for migraine Global Impression Item (mGI-I)
- Remove references to clinician consent as consent is not required
- Clarify consent requirements for subjects and key family members
- Clarify on-study exclusionary procedure requirements
- Clarify how medications will be recorded
- Clarify local lab requirements
- Correct grammatical and typographical errors throughout

Superseding Original Amendment

Protocol Title: Phase 4, Open-label Study to Evaluate Treatment Satisfaction With Erenumab in Patients With Migraine

Amgen Protocol Number 20190389

Amendment Date: 20 November 2020

Rationale:

Clarify the intent of exclusion criterion 204

Description of Changes

Section 5.2, Exclusion Criterion 204

Replace:

Malignancy (except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years)

With:

Malignancy (except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ**)** within the last 5 years~~)~~