Title Page

Protocol Title:		Biomarker and Genetic Predictors of Erenumab Treatment Response, a Phase 4 Investigational Open-label Study (INTERROGATE)
Short Protocol Title:		INTERROGATE
Protocol Number:		20190006
Investigational Product:		Erenumab
Trade Name:		AIMOVIG®
Sponsor	**Name of Sponsor:**	Amgen, Inc
	Address:	One Amgen Center Drive Thousand Oaks, CA, 91320, USA
	Telephone Number:	+1 (805) 447-1000
Protocol Approver	**Name:**	[redacted], MD
	Function:	Governance Body Chair
Key Sponsor Contact	**Name:**	[redacted], MD/PhD
	Address:	One Amgen Center Drive Thousand Oaks, CA, 91320, USA
	Telephone Number:	[redacted]
	Email Address:	[redacted]
EudraCT Number:		2019-002331-28
NCT Number:		NCT04265755
Protocol Date:		**Document Version** — **Date** Original — 05 September 2019 Amendment 1 (v2.0) — 01 February 2021 Superseding Amendment 1 (v3.0) — 15 March 2021 **Amendment 2 (v4.0) — 23 February 2022**
Version/Date:		**Data Element Standards Version** 6.2

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

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled B**i**omarker and Ge**n**etic Predic**t**ors of **Er**enumab T**r**eatment Resp**o**nse, a Phase 4 Investi**ga**tional Op**e**n-label Study (INTERROGATE), dated **23 February 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 the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____

Signature

_____ _____

Name of investigator Date (DD Month YYYY)

Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Protocol Synopsis

Protocol Title: Biomarker and Genetic Predictors of Erenumab Treatment Response, a Phase 4 Investigational Open-label Study (INTERROGATE)

Short Protocol Title: INTERROGATE

Study Phase: 4

Indication: episodic or chronic migraine

Rationale

Migraine is a clinically heterogeneous disorder with polygenic influences that can be summarized as a migraine polygenic risk score (mPRS). It is thought that the spectrum of pathophysiologies (eg, presence of aura, menstrual relatedness), the variable temporal onset and severity of disease, and responsiveness/non-responsiveness to acute or prophylactic migraine medications might reflect the fact that many different genes contribute to migraine risk and its phenotypic manifestations. Preliminary post-hoc analysis of erenumab-treated subjects with episodic or chronic migraine (EM or CM) has revealed an association of mPRS with several disease characteristics, such as the use of acute migraine-specific and prophylactic medications. The overarching objective of this study is to explore the potential association of several biomarker platforms, including DNA (single-nucleotide polymorphisms [SNPs], including those comprising the mPRS), RNA, proteomics, and plasma calcitonin gene-related peptide (CGRP) levels, with erenumab treatment response.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To explore the relationship between clinical response to erenumab and genetic biomarkers	• Achievement of at least a 50% reduction from baseline in mean monthly migraine days (MMD) over months 4, 5, and 6 in relation to each individual genome-wide significant single-nucleotide polymorphism (SNP) contributing to the migraine polygenic risk score (mPRS)

Hypotheses

No formal hypothesis testing will be performed. All analyses will be descriptive in nature.

Overall Design

This is a phase 4 open-label study that will enroll subjects with EM or CM without a predetermined allocation ratio. The study will comprise the following periods:

- A screening period of up to 3 weeks (21 days) for the assessment eligibility criteria. The screening visit may be performed on the same day as the baseline visit

- A baseline period of 4 weeks (28 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 at day 1 visit
- A 24-week open-label treatment period

Subjects will be screened at the screening visit, and if eligible, subjects may enter the baseline period at the same visit as screening or may begin baseline procedures up to 3 weeks after the screening visit. At completion of the baseline period, those who meet the eligibility criteria and demonstrate ≥ 75% compliance with eDiary use will be enrolled and will enter the open-label treatment period to receive either erenumab 70 mg or 140 mg subcutaneously (SC) every 4 weeks (Q4W) at the discretion of the investigator.

Number of Subjects

Approximately **1400** subjects will be enrolled in the study; all subjects are to receive erenumab 70 mg or 140 mg SC Q4W at the discretion of the investigator. One dose adjustment is allowed at week 12 visit.

Summary of Subject Eligibility Criteria

Subjects eligible for study include those who are age ≥ 18 years, have a history of migraine (with or without aura) for ≥ 12 months before screening, have ≥ 4 headache days that meet criteria as migraine days per month on average across the 3 months before screening, and demonstrate ≥ 75% compliance in eDiary usage during baseline period.

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

Treatments

Erenumab will be used according to the summary of product characteristics. The dose of erenumab, either 70 mg or 140 mg SC Q4W, is to be determined at the investigator's discretion and may be adjusted once during the study at the week 12 visit. Erenumab will be packaged in a SureClick® Autoinjector/Pen (AI)/Pens containing 1 mL of 70 mg/mL or 140 mg/mL of erenumab for SC injection. The site staff is to dispense erenumab AI/Pens to subjects at the day 1 visit (for treatment on day 1, week 4, and week 8) and week 12 visit (for treatment at weeks 12, 16, and 20). At the day 1 and week 12 visit erenumab will be administered on site to subjects by site staff or by subject self-administration as the last procedure of the visit. Administration will be performed by the subject or designee in a non-investigator site setting (eg, at home) at weeks 4, 8, 16, and 20.

Procedures

After signing the informed consent and meeting the entry criteria to be assessed before the baseline period, subjects are to use an eDiary to collect migraine-related parameters daily at home during the baseline period.

During the open-label treatment period, subjects will continue with their daily eDiary use and additionally complete the Migraine Functional Impact Questionnaire version 2.0 at required visits. Blood samples will be collected for biomarker research. Subjects who participate in the CGRP biomarker substudy will have **3** additional blood sample**s** collected at weeks 4, 12, and 24.

For a full list of study procedures, including the timing of each procedure, please refer to Section 8.2 and the Schedule of Activities in Section 1.3.

Statistical Considerations

The primary analysis will occur after all subjects have completed their week 24 or end of study visit.

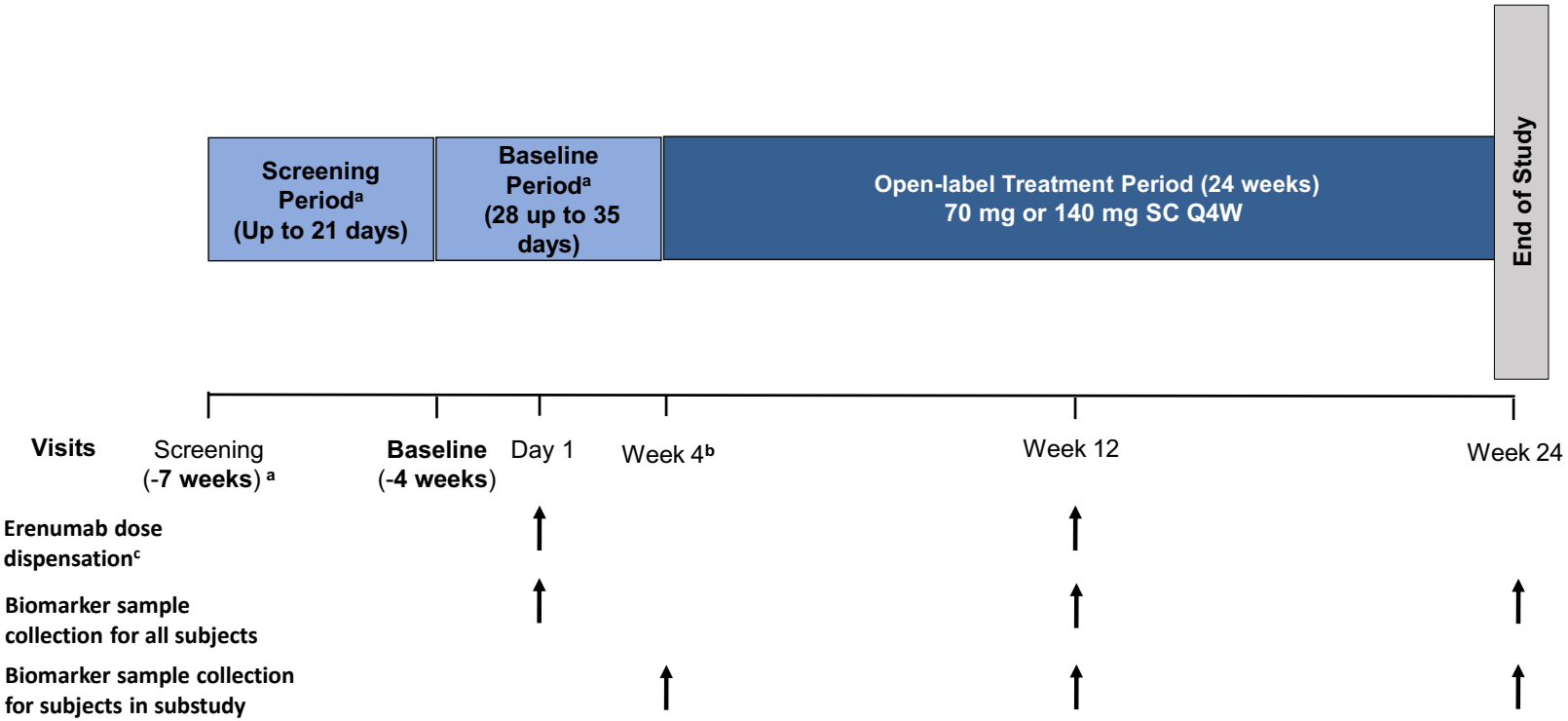
For the primary endpoint, a genome-wide association study (GWAS) of Icelandic and Danish data will be performed using logistic regression for binary phenotypes. Assuming an additive model, GWAS will be performed for the overall sample and by pre-specified subgroups, in addition to other phenotypes of interest that may be defined from the study data. Age and sex will be used as covariates in Icelandic associations and age, sex, and 10 principal components will be used as covariates (to account for population structure) in Danish data. We use linkage disequilibrium (LD)-score regression to account for inflation in test statistics due to cryptic relatedness and stratification. A likelihood-ratio test will be used to compute all P-values. The Icelandic and Danish GWAS will be meta-analyzed using a fixed effects model. Weighted Bonferroni adjustment will be used to maintain a family-wise error rate of 0.05 (2-sided) for the primary endpoint. Using summary statistics from these studies (excluding GWAS data from Denmark and Iceland), mPRS will be calculated for the individuals participating in the clinical trial by summing their identified risk alleles, weighted by effect sizes and accounting for linkage disequilibrium using the LDPred software package. This genetic marker analysis will include subjects with non-missing clinical responses (responder [yes/no] based on at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6).

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

Sponsor Name: Amgen, Inc

1.2 Study Schema

Figure 1-1. Study Schema



Q4W = once every 4 weeks; SC = subcutaneous;
[a]**Screening and baseline visits may be performed on the same day.**
[b]Substudy subjects only.
[c]Site staff is to dispense doses at the day 1 visit (for treatment on day 1, week 4, and week 8) and week 12 visit (for treatment at weeks 12, 16, and 20).

1.3 Schedule of Activities

Table 1. Schedule of Activities

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (± 7 days)	Wk 12 (± 7 days)	Wk 16 (± 7 days)	Wk 20 (± 7 days)	Wk 24/EOS[b] (± 7 days)	
GENERAL AND SAFETY ASSESSMENTS										
Informed consent	X									
Inclusion and exclusion criteria	X	X	X							Compliance with eDiary usage will be assessed prior to enrollment on day 1
Demographics	X									
Medical history	X									
Neurological medical history	X									
Gastro-intestinal medical history	X									Includes gastro-intestinal procedures and surgeries medical history
Headache and migraine frequency medical history	X									
Prior migraine prophylactic medications review	X	X								Includes all prior migraine prophylactic medications that ended 2 months before screening with no limit back in time.

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (± 7 days)	Wk 12 (± 7 days)	Wk 16 (± 7 days)	Wk 20 (± 7 days)	Wk 24/EOS[b] (± 7 days)	
Prior/concomitant therapies review	X	X	X			X			X	Includes all prior medications (other than prior migraine prophylactic medications) that were being taken/used within 120 days prior to screening through the signing of the informed consent and all concomitant medications including migraine prophylactic medications.
Most recent date of menses	X		X			X			X	Females of childbearing potential only

Footnotes after last page of table

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (± 7 days)	Wk 12 (± 7 days)	Wk 16 (± 7 days)	Wk 20 (± 7 days)	Wk 24/EOS[b] (± 7 days)	
SAFETY ASSESSMENTS										
Adverse events			Adverse events collected from day 1 to EOS							
Serious adverse events	Serious adverse events collected from screening to EOS									
Adverse device effects			Adverse device effects collected from day 1 to EOS							

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (± 7 days)	Wk 12 (± 7 days)	Wk 16 (± 7 days)	Wk 20 (± 7 days)	Wk 24/EOS[b] (± 7 days)	
LABORATORY ASSESSMENTS										
Urine pregnancy test	X		X			X			X	Females of childbearing potential only. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject may be pregnant or per local laws and regulations.
Hematology			X			X			X	
BIOMARKER ASSESSMENTS										
Sample collection for biomarker research			X			X			X	Samples include DNA, RNA, CGRP, and proteomics analyses. DNA and CGRP samples will be collected at day 1 visit only. However, DNA samples may be collected at a subsequent visit, if sample collection is not performed on day 1.
CLINICAL OUTCOME ASSESSMENTS										
Instructions in eDiary use		X								
eDiary		Daily								
MFIQ			X						X	
STUDY TREATMENT										

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (± 7 days)	Wk 12 (± 7 days)	Wk 16 (± 7 days)	Wk 20 (± 7 days)	Wk 24/EOS[b] (± 7 days)	
Erenumab dispensation/ administration at study site			X			X				Day 1 and week 12 administration may be performed by site staff or by subject self-administration as the last procedure of the visit. Investigational product will be dispensed for weeks 4 and 8 on day 1 and weeks 16 and 20 at week 12.
Erenumab administration at non-investigational site setting				X	X		X	X		Administration may be performed by the subject or designee in a non-investigative site setting (eg, at home) at weeks 4, 8, 16, and 20.
Site staff reconciliation of dispensed erenumab						X			X	Subject is to return empty AI/Pens and boxes at the wk 12 and wk 24 visits.

AI = autoinjector; CGRP = calcitonin gene-related peptide; eDiary = electronic diary; EOS = end of study; MFIQ = Migraine Functional Impact Questionnaire; Wk = Week

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

[b] A subject who discontinues the study during the open-label treatment period (before week 24) is to complete the assessments of the week 24/EOS visit.

Table 2. CGRP Biomarker Substudy Schedule of Assessments

	Screening[a] (up to 21 days before baseline)	Baseline[a] (28 [+7] days before day 1)	Open-label Treatment Period (24 weeks)							Notes
			Day 1 visit	Wk 4 (± 7 days)	Wk 8 (±7 days)	Wk 12 (±7 days)	Wk 16 (±7 days)	Wk 20 (±7 days)	Wk 24/EOS[b] (±7 days)	
SCHEDULE OF ADDITIONAL ACTIVITIES FOR SUBJECTS THAT PARTICIPATE IN THE OPTIONAL CGRP BIOMARKER SUBSTUDY, THESE ACTIVITIES ARE TO BE PERFORMED IN ADDITION TO THE ACTIVITIES DETAILED IN TABLE 1)										
Informed consent	X									
Sample collection for CGRP				X		X			X	At Wk 4, Subjects are to be instructed to administer erenumab dose at non-investigative site (eg, home) after the visit.

CGRP = calcitonin gene-related peptide; EOS = end of study; Wk = Week

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

[b] A subject who discontinues the study during the open-label treatment period (before week 24) is to complete the assessments of the week 24/EOS visit

2. Introduction

2.1 Study Rationale

Migraine is a clinically heterogeneous disorder with polygenic influences that can be summarized as a polygenic risk score (PRS) (Chalmer et al, 2018). A given individual's migraine PRS (mPRS), derived from the presence/absence of independent single-nucleotide polymorphisms [SNPs], has been demonstrated to be significantly associated with migraine risk (Gormley et al, 2016), with higher scores indicating higher risk. The mPRS SNPs are largely common (30 of the 38 of the primary SNP signals have an allele frequency $>$ 10%) with small effect sizes, but together contribute to genetic predisposition for migraine. It is thought that the spectrum of pathophysiologies (eg, presence of aura, menstrual relatedness), the variable temporal onset and severity of disease, and responsiveness/non-responsiveness to acute or prophylactic migraine medications might reflect the fact that many different genes contribute to migraine risk and its phenotypic manifestations. Preliminary post-hoc analysis of erenumab-treated subjects with episodic or chronic migraine (EM or CM) has revealed an association of mPRS with several disease characteristics, such as the use of acute migraine-specific and prophylactic medications. The overarching objective of this study is to explore the potential association of several biomarker platforms including (DNA [SNPs, including those comprising the mPRS], RNA, proteomics, and plasma calcitonin gene-related peptide [CGRP] levels) with erenumab treatment response.

2.2 Background

2.2.1 Disease

Migraine is a disabling disorder characterized by primary recurrent headaches (referred to as attacks) 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 has 2 major subtypes: migraine with aura (visual, sensory, and/or speech symptoms that occur just before or at the onset of migraine headache) and migraine without aura per the International Headache Classification Disorders (ICHD)-III.

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, which is why often the migraine spectrum is usually described according to frequency of migraine days per month, with 2 broad categories based on frequency of attacks: EM is typically defined as 0 to 14 migraine days per month (Katsarava et al, 2012) and CM as 15 or more headache days per months, at least 8 of which have to be typical migraine days (Headache Classification Committee of the International Headache Society, 2018). While all migraine patients can be treated with acute medications, not all migraine patients are appropriate for prophylactic treatment. Although there is no clear consensus on a minimal number of migraine days or attacks to start migraine prophylaxis, there is agreement in that it should be considered whenever there is significant disability induced by the attacks (Evers et al, 2006; Antonaci et al, 2010). Reports suggest that out of the approximately 25% of migraine patients in need of migraine prevention, only half of them are actually treated with migraine prophylactic treatments (Lipton et al, 2007).

2.2.2 Amgen Investigational Product Background: Erenumab

Erenumab is a human immunoglobulin G2 (IgG2) that is directed against the 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 administered subcutaneously [SC] once every 4 weeks [Q4W] [or once every month {QM}]) has been approved in approximately 40 countries including the United States (US) and European Union (EU).

A detailed description of the chemistry, pharmacology, efficacy, and safety of erenumab is provided in the Erenumab investigator's Brochure and regional label.

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 frequency of monthly migraine days (MMDs),

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 (QM 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, 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 open-label clinical trial. Reference should be made to the investigator's Brochure and regional label for further data on erenumab.

3. Objectives, Endpoints and Hypotheses

3.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To explore the relationship between clinical response to erenumab and genetic biomarkers	• Achievement of at least a 50% reduction from baseline in mean monthly migraine days (MMD) over months 4, 5, and 6 in relation to each individual genome-wide significant single-nucleotide polymorphism (SNP) contributing to the migraine polygenic risk score (mPRS)

Objectives	Endpoints
Exploratory	
• To describe the relationship between AMSM use and mPRS in erenumab-treated subjects	• Change from baseline in monthly AMSMD over months 4, 5, and 6, in relation to mPRS
• To describe the relationship between baseline calcitonin gene-related peptide (CGRP) levels and clinical response with erenumab treatment as assessed by MMD in erenumab-treated subjects	• Change from baseline in MMD over months 4, 5, and 6 in relation to baseline CGRP level • Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 in relation to baseline CGRP level • Achievement of at least a 75% reduction from baseline in mean MMD over months 4, 5, and 6, in relation to baseline CGRP level
• To describe the relationship between baseline CGRP levels and clinical response with erenumab treatment as assessed by acute migraine-specific medication days (AMSMD) in erenumab-treated subjects	• Change from baseline in AMSMD over months 4, 5, and 6, in relation to baseline CGRP level
• To describe the relationship between mPRS and baseline CGRP	• mPRS in relation to baseline CGRP level
• To describe the relationship between baseline CGRP levels and migraine disease characteristics	• Baseline CGRP level in relation to baseline MMD • Baseline CGRP level in relation to baseline AMSMD • Baseline CGRP level in relation to baseline AHMD • Baseline CGRP level in relation to each MFIQ individual domain score (physical function, usual activities, social function, and emotional function) and overall impact usual activities global item score at baseline • Baseline CGRP in relation to presence of aura during baseline • Baseline CGRP in relation to baseline mean migraine severity

Objectives	Endpoints
Exploratory (Continued)	
• To describe the relationship between mPRS and migraine disease characteristics	• mPRS in relation to baseline MMD • mPRS in relation to baseline AMSMD • mPRS in relation to baseline acute headache medication days (AHMD) • mPRS in relation to Migraine Functional Impact Questionnaire (MFIQ) individual domain scores (physical function, usual activities, social function, and emotional function) and overall impact usual activities global item score at baseline • mPRS in relation to presence of aura during baseline • mPRS in relation to baseline mean migraine severity
• To evaluate the effect of erenumab as assessed by change in MMD in erenumab-treated subjects	• Change from baseline in mean MMD over months 4, 5, and 6 • Change from baseline in MMD at assessment timepoints • Achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6 • Achievement of at least a 50% reduction from baseline in MMD at assessment timepoints • Achievement of at least a 75% reduction from baseline in mean MMD over months 4, 5, and 6 • Achievement of at least a 75% reduction from baseline in mean MMD at assessment timepoints

Objectives	Endpoints
Exploratory (Continued)	
• To evaluate the effect of erenumab as assessed by change in AMSMD in erenumab-treated subjects	• Change from baseline in mean monthly AMSMD over months 4, 5, and 6 • Change from baseline in monthly AMSMD at assessment timepoints
• To evaluate the effect of erenumab as assessed by change in monthly AHMD in erenumab-treated subjects	• Change from baseline in mean monthly AHMD over months 4, 5, and 6 • Change from baseline in monthly AHMD at assessment timepoints
• To evaluate the effect of erenumab on functional impact as assessed by the change from baseline MFIQ score in erenumab-treated subjects	• Change from baseline in MFIQ individual domain scores (physical function, usual activities, social function, and emotional function) and overall impact usual activities global item score at month 6
• To describe the relationship between change from baseline in MFIQ score and mPRS in erenumab-treated subjects	• Change from baseline in MFIQ individual domain scores (physical function, usual activities, social function and emotional function) and overall impact usual activities global item score at month 6, in relation to mPRS

3.2 Hypothesis

No formal hypothesis testing will be performed. All analyses will be descriptive in nature.

4. Study Design

4.1 Overall Design

This is a phase 4 open-label study that will enroll subjects with EM or CM without a predetermined allocation ratio. The study will comprise of the following periods:

- A screening period of up to 3 weeks (21 days) for the assessment eligibility criteria. The screening visit may be performed on the same day as the baseline visit
- A baseline period of 4 weeks (28 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 at day 1 visit
- A 24-week open-label treatment period

Subjects will be screened at screening visit, and if eligible, subjects may enter the baseline period at the same visit as screening or may begin baseline procedures up to 3 weeks after the screening visit. At completion of the baseline period, those who meet eligibility criteria and demonstrate $\geq$ 75% compliance with eDiary use will be enrolled and will enter the open-label treatment period to receive either erenumab 70 or 140 mg subcutaneously (SC) every 4 weeks (Q4W) at the discretion of the investigator.

Day 1 and week 12 administration may be performed by site staff or by subject self-administration. Site staff will dispense the doses at day 1 and week 12 necessary to continue erenumab monthly treatment between visits (ie, subject is to take home doses for week 4, 8, 16, and 20 for administration at non-investigative site [eg, home]), as detailed in Table 1. Subjects may contact the site at any time in between scheduled visits, and the investigator will determine if an additional unscheduled onsite visit is necessary.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.1.

4.2 Number of Subjects

Approximately **1400** subjects will be enrolled in the study; all subjects are to receive erenumab, either 70 mg or 140 mg SC Q4W, determined at the investigator's discretion and may be adjusted once during the study at the week 12 visit.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 9.1.

4.2.1 Replacement of Subjects

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

4.2.2 Number of Sites

Approximately 2 to 4 investigative sites in Europe will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 End of Study

4.3.1 End of Study Definition

End of Study: An individual subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of Activities (Table 1). 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.

4.3.2 Study Duration for Subjects

The study duration including screening/baseline period and 24-week open-label treatment period is approximately 28 to 33 weeks.

4.4 Justification for Investigational Product Dose

Erenumab 70 mg and 140 mg SC Q4W are approved in Europe and the United States 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, 2106; Goadsby et al, 2017;
Tepper et al, 2017; Dodick et al, 2018).

4.5 Patient Input on Study Design

Patient input was not solicited in the study design.

5. Study Population

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

Eligibility criteria will be evaluated during screening.

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:

Before baseline period

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

102 Age ≥ 18 years upon entry into screening

103 History of migraine (with or without aura) for ≥ 12 months before screening according to the International Headache Society (IHS) Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 2018) based on medical records and/or patient self-report

104 ≥ 4 headache days that meet criteria as migraine days per month on average across the 3 months before screening

After baseline period

105 Must have demonstrated ≥ 75% compliance in eDiary usage during baseline period

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 Inability to differentiate between migraine from other headaches

Other Medical Conditions

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

205 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

Prior/Concomitant Therapy

206 Previously received erenumab (Aimovig)

207 Received an anti-CGRP monoclonal antibody within 3 months prior to the start of the baseline period

215 Initiation, discontinuation, or change of dosing of migraine prophylactic medications within 2 months prior to the start of the baseline period, during the baseline period or planned during the study. Refer to Section 6.1.7 **for** additional information.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

209 Female subjects of childbearing potential with a positive pregnancy test assessed at screening or day 1 by a urine pregnancy test.

210 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 16 weeks after the last dose of investigational product.

211 Female subjects of childbearing potential unwilling to use 1 acceptable method of effective contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Section 11.5 for additional contraceptive information.

212 Evidence of current pregnancy or breastfeeding per subject self-report or medical records

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

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

5.3 Subject Enrollment

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

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

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. This should occur on day 1, after completion of the baseline period. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF).

Each subject who enters into the screening period for the study (defined as when the subject signs the ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned sequentially following format provided by Amgen. 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 the initial assignment, including if a subject is rescreened.

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if 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. Treatments

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

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

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 3 below.

6.1 Treatment Procedures

6.1.1 Investigational Products

Table 3. Study Treatments

Study Treatment Name	**Amgen Investigational Product:**[a] Erenumab
Dosage Formulation	Erenumab will be packaged in a SureClick® AI/Pen containing 1 mL of 70 mg/mL or 140 mg/mL of erenumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	Erenumab 70 mg or 140 mg will be administered Q4W. Dose is to be determined at the investigator's discretion and may be adjusted once during the study at the week 12 visit.
Route of Administration	SC injection
Accountability	The quantity, start date, and lot number of investigational product are to be recorded on each subject's eCRF.
Dosing Instructions	Site staff is to dispense erenumab AI/Pens to subjects at the day 1 visit (for treatment on day 1, week 4, and week 8) and week 12 visit (for treatment at weeks 12, 16, and 20). At the day 1 and week 12 visit erenumab will be administered to subjects by site staff or by subject self-administration as the last procedure of the visit. Administration will be performed by the subject or designee in a non-investigator site setting (eg, at home) at weeks 4, 8, 16, and 20. At week 4, subjects participating in the CGRP biomarker substudy are to be instructed to administer erenumab dose at non-investigative site (eg, home) after the visit. Refer to the IPIM for investigational product details.
Device	AI/Pen

AI = autoinjector; eCRF = electronic case report form; IPIM = Investigational Product Instruction Manual; Q4W = once every 4 weeks; SC = subcutaneous.

[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 following investigational medical device(s) provided by Amgen for use in this study is the erenumab SureClick® Autoinjector Pen (AI/Pen) (Table 3).

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.

Additional details are provided in the IPIM.

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

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

6.1.4 Other Protocol-required Therapies

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

6.1.5 Other Treatment Procedures

Other treatment procedures will not be conducted 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/non-investigational product(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen, including the erenumab AI/Pen.

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

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

Concomitant treatment with migraine prophylactic medications are allowed under the following conditions:

- Drug regimen (ie, formulation, frequency of use, route, and dose) is stable for ≥ 2 months (for oral migraine prophylactic medications) or ≥ 2 cycles (for botulinum toxin) prior to the start of the baseline period
- Drug regimen is at a generally accepted dose, frequency, and route for its use in migraine
- Drug regimen is not anticipated to change during baseline period or throughout the study

Allowable 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)
- Botulinum toxin (in the head and/or neck region)
- Other drugs used for migraine prevention (eg, clonidine, guanfacine, methysergide, cyproheptadine, pizotifen), except for anti-CGRP medications which are excluded.

6.2 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with either 70 mg or 140 mg SC Q4W, determined by the investigator's discretion and may be adjusted once during the study at the week 12 visit.

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

6.3 Blinding

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

6.4 Dose Modification

6.4.1 Dose-Cohort Study Escalation/De-escalation and Stopping Rules

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

6.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

6.4.2.1 Amgen Investigational Product: Erenumab

Dose adjustments between 70 mg and 140 mg erenumab are permitted at the week 12 visit per investigator discretion. The reason for change of planned dose 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 8.2.3.1 for details regarding adverse event reporting.

6.5 Preparation/Handling/Storage/Accountability

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

6.6 Treatment Compliance

Subject administration of investigational product will occur at sites at scheduled visits or at a non-investigator site setting (eg, at home). 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.

6.7 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.

6.8 Prior and Concomitant Treatment

6.8.1 Prior Treatment

All prior prophylactic migraine therapies ever taken and ending prior to start of baseline will be collected, including reason for ending therapy.

For all other prior therapies that were being taken/used from 120 days before screening through the signing of the informed consent, therapy name, start date, and stop date will be collected.

6.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. Refer to Section 6.1.7 for restrictions regarding migraine prophylactic medication.

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

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or 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, and/or protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) 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 and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 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.

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

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

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- Protocol deviation
- non-compliance
- adverse event
- subject request
- pregnancy

7.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1) 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, Run-in or Invasive Procedures

Wash-out, 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 can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

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

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

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

8.1 General Study Periods

8.1.1 Screening

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will assign subject identification numbers sequentially following format provided by Amgen and screen the subject in order to assess eligibility for participation.

All screening and baseline 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.

8.1.2 Baseline Period

The baseline period can begin after confirmation that all initial eligibility criteria have been met. This can be the same day as the screening visit or within 3 weeks (21 days) of the screening visit. The baseline period will end 1 day before the day 1 visit and must be at least 28 days and no more than 35 days in duration. The compliance in eDiary usage during the baseline period will be assessed on day 1. A subject will either be screen-failed if not demonstrating $\geq$ 75% compliance in eDiary usage, or enrolled into the open-label treatment period. Subjects who have screen failed may be eligible for rescreening only once, if in the opinion of the investigator, the reason for the initial screen failure has been resolved or is no longer applicable. Once the subject is 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.

8.1.3 Treatment Period

Visits will occur per the Schedule of Activities (Table 1). 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. Study visits after day 1 may be completed within $\pm$ 7 days of the scheduled visit. At the day 1 and week 12 visit erenumab will be administered on site to subjects by site staff or by subject self-administration as the last procedure of the visit. All other doses of erenumab are to be administered by subject or designee at a non-investigative site setting (eg, at home).

8.1.4 End of Study

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

8.2 Description of General Study Assessments and Procedures

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

8.2.1 General Assessments

8.2.1.1 Informed Consent

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

8.2.1.2 Demographics

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

8.2.1.3 Medical History

The investigator or designee will collect a complete medical history that started within 120 days prior to screening. Medical history will include information on the subject's concurrent medical conditions. 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 in the neurologic medical history eCRF, gastro-intestinal medical history eCRF, gastro-intestinal procedures and surgeries medical history and headache and migraine frequency medical history eCRF. The current severity will be collected for each condition that has not resolved.

8.2.2 Efficacy Assessments

8.2.2.1 Clinical Outcome Assessments and Electronic Diaries

8.2.2.1.1 Electronic Diary

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

- presence or absence of 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 baseline visit (after confirming the subject's eligibility), 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 every day. 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.

8.2.2.1.2 Migraine Functional Impact Questionnaire

The Migraine Functional Impact Questionnaire (MFIQ) version 2.0 is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including 4 domains: Impact on Physical Functioning (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.

Subjects are to complete the MFIQ using paper forms as specified in the Schedule of Activities (Table 1), and site staff will record entries onto eCRFs.

8.2.3 Safety Assessments

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

8.2.3.1 Adverse Events and Serious Adverse Events

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

8.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 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 the first dose of investigational product through the end of study are reported using the Event**s** eCRF.

8.2.3.1.1.2 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.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events. **For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.**

8.2.3.1.1.3 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 knowledge 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.

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

8.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

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

8.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

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

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

8.2.3.1.4 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.

8.2.3.2 Safety Monitoring Plan

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

8.2.3.2.1 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until end of study.

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.

8.2.3.2.2 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.

8.2.4 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) for the timing and frequency.

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

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).

8.2.4.1 Pregnancy Testing

A urine pregnancy test should be completed at screening and before administration of investigational product on day 1 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 Worksheet, see 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 or as required per local laws and regulations.

8.2.5 Biomarkers

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

8.2.5.1 Biomarker Research

Samples will be collected for biomarker analysis, eg, to evaluate potential biomarkers that may correlate with treatment response.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (Table 1). Blood samples may be tested for genotyping, RNA sequencing, proteomics, and plasma CGRP levels.

8.2.5.2 Optional CGRP Biomarker Substudy

Approximately **315** subjects will provide additional informed consent in order to participate in the optional CGRP biomarker substudy. Subjects participating in this substudy will have an additional CGRP sample collected at weeks 4, 12 and 24 as indicated in the CGRP Substudy Schedule of Activities **(**Table 2). These additional CGRP samples will be used to explore whether the changes from baseline in CGRP levels might predict erenumab response.

Obtain confirmation that the optional substudy ICF has been signed prior to performing optional substudy procedures.

9. Statistical Considerations

9.1 Sample Size Determination

The primary objective is the identification of genome-wide significant SNPs contributing to the mPRS that are significantly associated with clinical response to erenumab treatment (based on achievement of at least a 50% reduction from baseline in mean MMD over months 4, 5, and 6). Based on erenumab pivotal EM and CM studies, the $\geq$ 50% response rate with respect to MMD reduction is expected to be approximately 50% after 24 weeks of erenumab treatment. It is hypothesized that the mPRS SNPs with genome-wide significance ($p < 5 \times 10^{-8}$) have an additive effect on clinical response, ie, for each of these mPRS SNPs, each additional copy of the allele (with 0 as the reference) is associated with increased clinical response and will result in an odds ratio of 1.8 or higher (allelic odds ratio). **Given the currently known 123 migraine** SNPs with genome-wide significance and a minor allele frequency (MAF) of at least 0.1, **a** study of **1400** subjects with 10% dropouts (resulting an effective sample size of **1260** at week 24) is at least 90% powered to identify **five of the** genome-wide significant **migraine** SNPs that are statistically significantly associated with clinical response. **This is based on a two-sided power analysis, with Bonferroni adjustment, bootstrapping the data from the pivotal EM Study 20120296 (Mikol et al, 2020), using a logistic regression model to predict clinical response with each SNP, and adjusting for sex, age, BMI and principal components.**

9.2 Analysis Sets, Subgroups, and Covariates

9.2.1 Analysis Sets

9.2.1.1 Full Analysis Set

The full analysis set (FAS) consists of all subjects who enroll in the study. Analysis of disposition, demographic and baseline characteristics, and important protocol deviations will utilize the FAS.

9.2.1.2 Observed Data Analysis Set

The observed data analysis set consists of a subset of subjects in FAS who receive at least 1 dose of investigational product and have an observed value for the endpoint of interest. Primary analysis of the efficacy endpoints related to the genetic biomarkers will utilize the observed data analysis set.

9.2.1.3 Efficacy Analysis Set

The efficacy analysis set (EAS) consists of a subset of subjects in FAS who receive at least 1 dose of investigational product and have at least 1 postbaseline change from baseline measurement for the endpoint of interest. Primary analysis of the exploratory efficacy endpoints **not involving biomarkers** will utilize the EAS.

9.2.1.4 Safety Analysis Set

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

9.2.2 Covariates

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

9.2.3 Subgroups

The primary endpoint will be summarized in the subgroups defined by the following:

- sex (female/male)
- aura (yes/no)
- menstrual-related migraine (yes/no)
- country (Iceland/Denmark)
- migraine classification (EM/CM)
- prior migraine prophylactic treatment failure (yes/no)

9.2.4 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of reasons. In general, data could be missing because of a subject's early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a time point. For this study, efficacy endpoints will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe how missing data will be handled.

For the eDiary data, if at least 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements (eg, migraine days or acute migraine-specific medications days [AMSMD]) will be prorated based on the number of days with available information. If less than 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements will be set to missing. Missing clinical outcome assessments (MFIQ) will not be imputed.

Missing safety endpoints will not be imputed. Missing or incomplete dates will be listed as reported, except for incomplete start date of an adverse event or concomitant medication (Table 4).

Table 4. Imputation for Incomplete Start Date of an Adverse Event or Concomitant Medication

Missing	Imputation	Exception on Adverse Event Start Date
Day	01	Default to study day 1 if an adverse event started the same year and month as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month	01 Jan	Default to study day 1 if an adverse event started the same year as study day 1 and the flag indicates that the adverse event started on or after the first dose of investigational product on the Events eCRF
Day/Month/Year	None	—

eCRF = electronic case report form

9.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the primary analysis will be conducted and reported following the end-of-study, as defined in Section 4.3.1.

9.3.1 Planned Analyses

9.3.1.1 Primary Analysis

The primary analysis (or final analysis, as this study has only 1 milestone analysis) will be performed after all subjects have completed their week 24 or end of study visit. The data will be cleaned, and the database will be locked for the primary analysis.

9.3.2 Methods of Analyses

9.3.2.1 General Considerations

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

9.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	A GWAS of Icelandic and Danish data will be performed using logistic regression for binary phenotypes. Assuming an additive model, GWAS will be performed for overall sample and by pre-specified subgroups, in addition to other phenotypes of interest that may be defined from the study data. Age and sex will be used as covariates in Icelandic associations and age, sex, and 10 principal components will be used as covariates (to account for population structure) in Danish data. Linkage disequilibrium (LD)-score regression will be used to account for inflation in test statistics due to cryptic relatedness and stratification. A likelihood-ratio test will be used to compute all P-values. The Icelandic and Danish GWAS will be meta-analyzed using a fixed effects model. Weighted Bonferroni adjustment will be used to maintain a family-wise error rate of 0.05 (2-sided) for primary endpoint. Using summary statistics from these studies (excluding GWAS data from Denmark and Iceland), migraine polygenic risk scores (mPRS) will be calculated for the individuals participating in the clinical trial by summing their identified risk alleles, weighted by effect sizes and accounting for linkage disequilibrium using the LDPred software package. This analysis is planned to be performed by deCODE and details of the analysis are described in deCODE Analysis Plan (Appendix B of the statistical analysis plan).
Exploratory	The analyses will be described in the statistical analysis plan, which will be finalized before database lock.

9.3.2.3 Safety Analyses

9.3.2.3.1 Adverse Events

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

9.3.2.3.2 Exposure to Investigational Product

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

9.3.2.3.3 Exposure to Concomitant Medication

Number and proportion of subjects receiving acute headache medications will be summarized by medication category.

10. References

Antonaci F, Dumitrache C, De Cillis I, et al A review of current European treatment guidelines for migraine. *J Headache Pain*. 2010;11(1):13-19.

Chalmer MA, Esserlind AL, Olesen J, et al Polygenic risk score: use in migraine research. *J Headache Pain*. 2018;19(1):29.

Dodick DW, Ashina M, Brandes JL, et al ARISE: A phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38(6):1026-1037.

Erenumab investigator's Brochure. Thousand Oaks, CA. Amgen Inc.

Evers S, Afra J, Frese A, et al EFNS guideline on the drug treatment of migraine - report of an EFNS task force. *Eur J Neurol*. 2006;13(6):560-572.

Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553-622.

Goadsby PJ, Lipton RB, Ferrari MD Migraine—current understanding and treatment. *N Engl J Med*. 2002;346(4):257-270.

Gormley P, Anttila V, Winsvold B, et al Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet*. 2016;48(8):856-866.

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

Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16:86-92.

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

Mikol DD, Picard H, Klatt J, Wang A, Peng C, Stefansson K. Migraine Polygenic Risk Score Is Associated with Severity of Migraine–Analysis of Genotypic Data from Four Placebo-controlled Trials of Erenumab. Neurology. 2020;94 (15 supplements): 1214.

Robbins MS, Lipton RB. The epidemiology of primary headache disorders. *Semin Neurol*. 2010;30(2):107-119.

Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *J Headache Pain*. 2010;11(4):289-299.

Sun H, Dodick DW, Silberstein S, et al Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(4):382-390.

Tajti J, Uddman R, Möller S, Sundler F, Edvinsson L. Messenger molecules and receptor mRNA in the human trigeminal ganglion. *J Auton Nerv Syst*. 1999;76:176-183.

Tepper S, Ashina M, Reuter U, et al Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425-434.

11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AHMD	acute headache medication days
AI/Pen	Autoinjector Pen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMSMD	acute migraine-specific medication days
AST	aspartate aminotransferase
BIL	bilirubin
CFR	United States Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CM	chronic migraine
CTCAE	Common Terminology Criteria for Adverse Events
EAS	efficacy analysis set
eCRF	electronic case report form
EDC	electronic data capture
Enrollment	defined as the date when the subject has been assessed to pass all eligibility criteria after completion of the screening and baseline period
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EM	episodic migraine
EU	European Union
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GWAS	genome-wide association study
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD	International Headache Classification Disorders

Abbreviation or Term	Definition/Explanation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHS	International Headache Society
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
LD	linkage disequilibrium
MAF	minor allele frequency
MFIQ	Migraine Functional Impact Questionnaire
MMD	monthly migraine day
mPRS	migraine polygenic risk score
NCT	National Clinical Trials
PROs	patient-reported outcomes
PRS	polygenic risk score
Q4W	Every 4 weeks
QM	once every month
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous
SmPC	summary of product characteristics
SNP	single-nucleotide polymorphism
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study **day 1**	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 5 will be performed.

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.

Table 5. Analyte Listing

Hematology
WBC count Differential
Other Labs
Urine pregnancy Biomarker research samples (DNA, RNA, proteomics, and CGRP analyses) Biomarker samples for CGRP biomarker substudy (CGRP analysis)

CGRP = calcitonin gene-related peptide; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

11.3.1 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 (ICF), 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 ICF 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 United States Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

11.3.2 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.

11.3.3 Informed Consent Process

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

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

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

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

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

The acquisition of informed consent is to be documented in the subject's medical records, and the ICF 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 ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

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

11.3.4 Data Protection/Subject Confidentiality

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

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

On the 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 ICFs) are to be kept in confidence by the investigator, except as described below.

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

verifying, and reproducing any records and reports that are important to the evaluation of the study.

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

11.3.5 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.

11.3.6 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

11.3.7 Data Quality Assurance

All subject data relating to the study will be recorded on printed or 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.

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

11.3.8 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).

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

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

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

11.3.10 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

11.4.1 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 statistical analysis plan

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.

11.4.2 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.

11.4.3 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 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.**

11.4.4 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 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;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product(s), other protocol-required therapies, 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**s** 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**s** 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.

11.4.5 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 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.

11.4.6 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 an electronic Serious Adverse Contingency Report Form (see Figure 11-1) within 24 hours of the investigator's knowledge 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 has been taken off-line, then the site can report this information on a paper Serious Adverse Event 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.**

11.4.7 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**s** 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 Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

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

General Instructions

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

Types of Events to be reported on this form

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

1. **Site Information**

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

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

2. **Subject Information**

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

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

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

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

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

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

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

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

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

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

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

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

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

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

4. **Hospitalization**

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

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

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

Protocol specified hospitalizations are exempt.

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

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

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

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

AMGEN
Study # 20190006
Erenumab (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? Erenumab (AMG 334) No / Yes	Prefilled Autoinjector No / Yes	<Revise> No / Yes	<Revise> No / Yes	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 #
Erenumab (AMG 334)	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Amgen Prefilled Autoinjector (AI)	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____

AMGEN
Study # 20190006
Erenumab (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											

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 # 20190006 Erenumab (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 protocol-required therapies.

11.5.1 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 (IUD)

- intrauterine hormonal-releasing system (IUS)
- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- male or female condom with or without spermicide
- cap, diaphragm, or sponge with spermicide
- double-barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

11.5.2 Unacceptable Methods of Birth Control for Female Subjects

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

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

11.5.3 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 Worksheet (see Figure 11-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks 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 Worksheet. The worksheet (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 Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

11.5.4 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 protocol-required therapies.

- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 212.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Worksheet

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: **_protocol# 20190006**_____

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: Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: **_protocol# 20190006**_____

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

11.6 Appendix 6. Sample Storage and Destruction

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

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

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

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns

the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

Amendment 2

Protocol Title: Biomarker and Genetic Predictors of Erenumab Treatment Response, a Phase 4 Investigational Open-label Study (INTERROGATE)

Amgen protocol Number Erenumab 20190006

NCT04265755

Amendment Date: 23 February 2022

Rationale:

This protocol is being amended to:

- Reduce the sample size from 2000 subjects to 1400 subjects throughout the protocol as the sites will not be able to achieve the enrollment target and it was determined that a lower sample will still provide sufficient analytical power.
- Update Sample Size Determination for align with the sample size.
- Update section on serious adverse events after the protocol-required reporting period, Product Complaints, Adverse Device Effect Definition, Serious Adverse Event Reporting via Electronic Data Collection Tool as per the latest template text.
- Increase the sample from 200 subjects to 315 subjects in optional CGRP biomarker substudy.
- Perform administrative and formatting updates.

Amendment 1

Protocol Title: Biomarker and Genetic Predictors of Erenumab Treatment Response, a Phase 4 Investigational Open-label Study (INTERROGATE)

Amgen Protocol Number Erenumab 20190006

Amendment Date:	01 February 2021
Superseding Amendment Date:	15 March 2021

Rationale: Changes have been made to facilitate enrollment and provide subjects with flexibility, including the option to separate screening from the start of the baseline period; adding the option for self-administration of the investigational product on day 1, and a rescreening option. Changes were also made to clarify aspects of the protocol, including the collection of DNA samples from all subjects; requirements for allowable use of other migraine preventive medication; and calcitonin gene-related peptide assessments after day 1 to be only conducted in an optional sub-study. Updates were also made to reflect current data in the risk and statistical analysis sections.

The following changes have been made:

- The screening and baseline periods have been separated
- Statistical analyses have been updated
- Notes have been added to the schedule of assessments (SOA) to clarify activities
- Optional sub-study assessments have been put into a separate SOA
- References to some exploratory objectives have been removed
- Benefit risk-assessment language has been updated to reflect current assessments
- End of study language edited to reflect current template format
- Exclusion criteria 215 added: “Initiation, discontinuation, or change of dosing of migraine prophylactic medications within 2 months prior to the start of the baseline period, during the baseline period or planned during the study.”
- Screen failure and rescreening language updated: a subject 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
- Excluded treatments, medical devices, and/or procedures during the study period have been updated
- Hepatotoxicity sections have been removed per template language regarding it as optional
- Sampling has been updated for the plasma calcitonin gene-related peptide **(**CGRP) biomarker substudy
- Editorial and administrative updates have been made throughout

On 15 March 2021, the protocol amendment was superseded to include the following:

- To include CGRP samples for biomarker research
- Remove abbreviation drug induced liver injury (DILI) from the abbreviation list

Amendment 1

Protocol Title: Biomarker and Genetic Predictors of Erenumab Treatment Response, a Phase 4 Investigational Open-label Study (INTERROGATE)

Amgen Protocol Number Erenumab 20190006

Amendment Date: 01 February 2021

Rationale: Changes have been made to facilitate enrollment and provide subjects with flexibility, including the option to separate screening from the start of the baseline period; adding the option for self-administration of the investigational product on day 1, and a rescreening option. Changes were also made to clarify aspects of the protocol, including the collection of DNA samples from all subjects; requirements for allowable use of other migraine preventive medication; and calcitonin gene-related peptide assessments after day 1 to be only conducted in an optional sub-study. Updates were also made to reflect current data in the risk and statistical analysis sections.

The following changes have been made:

- The screening and baseline periods have been separated
- Statistical analyses have been updated
- Notes have been added to the schedule of assessments (SOA) to clarify activities
- Optional sub-study assessments have been put into a separate SOA
- References to some exploratory objectives have been removed
- Benefit risk-assessment language has been updated to reflect current assessments
- End of study language edited to reflect current template format
- Exclusion criteria 215 added: “Initiation, discontinuation, or change of dosing of migraine prophylactic medications within 2 months prior to the start of the baseline period, during the baseline period or planned during the study.”
- Screen failure and rescreening language updated: a subject 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
- Excluded treatments, medical devices, and/or procedures during the study period have been updated
- Hepatotoxicity sections have been removed per template language regarding it as optional
- Sampling has been updated for the CGRP biomarker substudy
- Editorial and administrative updates have been made throughout